

COMPUTATIONAL MODELING OF CARDIAC DYSFUNCTIONS

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ABSTRACT

COMPUTATIONAL MODELING OF CARDIAC DYSFUNCTIONS

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Computational modeling of the cardiovascular system has improved remarkably with the advances in the computer technology and mathematical modeling. The cardiac models can play a crucial role in understanding the major electromechanical, biophysical, and biochemical processes for the both healthy and pathological cases. The capability of heart models to capture the real physiological behavior depends on physiologically sound constitutive models accounting for the intrinsically non-linear, electromechanically coupled response of anisotropic cardiac tissue. It is also necessary to incorporate the efficient, robust, and stable numerical algorithms into these models. To this end, we propose a micro-structurally based, unified implicit finite element approach to the fully coupled problem of cardiac electromechanics incorporating cardiac dysfunctions. In this thesis, we formulate the coupled problem of cardiac electromechanics through the conservation of linear momentum and the excitation equation in the Eulerian setting. These equations are solved monolithically through an entirely finite element-based implicit algorithm. Different from the existing literature, the deformation

gradient is multiplicatively decomposed into active and passive parts in addition to the additive split of the free energy function to model the electromechanical coupling. This framework allows us to combine the advantages of the active-stress and the active-strain approaches. The left ventricular pressure evolution is modeled by incorporating a Windkessel-like model. The proposed model is then employed to investigate different pathological cases that cover myocardial infarction, eccentric and concentric hypertrophy. The computational results are shown to be in agreement with the clinical symptoms observed in the associated dysfunction.

Keywords: Coupled Cardiac Electromechanics, Cardiac Diseases, Pressure-Volume Curves, Finite Element Method

ÖZ

KALP HASTALIKLARININ HESAPLAMALI OLARAK MODELLENMESİ

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Kardiyovasküler sistemin hesaplamalı nicel modellenmesinde; bilgisayar teknolojisi ve matematiksel modellemedeki gelişmelerle birlikte, önemli yol katedilmiştir. Kalp modelleri; sağlıklı ve patolojik durumlarda, başlıca elektromekanik, biyofiziksel ve biyokimyasal süreçlerin anlaşılmasında önemli rol oynamaktadır. Kalp modellerinin gerçek fizyolojik davranışı yakalayabilmesi, eşyönsüz kalp dokusunun doğrusal olmayan, bağlaşıklık elektromekanik etkiyi dikkate alan sağlam bünye denklemlerine dayanmasına bağlıdır. Ayrıca, verimli, sağlam ve kararlı algoritmaların da bu modellere tamamlayıcı olarak eşlik etmeleri gerekmektedir. Bu amaç ışığında; eldeki tez çalışmasında, kalpteki işlevsel bozuklukların benzetimi için kalbin tamamen bağlaşıklık elektromekaniksel davranışının modellenmesinde mikro-yapıya dayanan tamamen kapalı adımlı sonlu elemanlar yöntemi önerilmektedir. Bu çalışmada, kalbin bağlaşıklık elektromekaniksel modellenmesi, doğrusal momentumun korunumu ve elektriksel uyarılma denklemleri ile oluşturulmuştur. İlgili denklemler tamamen sonlu elemanlar esaslı kapalı adımlı algo-

ritmalar kullanılarak monolitik olarak çözülmüştür. Literatürden farklı olarak, elektromekanik bağlaşıklığın modellenmesinde, şekil değiştirme gradyanı aktif ve pasif bileşenlerine çarpımsal olarak ayrılmış ve serbest enerji fonksiyonu toplam-sal olarak parçalanmıştır. Böylece, aktif-gerilme ve aktif birim şekil değiştirmeye dayanan yaklaşımların avantajları tek bir modelde birleştirilmiştir. Sol karıncığın basınç oluşumu Windkessel benzeri bir modelle hesaplanmıştır. Önerilen model, miyokard enfarktüsü, dış merkezli ve eş merkezli hipertrofi (aşırı büyüme) hastalıklarının araştırılması için kullanılmıştır. Hesaplamalı benzetim sonuçlarının ilgili hastalıklar için gözlemlenmiş klinik bulgularla uyduğu gösterilmiştir.

Anahtar Kelimeler: Bağlılık Kalp Elektromekanik, Kalp Hastalıkları, Basınç-Hacim Eğrileri, Sonlu Elemanlar Yöntemi

Dedicated to my dear parents,
and
my husband, Alikan.

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CHAPTER 1

INTRODUCTION

In this thesis, it is aimed to develop a mathematical model to simulate the cardiac pressure-volume curves for both the healthy and dysfunctional cases. For this purpose, the three-dimensional coupled problem of cardiac electromechanics is solved and the potential of our model in simulating cardiac diseases, covering the myocardial infarction, eccentric hypertrophy, and the concentric hypertrophy, is demonstrated.

This chapter gives an overview of the present study. After a brief motivation part, the basic concepts about the cardiovascular system are explained. The mechanical and electrical events taking place during the contraction of the heart are elucidated and the previous studies on the topic are addressed. Pressure-volume curve, one of the most commonly used diagnostic tools for the detection of several cardiac disorders, is also introduced and explained in detail.

1.1 Motivation

Recent improvements in computer science and also the experimental techniques in biology have increased the number of studies on the modeling of physiological systems, providing a way to explain the physiological processes in the mathematical setting. Lately, as the research on computational modeling of these systems has increased, more realistic models have been developed to simulate the complex processes within the human body, necessitating a sound knowledge of advanced mathematics and biology.

Computational modeling of the cardiovascular system is one of the popular research areas, on which extensive studies have been conducted over several decades. The motivation behind the modeling is to understand the underlying working principles of the cardiovascular system both in the healthy and dysfunctional cases. This will allow the researchers to come up with new diagnostic and therapeutic techniques in collaboration with medical doctors.

Among many other physiological systems, one of the reasons for the cardiovascular system to become a popular research topic is the high rate of deaths and morbidity stemming from the cardiovascular diseases. According to the World Health Organization (WHO) statistics, cardiovascular diseases are the leading cause of death when compared to other disease-related mortalities [7]. Almost 17.3 million people died from cardiac-related problems in 2008 [8]. In the United States alone, cardiovascular diseases cause the death of more than 600,000 people annually, 25% of total deaths [2]. The situation in European countries is not much different. Cardiovascular diseases are still the number one killer, causing the death of 4 million people in Europe and 1.9 million people in the European Union annually, constituting 47% and 40% of total deaths, respectively [1]. When the number of deaths in different countries is considered according to their level of income, it is seen that 80% of the deaths from cardiovascular diseases is observed in the developing countries [7]. Unfortunately, the number of annual deaths from the heart disease and stroke is expected to increase to 23.3 million by 2030 [59].

The cardiovascular disease is not only the cause of loss of lives, but it also leads to a huge amount of financial cost. In the U.S., the total cost of heart diseases is about \$273 billion [40] while it is \$196 billion for the European Union a year [1]. As it is expected that the number of people suffering from cardiovascular diseases will increase, it is certain that the medical cost will also be scaled accordingly. According to the American Health Association report, the total direct medical costs will be three times of what it is today, in the next 20 years [40].

Several factors can trigger a cardiac disorder. These may include high blood pressure and cholesterol, smoking, obesity, physical inactivity, unhealthy diet,

and genetics. However, cardiovascular diseases are generally preventable. It is possible to reduce the risk factors to decrease the effects of the cardiac diseases. At that point, early diagnosis and advanced treatment procedures increase the probability to save the patient's life and increase the life quality.

There have been significant advances in computational cardiology recently to improve the existing medical techniques. It is expected that the mechanical changes within the diseased heart can be better assessed with the mathematical models developed. Together with these models, developments in data acquisition techniques, especially the cardiac imaging, provide the researchers with patient-specific heart models [81]. Individualization of the models offers more accurate diagnostic and therapeutic options in a shorter time. To diagnose the cardiac disease, the commonly used clinical tools are the electrocardiograms and pressure-volume curves, on which several diseases cause certain changes. Therefore, electrical and mechanical disorders in the heart can be clearly observed in these two clinical measurements. However, the existing invasive and non-invasive methods are still not enough to measure some of the biological quantities that directly reflect cardiac disorders [77]. At this stage, cardiac modeling, especially the patient-specific models, gain importance to design and develop new therapeutic methods and also to test the new treatment options.

1.2 Anatomy of the Human Heart

The heart, a muscular organ behind the sternum between the lungs, can be considered to be the center of the cardiovascular system. The heart is composed of a network of blood vessels. It functions to pump blood through a coordinated contraction of both the upper and lower chambers for the purpose of keeping the amount of life-sustaining liquids such as hormones, electrolytes etc. at a physiologically appropriate level. It provides the circulation of the blood throughout the body, thereby supplying the organs and the peripheral tissue with oxygen and nutrients, vital to maintain the metabolic functions.

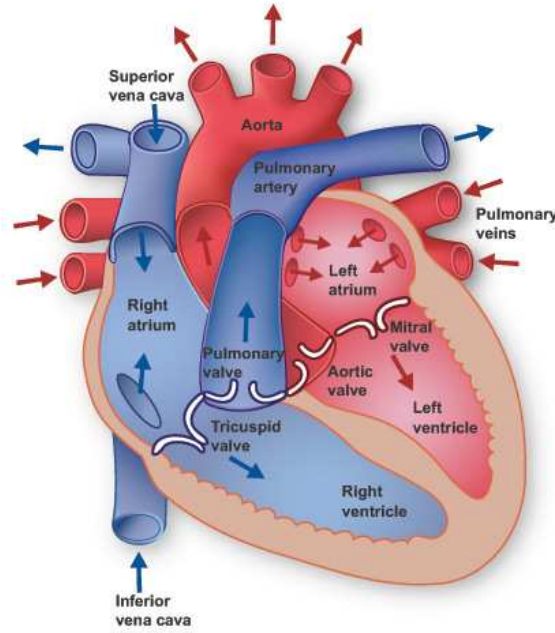


Figure 1.1: The anatomy of the human heart [5].

In Figure 1.1, the anatomy of the human heart is depicted. The heart consists of four chambers; right atrium, left atrium, right ventricle, and left ventricle. The right and left atria, upper chambers of the heart, are divided by the interatrial septum and have the role of a reservoir; that is, to collect blood from the body. The right atrium receives deoxygenated blood from the body and the heart muscle, then, directs it to the right ventricle. On the other hand, the left atrium, having a thicker wall compared to the right atrium, collects oxygenated blood through the pulmonary veins from the lungs and directs it to the left ventricle. Blood flow from the atria to the ventricles is maintained by the atrioventricular valves, namely the tricuspid valve (right atrioventricular valve) and bicuspid valve (mitral or left atrioventricular valve). The lower chambers of the heart, right and left ventricles, are divided by the interventricular septum. The right ventricle carries blood to the lungs through the pulmonary arteries while the left ventricle, having a thicker wall, pumps the blood to the body through the aorta, the main artery in the body. Unidirectional blood flow through the ventricles to the lungs and to the body is provided by the semilunar valves, namely the pulmonary and aortic valves, respectively.

1.3 Electrophysiology of the Heart

The heart achieves its primary function, pumping, as the myocardial fibers contract and relax rhythmically. The coordination between the contraction of the ventricles is maintained by the electrical system within the heart, generating the impulses and conducting them throughout the heart [78]. Similar to the other muscle cells in the body, the cardiac myocytes have the property of getting excited and conducting the electrical signals. At the cellular level, the contraction of the cardiac cells is triggered by a change in the transmembrane potential giving rise to the mechanical contraction of the myocytes. The generation of the action potential is generally achieved as the cardiac cells are excited by the opening and closing of the ion channels, changing the membrane potential through the ion fluxes.

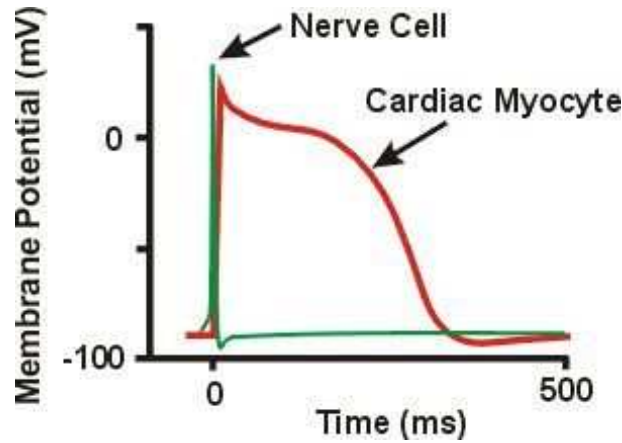


Figure 1.2: Comparison of action potentials within a nerve cell and a cardiac myocyte [52]. The difference in their action potential durations and the shapes is clearly indicated.

When compared to action potentials generated by the neurons, cardiac action potentials have significant differences. As shown in Figure 1.2, while the duration of the action potential of a nerve cell is only about 1 millisecond (ms), the action potentials generated at the ventricular myocytes have different phases that are significantly separated by each other and last for about 200 to 400 ms [52]. Moreover, the type of the ionic currents generating the depolarizing waves for

the neural and ventricular muscle cells also differs.

Although there are several types of ions within the cell membrane, Cl^- , Ca^{2+} , and K^+ are the primary ions determining the transmembrane potential in cardiac cells [52]. The intracellular and extracellular concentrations of the ions controlling the membrane potential can be calculated by the Nernst and Goldman-Hodgkin-Katz equations. When the effect of only one ion on the equilibrium potential is considered, the potential is calculated by the Nernst equation, given as

$$\phi_m = \frac{RT}{zF} \ln \frac{Pc_e}{Pc_i}, \quad (1.1)$$

where ϕ_m is the cell membrane potential in *Volts*, R is the universal gas constant $8.315J/(molK)$, T the absolute temperature in *Kelvin*, z is the valence of the particular ion, F is the Faraday constant, P is the permeability of the ion, and c_e and c_i are the extracellular and intracellular ionic activities, respectively. For the detailed derivation of the Nernst equation, the reader is referred to [26]. However, it is not accurate to calculate the membrane potential considering the activity of only one ion. Better estimates for the membrane potential can be obtained by using the Goldman-Hodgkin-Katz equation

$$\phi_m = \frac{RT}{zF} \ln \left(P_K \frac{c_{K_e}}{c_{K_i}} + P_{Na} \frac{c_{Na_e}}{c_{Na_i}} + P_{Cl} \frac{c_{Cl_e}}{c_{Cl_i}} \right). \quad (1.2)$$

In the above equation, the effects of primary ionic currents within the cell membrane are taken into account to calculate the resting membrane potential. Looking at both the Nernst equation (1.1) and the Goldman-Hodgkin-Katz equation (1.2), it can be said that the intracellular and extracellular ionic concentrations and the permeability of the cell membrane to the ions are the main factors determining the membrane potential.

Action potentials within the heart are generated by the electrical waves as the intracellular and extracellular ionic concentrations change within the cell membrane, triggering the movement of the ions. However, not every electrical wave generates the action potentials. In order to have the cell membrane depolarized,

the depolarization threshold should be exceeded. Otherwise, there is only local depolarizations within the cell [45].

The shape of the action potentials generated through the heart changes as the function of the cardiac cells differs from each other. It is possible to classify the action potentials in the heart into two general groups: pacemaker and non-pacemaker action potentials. As it is explained in the next section, the electrical conduction system in the heart has several components taking place in the generation and the propagation of the action potentials. While there are nodal cells that show pacemaker activity, atrial and ventricular muscle cells have the only property to get excited when stimulated by an electrical impulse. The pacemaker cells control the rate of heartbeat by generating action potentials autonomously, however, non-pacemaker cells need to be excited by the adjacent cells. All these differences in the electrophysiological behavior result in significant changes in the action potentials. For further information on the action potential of cardiac cell types, we refer to [46].

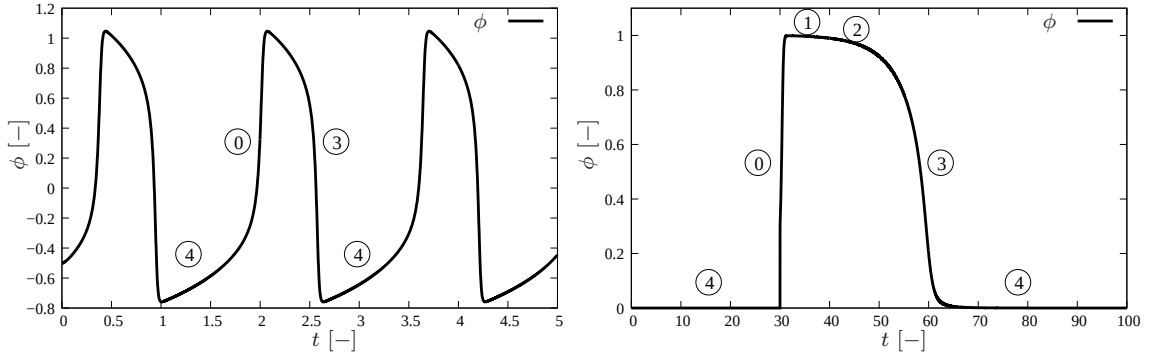


Figure 1.3: Action potentials in the pacemaker (left) and nonpacemaker (right) cells.

Pacemaker Action Potentials: Pacemaker cells in the heart have the property of automatically generating action potentials that can be divided into three phases, Figure 1.3 (left). When the membrane is depolarized to the threshold in Phase 4, called as pacemaker potential, the membrane potential starts to increase as the calcium ions flow into the cell (Phase 0). When the voltage-gated potassium channels open, the membrane potential decreases, that is the repolarization (Phase 3). During Phase 3, the resting potential is not stable, allowing

the cell membrane to get excited again. The ionic currents, primarily the slow sodium currents, cause Phase 3 to be unstable.

Non-pacemaker Action Potentials: Non-pacemaker action potentials are observed in the atrial and ventricular muscle cells and Purkinje fibers. These are also named as fast response action potentials due to a sharp increase in the depolarization phase, see Figure 1.3 (right). These cardiac cells are depolarized when stimulated by adjacent cells as the sodium ions enter the cell membrane [20]. Depolarization of one cell is transferred to the adjacent cells through gap junctions, thereby making the electrical impulses to propagate [76]. The inward sodium flux into the cell membrane increases the transmembrane potential by the positive charges carried. The cardiac cell is said to be depolarized when the depolarization threshold is exceeded, that is called Phase 0 in Figure 1.3 (right). Next, K^+ channels open, starting the repolarization of the cell membrane that corresponds to Phase 1. Meanwhile, opening of Ca^{2+} channels results in a plateau phase, called Phase 2. The Ca^{2+} channels start to close while the potassium current increases, resulting in a decrease in the membrane potential. This initiates the repolarization phase (Phase 3). Then, the membrane stays at its resting potential that is about the K^+ equilibrium potential (Phase 4).

Development of the mathematical models for the action potential in the cardiac cells is still an active research area today. Although there have been numerous studies on that topic since 1960s, there are still some difficulties involved in determining the behavior of the cardiac cells. The biggest problem is the variety of the cardiac cell types and ionic channels, increasing the complexity to model the electrophysiology of the cell [46]. The first quantitative formulation describing the electrophysiological behavior at the cellular level was proposed by Alan Hodgkin and Andrew Huxley in 1950s [41], explaining how the electrical signals are propagated in a squid giant axon. In their experiments, voltage clamp technique is utilized to formulate the change in the ionic currents as mathematical models. They defined the evolution of the transmembrane voltage, that is the difference between extracellular and intracellular potentials in the monodomain

setting, using the circuit model given in Figure 1.4 as

$$C_m \frac{d\phi}{dt} + I_{ion} = I_{app} \quad (1.3)$$

where C_m , I_{ion} , and I_{app} represent the membrane capacity, the summation of the transmembrane currents, and the externally applied current, respectively.

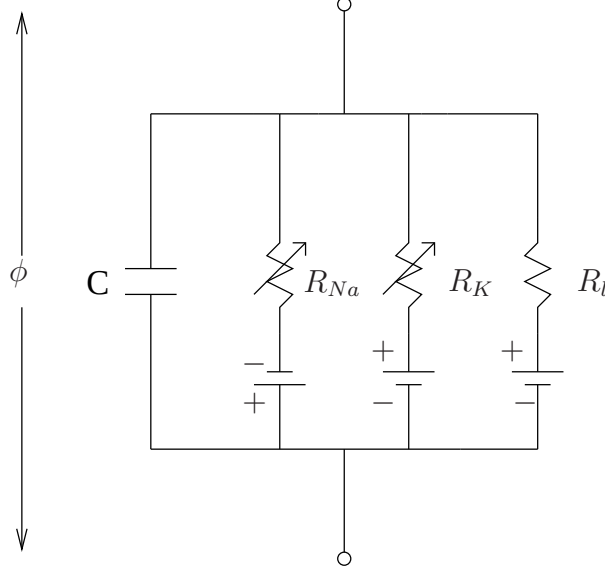


Figure 1.4: Electric circuit diagram for the Hodgkin-Huxley model.

Within the cell membrane, the transmembrane potential can be represented as the summation of the primary ionic currents

$$I_{ion} = I_{Na} + I_K + I_l \quad (1.4)$$

where the effects of the sodium current I_{Na} , potassium current I_K , and leakage current I_l are considered. These ionic currents depend on the conductances, transmembrane potential, and the equilibrium voltages through the equations

$$\begin{aligned} I_{Na} &= g_{Na}(\phi - \phi_{Na}), \\ I_K &= g_K(\phi - \phi_K), \\ I_l &= g_l(\phi - \phi_l), \end{aligned} \quad (1.5)$$

where g_{Na} , g_K , and g_l stand for the ionic conductances and ϕ_{Na} , ϕ_K , and ϕ_l are the equilibrium potentials for the corresponding ions. The ionic currents, $i_{ion} = g_{ion}(\phi - \phi_{ion})$, depend on the conductance of the membrane to the ion

g_{ion} and electromotive force that drives the ion across the membrane, that is $(\phi - \phi_{ion})$, difference between the actual transmembrane potential and the equilibrium potential for the ion [45].

The sodium and potassium conductances depend on both time and voltage. The Hodgkin Huxley model assumes that there are three m gates and one h gate in a Na^+ channel. These gates may change their states during depolarization and repolarization of the cell membrane. It is possible to describe the sodium conductance as $g_{Na} = \bar{g}_{Na}m^3h$, where $\bar{g}_{Na}$ is the maximum sodium conductance and m and h are the sodium activation and inactivation variables. In this equation, m^3h represents the fraction of open Na^+ channels knowing that the states of the gates are independent of each other. The potassium channels, however, assumed to have four n gates that are open during the potassium flow. Similarly, the potassium conductance can be formulated as $g_K = \bar{g}_Kn^4$ where $\bar{g}_K$ represents the maximum potassium conductance and n is the potassium activation variable while n^4 is the open K^+ channel fraction [46]. The evolution of the variables m, h , and n is governed by the following first-order ordinary differential equations

$$\begin{aligned}\frac{dm}{dt} &= \alpha_m(\phi)(1 - m) - \beta_m(\phi)m, \\ \frac{dh}{dt} &= \alpha_h(\phi)(1 - h) - \beta_h(\phi)h, \\ \frac{dn}{dt} &= \alpha_n(\phi)(1 - n) - \beta_n(\phi)n.\end{aligned}\tag{1.6}$$

The evolutions of the transmembrane potential and the gating variables are depicted in Figure 1.5 (left) and Figure 1.5 (right), respectively.

FitzHugh-Nagumo Model: The reduced form of the Hodgkin Huxley model to a two-parameter system is called the FitzHugh-Nagumo model [29, 30], that approximates the electrophysiological behavior of the cell membrane in terms of one fast and one slow variable. As the evolutions of the action potential (Figure 1.5, (left)) and gating variables (Figure 1.5, (right)) are observed, it is clear that the action potential follows the same pattern with the sodium activation m . Moreover, the sum of the potassium activation n and the sodium inactivation h is almost constant, that is $n + h \approx 0.8$ at any time during the action potential. [46]. The main advantage of decreasing the number of variables is to better

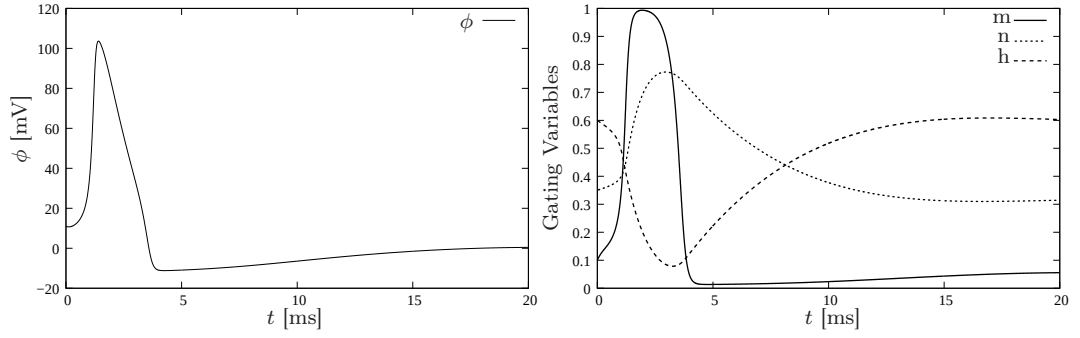


Figure 1.5: Evolution of the action potential (left) and the gating variables, m , n , and h (right) calculated using the four-variable Hodgkin-Huxley model.

understand the behavior of the model by analyzing it on the phase plane. More detailed information on the Fitzhugh-Nagumo equations, used in this study, is introduced in the next chapter.

Although Hodgkin-Huxley and Fitzhugh-Nagumo equations were initially developed for the nerve cells [30, 63], the electrophysiological processes within the cardiac cells can also be expressed based on these models. In the literature, there are also studies on making the action potential duration longer [17, 32] to mimic the behavior of the cardiac cells. The cardiac action potential was first modeled for the Purkinje fibers [69] by modifying the Hodgkin-Huxley equations. Although the model, developed by Noble, was successful at simulating the Purkinje fiber action potentials, the theory behind the modeling approach does not reflect the real physiological processes within the Purkinje fiber cells. The main reason is that the measurement of ionic currents within the cardiac cell membrane was achieved later [25], in 1964. This model was further developed by McAllister, Noble, and Tsien in 1951, see [60]. Having the data on the ionic currents obtained from the voltage-clamp technique, the action potentials for the ventricular cells were modeled [14], that was further improved by Luo and Rudy [58]. Later, the action potential models for the pacemaker cells, e.g., the sinoatrial node, were developed. The one that is widely used was proposed by Yanagihara et al. in 1980 [91]. There are also studies on modeling the electrophysiology of the atrial cells [23]. The reader is referred to [88] for modeling the electrical behavior of different cardiac cells.

1.4 Electrical Conduction System within the Heart

The electrical activity of the heart is automatically started at the Sinoatrial (SA) Node, the natural pacemaker of the heart located at the wall of the right atrium, see Figure 1.6. The heart rate is determined by the number of pulses generated by the SA node per minute. As the right atrium is filled with blood by the vena cavae, the SA Node fires the impulses that are conducted throughout the atria at a velocity of 0.5 m/s causing the atria to contract. Squeezing the atria gives rise to the opening of the atrioventricular valves and pushes the blood into the ventricles. Then, the signal moves thorough the atrioventricular (AV) Node, a specialized tissue at the interatrial septum. The speed of the impulses decreases here approximately to 0.05 m/s to allow the atria to depolarize, contract, and empty the blood into the ventricles completely. This property is of vital importance for the heart to function properly. If the delivery of the electrical signal is not delayed at the AV Node, ventricles and the atria may contract simultaneously, causing the blood to flow backwards.

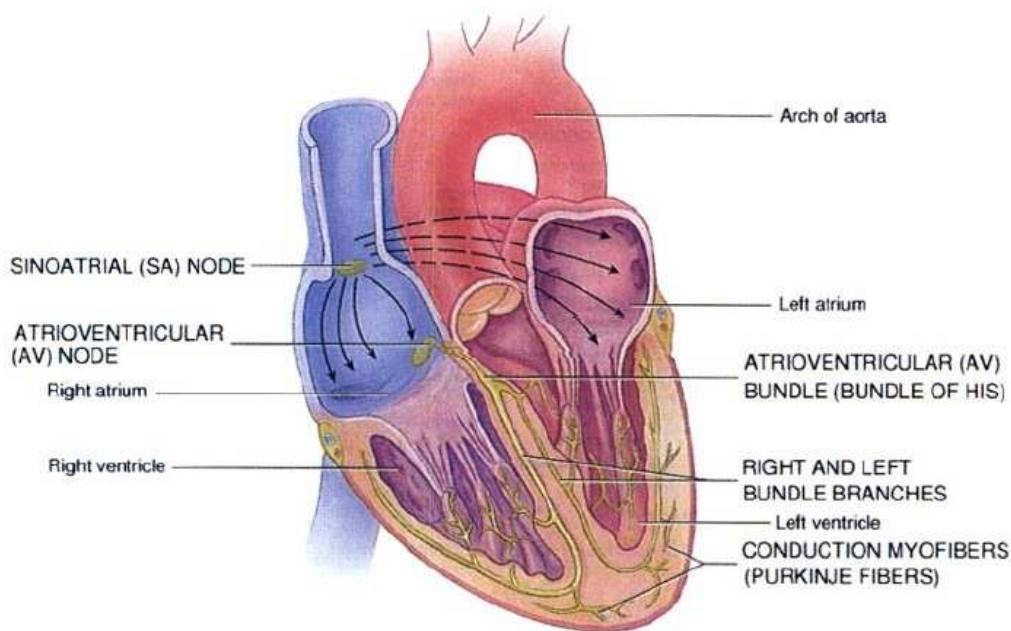


Figure 1.6: Electrical conduction system within the heart [70].

Then, the signal is transmitted through the His Bundle that is divided into two branches on the interventricular septum. On these branches, the speed of the impulses is almost 2 m/s. The right and left bundle branches split into a network of Purkinje fibers on which the impulses reach the highest velocity, about 4 m/s. The cell-to-cell conduction is completed as the impulses arrive at the ventricular myocytes, the final point where the Purkinje fibers are connected to. The contraction of the ventricles pushes the blood to the lungs and the body as the pulmonary and aortic valves open, respectively. As the depolarization of the ventricles is completed, they relax to fill with blood. These phases are repeated as the SA node fires, a process named as the cardiac cycle. The above-mentioned components of the electrical conduction system are indicated in Figure 1.6.

1.5 Cardiac Cycle

A cardiac cycle is composed of two main phases, systole and diastole in which the cardiac muscles contract and relax, respectively, see Figure 1.7. These phases are further subdivided into two more phases that are isovolumic contraction and ejection phases for systole and filling and isovolumic relaxation phases for diastole.

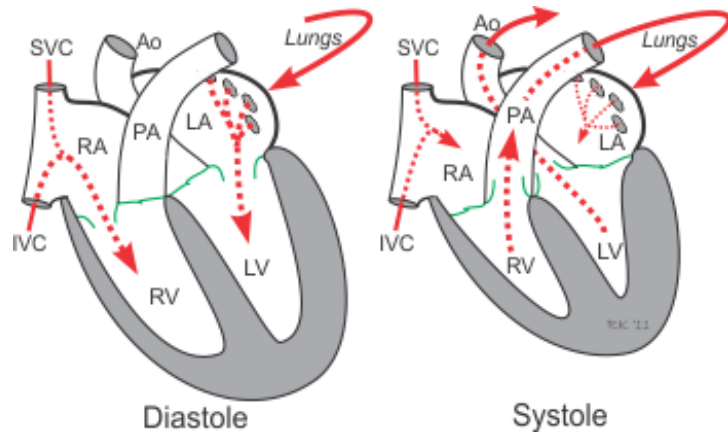


Figure 1.7: The main phases of the cardiac cycle, diastolic and systolic phases are shown. Direction of the blood flow for these two phases are indicated with the red arrows [52].

In Figure 1.8, the change in left ventricular pressure (LVP) and left ventricular volume (LVV) are depicted during a cardiac cycle. The cardiac cycle is assumed to start at the end of Phase a, where the isovolumic contraction begins. Starting from that point, the cardiomyocytes are depolarized by the electrical impulses propagating through the heart and the left ventricular pressure increases as the contraction continues. In this phase (Phase b), both the mitral and aortic valves are closed because the left ventricular pressure lies between the left atrial pressure and the aortic pressure. Therefore, there is no blood flow through these valves and the ventricular volume is kept constant.

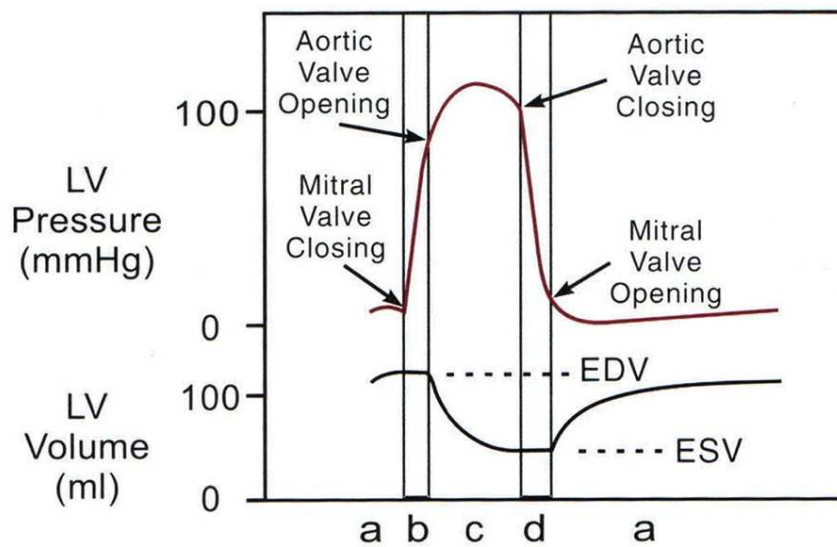


Figure 1.8: The change of left ventricular (lv) pressure (top) and lv volume (bottom) during a complete cardiac cycle indicating the phases of a complete heartbeat. The isovolumic contraction, ejection, isovolumic relaxation and filling phases are represented with the letters, b,c,d, and a, respectively. End-diastolic volume (EDV) and end-systolic volume (ESV) are also indicated [52].

As the ventricular pressure reaches the aortic pressure, the aortic valve opens with an accompanying decrease in the ventricular volume as the blood flows into the aorta and the ejection phase begins (Phase c). During this phase, the left ventricular volume decreases until it reaches the left ventricular end-systolic volume, where the ventricular volume is minimum. Next, the isovolumic relaxation phase (Phase d) begins as the ventricular pressure falls below the

aortic pressure. In this phase, the ventricular volume does not change because the mitral and aortic valves are closed. There is a decrease in ventricular pressure until it is lower than the pressure in the left atrium which causes mitral valve to open. Then, the filling phase (Phase a) begins and the left ventricular volume increases as there is blood flow from the left atrium into the left ventricle.

1.6 Pressure Volume Curves

As explained in the previous section, with each cardiac cycle, the ventricular pressure changes depending on a change in the ventricular volume, varying the mechanical properties of the ventricular muscles. In practice, it is more meaningful to observe the mechanical changes within the ventricles in the pressure-volume curves. Cardiac pressure-volume curves help the interpreter to assess the mechanical activities within the heart under normal and pathological conditions. These mechanical changes within the chambers initiate the blood movement through the valves. Real pressure-volume curves, used to assess the ventricular functionality, are obtained by plotting the ventricular pressure with respect to the ventricular volume at any time during a cardiac cycle using a conductance catheter. It is a commonly used diagnostic tool for the detection of several cardiac disorders.

In Figure 1.9, the real pressure-length loops are introduced [57]. These loops are obtained during a control period for an acute volume overload. This figure clearly demonstrates the relation between the left-ventricular pressure and anterior segment length whose variation can be related with the change in ventricular volume.

Pressure-volume curves clearly indicate the phases of a cardiac cycle that are explained above. Transition between these phases are determined by the pressure gradients within the heart that cause the opening and closing of the heart valves. The pressure-volume curves start with the end-diastolic pressure-volume relationship and continue with the isovolumic contraction phase in a counterclockwise direction.

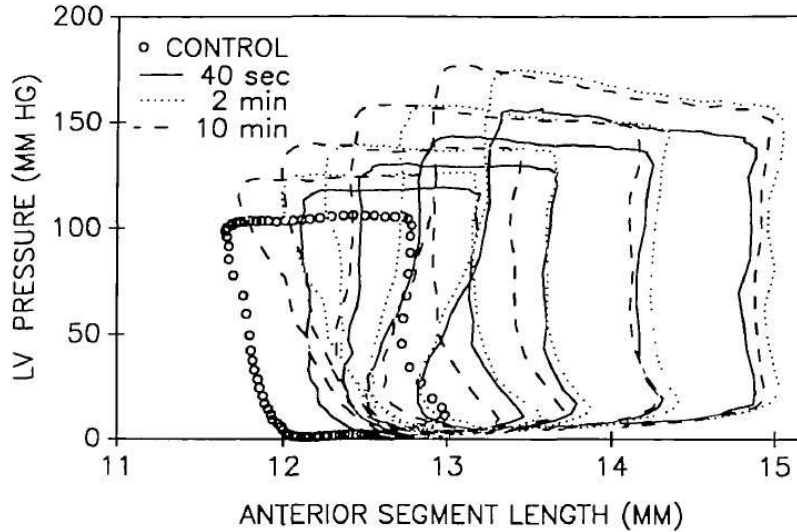


Figure 1.9: Pressure-length loops for a dog heart [57]. The one represented with the open circles stands for the control period. The others represent the pressure-length relation after 40 seconds, 2 minutes and 10 minutes under an acute volume load, resulting in an increase in ventricular pressure.

In Figure 1.10, Point A is the starting point and the ventricular pressure increases while the volume is kept constant in the interval A-B (isovolumic contraction). Then, the ejection phase (B-C) starts with a decrease in the ventricular volume until the end-systolic pressure-volume relationship is reached at Point C. At that point, the ventricular volume is minimum. The interval C-D corresponds to the isovolumic relaxation phase where the pressure decreases without a change in ventricular volume. Point D is where the filling begins as the blood moves into the ventricles until Point A, where the ventricular volume is maximum. The pressure-volume relationship obtained for a cycle is repeated with each heartbeat. Although the cardiac phases are explained for the left ventricle, the right ventricular mechanics is similar. Compared to the left ventricle, the right ventricle has major differences both in its anatomy and functions. The left ventricle has thicker walls because it pumps blood through the body, necessitating higher pressures compared to pulmonary circulation. For the right and left ventricles, cardiac phases order are similar to each other although the pressure-volume curve of the right ventricle has lower values than that of the left ventricle.

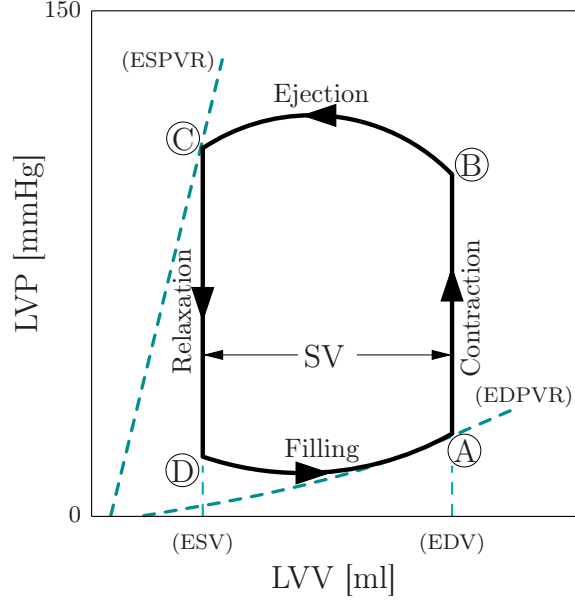


Figure 1.10: Left ventricular pressure-volume loop is shown with the solid line. The four main cardiac phases, isovolumic contraction, ejection, isovolumic relaxation and filling, are indicated on the figure, following each other in counter-clockwise direction. The clinical metrics, end-systolic pressure-volume relationship (ESPVR) and the end-diastolic pressure-volume relationship (EDPVR) are shown by dashed curves. Stroke volume (SV) is defined as the difference between the end-diastolic volume (EDV) and the end-systolic volume (ESV).

Pressure-volume curves not only reveal the instantaneous pressure-volume relation within the ventricle, but it is also possible to retrieve several hemodynamic parameters that have physiological importance such as stroke volume, ejection fraction, end-diastolic and end-systolic pressure volume relationships. These parameters are of clinical importance because they reveal the cardiac performance allowing the medician to diagnose several pathologies such as ventricular wall thickening, dilated cardiomyopathy, and myocardial infarction.

1.7 Aim of the Thesis

The aim of this thesis is to model the electromechanical behavior of the heart incorporating dysfunctional cases using a generic three-dimensional heart model. In this contribution, pressure-volume curves are simulated for different pathological cases that are most commonly observed among the patients. These cases

include the myocardial infarction, concentric hypertrophy and eccentric hypertrophy, all of which have several damages on both the electrical conduction and mechanical system of the heart. Most of the time, these diseases may result in the loss the patient's life if not diagnosed timely.

Pressure-volume curves, one of the non-invasive clinical tools commonly used for the diagnostic purposes, provide the interpreter with the cardiac performance by indicating some clinical metrics such as stroke volume, end-diastolic and end-systolic pressure-volume relationships. In this thesis, the changes observed in these metrics for the pathological cases are compared with the clinical findings to demonstrate the potential of our model in simulating diseases.

1.8 Scope and Outline

In **Chapter 1**, we define the basic terms used in the thesis and introduced the previous research carried on the computational cardiology. In **Chapter 2**, the three-dimensional continuous formulation of the coupled initial boundary-value problem of cardiac electromechanics is introduced. For this purpose, two fundamental differential equations, namely the balance of linear momentum and a reaction-diffusion type equation of excitation are introduced. Before going into details of the formulation, non-linear continuum mechanics is briefly explained to describe the deformation that the heart undergoes. Additionally, the essential and natural boundary conditions are given to complete the mathematical formulation of the problem. Then, the equations describing the constitutive relations are explained in detail. **Chapter 3** is on the finite element formulation of the equations described in Chapter 2. After deriving the weak forms of the governing equations, they are linearized and discretized both in time and space. **Chapter 4** is devoted to the mathematical models used to simulate the pressure-volume curves in this study. Two models, the Signorini model and the three-element Windkessel model, are explained in detail. In **Chapter 5**, the numerical examples for the simulation of the pressure-volume curves are introduced. After obtaining the pressure-volume curves for the healthy heart, the cardiac dysfunctions are modelled. In this contribution, three cases; the myocardial infarction,

concentric hypertrophy, and eccentric hypertrophy are investigated. The simulation results are compared with the clinical data and it is shown that our model can simulate the specific properties of the dysfunctions in the pressure-volume curves.

CHAPTER 2

CONTINUOUS FORMULATION OF THE COUPLED CARDIAC ELECTROMECHANICS

The aim of this chapter is to introduce the governing differential equations of the coupled boundary-value problem of cardiac electromechanics, referring to the model developed by Göktepe and Kuhl [36]. After introducing some basic concepts of continuum mechanics, strong forms of the field equations are introduced with the corresponding boundary conditions. The constitutive model is introduced to complete the mathematical formulation.

2.1 Kinematics

Assuming the heart to be a material body composed of infinitely many points $\mathbf{X}$ in the reference configuration $\mathcal{B} \subset \mathbb{R}^3$ at time $t \in \mathbb{R}_+$, the deformed configuration of that point can be represented by $\mathbf{x}$ in the current domain $\mathcal{S} \subset \mathbb{R}^3$. As indicated in Figure 2.1, the motion of the material body in the Euclidean space is described by the non-linear deformation map $\mathbf{x} = \boldsymbol{\varphi}_t(\mathbf{x}) : \mathcal{B} \rightarrow \mathcal{S}$, that relates the material points $\mathbf{X} \in \mathcal{B}$ with the deformed ones $\mathbf{x} \in \mathcal{S}$ in the current domain at time $t \in \mathbb{R}_+$. The deformation gradient, $\mathbf{F} := \text{Grad } \boldsymbol{\varphi}_t(\mathbf{X}) : \mathcal{B} \rightarrow \mathcal{S}$ measures the large deformations that the body is subjected to, as it maps the tangential reference vectors onto the spatial ones in the current configuration. The operator $\text{Grad}[\bullet]$ is defined as the gradient with respect to material coordinates $\mathbf{X}$. Moreover, the reference volume elements are mapped onto their spatial counterparts through the determinant of the deformation gradient, that

is $J := \det(\mathbf{F}) > 0$.

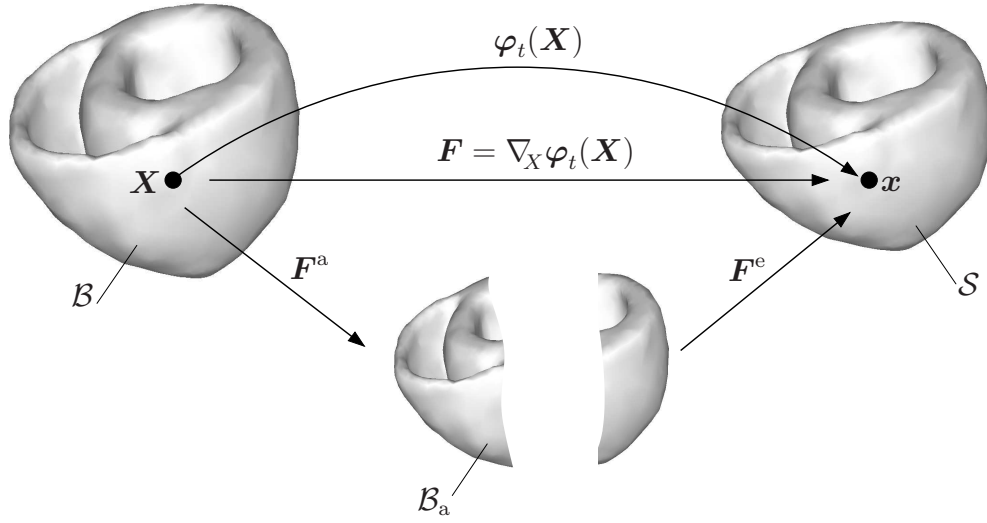


Figure 2.1: Motion of an excitable and deformable solid body in the Euclidean space $\mathbb{R}^3$ through the non-linear deformation map $\varphi_t(\mathbf{X})$ at time t . The deformation gradient $\mathbf{F} = \text{Grad } \varphi_t(\mathbf{X})$ describes the tangent map between the respective tangent spaces. The deformation gradient $\mathbf{F}$ is multiplicatively decomposed into the passive part $\mathbf{F}^e$ and the active part $\mathbf{F}^a$ with $\mathcal{B}_a$ denoting the fictitious, incompatible intermediate vector space.

Referring to the research carried by Cherubini et al. [19], the multiplicative decomposition of the deformation gradient is utilized to model the electro-mechanical behavior of the cardiac myocytes,

$$\mathbf{F} = \mathbf{F}^e \mathbf{F}^a \quad (2.1)$$

where, $\mathbf{F}^e$ and $\mathbf{F}^a$ represent the passive and active parts of the deformation gradient $\mathbf{F}$. In addition to the total deformation gradient, the use of the active part of the deformation gradient $\mathbf{F}^a$ makes it possible to account for the active contraction. Through second-order structural tensors $\mathbf{A}_m, \mathbf{A}_n$, and $\mathbf{A}_k$, the active part of the deformation gradient reflects the anisotropic architecture of the cardiac tissue. Therefore, it is appropriate to write the relation

$$\mathbf{F}^a = \hat{\mathbf{F}}^a(\Phi, \mathbf{A}_m, \mathbf{A}_n, \mathbf{A}_k). \quad (2.2)$$

The passive part of the deformation gradient $\mathbf{F}^e$ is obtained from the equality (2.1) as $\mathbf{F}^e = \mathbf{F} \mathbf{F}^{a-1}$. As it is indicated in Figure 2.1, the decomposition of the

deformation gradient introduces a new fictitious configuration, $\mathcal{B}_a$, other than $\mathcal{B}$ and $\mathcal{S}$. It should be noted that contrary to the definition of $\mathbf{F}$, the active and passive parts of the deformation gradient cannot be defined as the gradient of any deformation map.

For an orthotropic material, active part of the deformation gradient can be formulated as

$$\mathbf{F}^a = \mathbf{1} + (\lambda_m^a - 1) \mathbf{A}_m + (\lambda_n^a - 1) \mathbf{A}_n + (\lambda_k^a - 1) \mathbf{A}_k \quad (2.3)$$

where λ_m^a , λ_n^a , and λ_k^a are the functions of the action potential and represent the active stretches in the preferred directions.

2.2 Governing Differential Equations of Cardiac Electromechanics

The coupling due to excitation-induced contraction and the deformation-induced current generation can be formulated by two primary variables that are the placement $\boldsymbol{\varphi}(\mathbf{X}, t)$ defined in the previous section as the deformation map, and the action potential $\Phi(\mathbf{X}, t)$. In the monodomain model of cardiac electrophysiology, the action potential is the same as the transmembrane potential, the difference between the extracellular and intracellular membrane potentials. The evolution of the mechanical field is governed by the conservation of linear momentum equation. Its local spatial form describing the quasi-static stress equilibrium is written as

$$J \operatorname{div}[J^{-1} \hat{\boldsymbol{\tau}}] + \mathbf{B} = \mathbf{0} \quad \text{in } \mathcal{B} \quad (2.4)$$

where $\hat{\boldsymbol{\tau}}$ is a second order tensor field representing the Eulerian Kirchhoff stress tensor and $\mathbf{B}$ is the body force per unit reference volume. The operator $\operatorname{div}[\bullet]$ is defined as the divergence with respect to spatial coordinates $\mathbf{x}$. In order to complete the definition of the mechanical problem, the essential and natural boundary conditions,

$$\boldsymbol{\varphi} = \bar{\boldsymbol{\varphi}} \quad \text{on } \partial\mathcal{S}_\varphi \quad \text{and} \quad \mathbf{t} = \bar{\mathbf{t}} \quad \text{on } \partial\mathcal{S}_t, \quad (2.5)$$

that are geometrically shown in Figure 2.2 (left) are introduced.

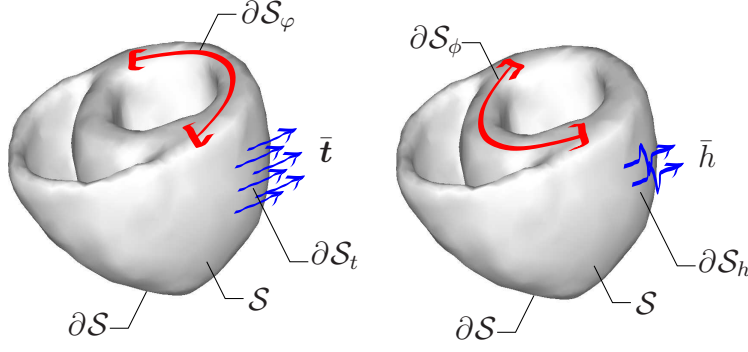


Figure 2.2: Illustration of the mechanical (left) and electrophysiological (right) natural and essential boundary conditions.

The vector, $\bar{\mathbf{t}}$ stands for the spatial surface traction vector and is defined through the Cauchy stress theorem as $\bar{\mathbf{t}} := J^{-1} \boldsymbol{\tau} \cdot \mathbf{n}$ where $\mathbf{n}$ is the unit surface normal. Here, the Eulerian surface domain is represented by $\partial\mathcal{S}$ composed of the surface subdomains $\partial\mathcal{S}_\varphi$ and $\partial\mathcal{S}_t$ satisfying the criteria $\partial\mathcal{S} = \partial\mathcal{S}_\varphi \cup \partial\mathcal{S}_t$ and $\partial\mathcal{S}_\varphi \cap \partial\mathcal{S}_t = \emptyset$. The governing differential equation used for the evolution of the action potential is

$$\dot{\Phi} - J \operatorname{div}[J^{-1} \hat{\mathbf{q}}] - \hat{I}^\phi = 0 \quad \text{in } \mathcal{B} \quad (2.6)$$

where $\operatorname{div}[J^{-1} \hat{\mathbf{q}}]$ and $\hat{I}^\phi$ represent the diffusion term and the nonlinear current source, respectively. The material time derivative of the action potential field is introduced by the notation $\dot{\Phi}$. The definition of the electrophysiological problem is completed by the boundary conditions and the initial condition. The essential and natural boundary conditions are

$$\Phi = \bar{\Phi} \quad \text{on } \partial\mathcal{S}_\phi \quad \text{and} \quad h = \bar{h} \quad \text{on } \partial\mathcal{S}_h \quad (2.7)$$

defined on the surface domain $\partial\mathcal{S}$ that includes $\partial\mathcal{S}_\phi$ and $\partial\mathcal{S}_h$, satisfying $\partial\mathcal{S}_\phi \cap \partial\mathcal{S}_h = \emptyset$ and $\partial\mathcal{S} = \partial\mathcal{S}_\phi \cup \partial\mathcal{S}_h$. In (2.7), $\bar{h}$ is the electrical surface flux term that depends on the spatial flux vector $\hat{\mathbf{q}}$ by the relation $\bar{h} := J^{-1} \hat{\mathbf{q}} \cdot \mathbf{n}$ where $\mathbf{n}$ is the spatial surface normal. Also, the initial boundary condition is introduced at $t = t_0$ as

$$\Phi_0(\mathbf{X}) = \Phi(\mathbf{X}, t_0) \quad \text{in } \mathcal{B}. \quad (2.8)$$

2.3 Constitutive Equations

Having defined the governing differential equations and boundary conditions necessary to complete the definition of the strong forms of the equations, the solution of this system of equations necessitates the specification of the constitutive model, from which the electromechanical coupling arises. Moreover, the description of the variables reflecting the material properties should reflect the micro-structure of the cardiac cells and account for both the geometrical and material nonlinearities.

For the mechanical problem, the conservation of linear momentum equation (2.4) depends on the Kirchhoff stress tensor $\hat{\boldsymbol{\tau}}$. Moreover, the potential flux $\hat{q}$ and the current source $\hat{I}^\phi$ that are included in the excitation equation have not been defined yet. In this section, the equations describing these three quantities are explained in detail. After introducing the approach followed in modeling the stress response, the spatial potential flux, and the current source term are elucidated.

2.3.1 Modeling the Stress Response

The two main approaches followed in modeling the stress response of the ventricular myocardium are the active-strain and active-stress based models. In the active-strain based approach, the deformation gradient is multiplicatively decomposed into the active and passive parts. The stress response is derived from a free energy function that is a function of only the passive part of the deformation gradient [19, 64]. However, in the active-stress based models, the stress response of the material is additively divided into passive and active components. Formulation of the passive stress response accounts only for the deformation, while the active part is dependent on the transmembrane potential [65, 71, 66, 47, 68, 36, 56, 28, 27].

In this study, similar to the active-strain models, the deformation gradient is multiplicatively decomposed into the active and passive parts. Different from the existing approaches in the literature, [19, 13], however, the free energy function

is additively split into its active $\hat{\Psi}^a$ and passive parts $\hat{\Psi}^p$, see [37],

$$\Psi = \hat{\Psi}^p(\mathbf{g}; \mathbf{F}) + \hat{\Psi}^a(\mathbf{g}; \mathbf{F}^e). \quad (2.9)$$

Writing the free energy function in a decomposed form (2.9) allows also for the decomposition of the Kirchhoff stress tensor $\hat{\boldsymbol{\tau}}$ as

$$\boldsymbol{\tau} = \hat{\boldsymbol{\tau}}^p(\mathbf{g}; \mathbf{F}) + \hat{\boldsymbol{\tau}}^a(\mathbf{g}; \mathbf{F}^e) \quad (2.10)$$

that is calculated using the Doyle-Ericksen formula $\boldsymbol{\tau} := 2\partial_{\mathbf{g}}\Psi$. The specific forms of the passive and active response are set out in the subsequent sections.

2.3.1.1 Passive Stress Response

When the architecture of the ventricular myocardium is investigated, three distinct planes with varying material properties are observed. As depicted in Figure 2.3, there are three axes that are mutually orthogonal to each other, that are $\mathbf{f}_0$, $\mathbf{s}_0$, and $\mathbf{n}_0$. These are the unit vectors representing the orientation of the muscle fibers, sheet directions, and the one that is normal to both the sheet and fiber directions, respectively. The identification of the three-dimensional structural properties of the myocardium is fundamental to assess both the mechanical and electrophysiological behavior of the cardiac tissue. The contraction and relaxation of the myocytes in the one-dimensional space give rise to the overall pumping and twisting function of the heart. Therefore, it is necessary to define all the constitutive equations describing the material properties of the cardiac cells in terms of this set of orthogonal basis vectors.

For the passive response of the myocardium, the orthotropic hyperelasticity model, proposed by Holzapfel and Ogden [42], is utilized. The following free energy function is used to represent the passive response in terms of the volumetric part $U(J)$ and the orthotropic part $\tilde{\Psi}(I_1, I_{4m}, I_{4n}, I_{4k})$

$$\hat{\Psi}^p(\mathbf{g}; \mathbf{F}) = U(J) + \tilde{\Psi}(I_1, I_{4m}, I_{4n}, I_{4k}) \quad (2.11)$$

where

$$\tilde{\Psi} = \frac{a_1}{2b_1} \exp[b(I_1-3)] + \sum_{i=m,n} \frac{a_i}{2b_i} \{\exp[b_i(I_{4i}-1)^2]-1\} + \frac{a_k}{2b_k} [\exp(b_k I_{4k}^2)-1] \quad (2.12)$$

is a function of the material parameters $a_1, b_1, a_m, b_m, a_n, b_n, a_k, b_k$ and the invariants I_1, I_{4m}, I_{4n} , and I_{4k} given below

$$I_1 := \mathbf{g} : \mathbf{b}, \quad I_{4m} := \mathbf{g} : \mathbf{m}, \quad I_{4n} := \mathbf{g} : \mathbf{n}, \quad I_{4k} := \mathbf{g} : \mathbf{k} \quad (2.13)$$

where $\mathbf{m}, \mathbf{n}$, and $\mathbf{k}$ are defined as

$$\mathbf{m} := \mathbf{F} \mathbf{M} \mathbf{F}^T, \quad \mathbf{n} := \mathbf{F} \mathbf{N} \mathbf{F}^T, \quad \mathbf{k} := \mathbf{F} \mathbf{K} \mathbf{F}^T.$$

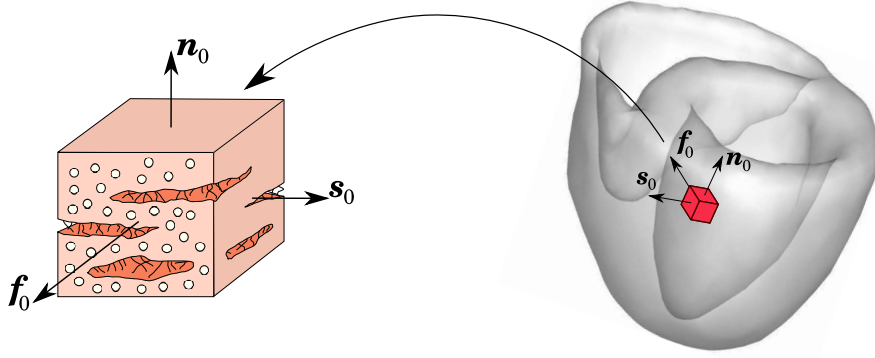


Figure 2.3: Anisotropic architecture of the myocardium. The orthogonal unit vectors $\mathbf{f}_0$ and $\mathbf{s}_0$ designate the preferred fiber and sheet directions in the undeformed configuration, respectively. The third direction $\mathbf{n}_0$ is orthogonal to the latter by its definition $\mathbf{n}_0 := (\mathbf{f}_0 \times \mathbf{s}_0)/|\mathbf{f}_0 \times \mathbf{s}_0|$.

The passive response accounts for the anisotropic microstructure through its dependence on the Eulerian structural tensors $\mathbf{m}, \mathbf{n}$, and $\mathbf{k}$ given above. Their Lagrangean counterparts depend on the preferred fiber and sheet directions in the reference configuration through the following relationships

$$\mathbf{M} := \mathbf{f}_0 \otimes \mathbf{f}_0, \quad \mathbf{N} := \mathbf{s}_0 \otimes \mathbf{s}_0, \quad \mathbf{K} := \text{sym}(\mathbf{f}_0 \otimes \mathbf{s}_0)$$

Having defined the free energy function, the passive Kirchhoff stress tensor $\hat{\boldsymbol{\tau}}^p$ can be obtained through the Doyle-Ericksen formula as

$$\hat{\boldsymbol{\tau}}^p(\mathbf{g}; \mathbf{F}) = J \hat{p} \mathbf{g}^{-1} + \tilde{\boldsymbol{\tau}}^p(\mathbf{g}; \mathbf{F}). \quad (2.14)$$

In this equation, the orthotropic part of the passive stress is defined as $\tilde{\boldsymbol{\tau}}^p(\mathbf{g}; \mathbf{F}) := 2\partial_{\mathbf{g}}\tilde{\Psi}$ and $\hat{p} := U'(J) = dU/dJ$. The explicit form of the orthotropic part of passive Kirchhoff stress tensor in terms of the invariants (2.13) is

$$\tilde{\boldsymbol{\tau}}^p(\mathbf{g}; \mathbf{F}) = 2\Psi_1 \mathbf{b} + 2\Psi_{4m} \mathbf{m} + 2\Psi_{4n} \mathbf{n} + 2\Psi_{4k} \mathbf{k} \quad (2.15)$$

where $\mathbf{b} := \mathbf{F}\mathbf{G}^{-1}\mathbf{F}^T$ is the left Cauchy-Green tensor and $\Psi_1, \Psi_{4m}, \Psi_{4n}$, and Ψ_{4k} are the scalar derivatives of the passive free energy (2.12) with respect to the invariants given as

$$\begin{aligned} \Psi_1 &:= \partial_{I_1} \tilde{\Psi} = \frac{a_1}{2} \exp[b_1(I_1 - 3)], \\ \Psi_{4m} &:= \partial_{I_{4m}} \tilde{\Psi} = a_m(I_{4m} - 1) \exp[b_m(I_{4m} - 1)^2], \\ \Psi_{4n} &:= \partial_{I_{4n}} \tilde{\Psi} = a_n(I_{4n} - 1) \exp[b_n(I_{4n} - 1)^2], \\ \Psi_{4k} &:= \partial_{I_{4k}} \tilde{\Psi} = a_k I_{4k} \exp[b_k I_{4k}^2]. \end{aligned} \quad (2.16)$$

2.3.1.2 Active Stress Response and Active Contraction

The active stress response is again obtained from the Doyle-Ericksen formula $\hat{\boldsymbol{\tau}}^a(\mathbf{g}; \mathbf{F}^e, \mathbf{M}) := 2\partial_{\mathbf{g}}\tilde{\Psi}^a$ where the active part of the free energy function is assumed to be transversely isotropic

$$\tilde{\Psi}^a(\mathbf{g}; \mathbf{F}^e, \mathbf{M}) = \frac{1}{2}\eta(I_{4m} - 1)^2. \quad (2.17)$$

Then, the active part of the Kirchhoff stress tensor is found as

$$\begin{aligned} \hat{\boldsymbol{\tau}}^a(\mathbf{g}; \mathbf{F}^e, \mathbf{M}) &= 2\partial_{\mathbf{g}}\left[\frac{1}{2}\eta(I_{4m}^e - 1)^2\right] \\ &= 2\eta(I_{4m}^e - 1)\mathbf{m}^e \end{aligned} \quad (2.18)$$

where $I_{4m}^e := \mathbf{g} : \mathbf{m}^e$ is the invariant and $\mathbf{m}^e$ is defined as $\mathbf{m}^e := \mathbf{F}^e \mathbf{M} \mathbf{F}^{eT}$ that necessitates the calculation of the elastic part of the deformation gradient. As it is explained in Chapter 1, the active contraction of myocytes is triggered by the electrical activation of the cardiac cells. In microcellular level, the cardiomyocytes get excited when there is a calcium flux from the sarcoplasmic reticulum. Therefore, there is a strong coupling between the calcium release and the active contraction. The active stretch $\hat{\lambda}^a$ is formulated as

$$\hat{\lambda}^a(\bar{c}) = \frac{\xi}{1 + f(\bar{c})(\xi - 1)} \lambda_{\max}^a \quad (2.19)$$

in terms of the normalized calcium concentration $\bar{c}$ [72]. In this equation, ξ and $f(\bar{c})$, a kind of switch function, are defined as

$$\begin{aligned} f(\bar{c}) &:= \frac{1}{2} + \frac{1}{\pi} \arctan(\beta \ln \bar{c}), \\ \xi &:= \frac{f(\bar{c}_0) - 1}{f(\bar{c}_0) - \lambda_{\max}^a}. \end{aligned} \tag{2.20}$$

2.3.2 Spatial Potential Flux

The reaction-diffusion type equation of excitation depends on the potential flux $\hat{\mathbf{q}}$ described by the following equation

$$\hat{\mathbf{q}} = \hat{\mathbf{D}}(\mathbf{g}; \mathbf{F}) \cdot \text{grad } \Phi \tag{2.21}$$

where $\text{grad } \Phi$ and $\hat{\mathbf{D}}(\mathbf{g}; \mathbf{F})$ stand for the spatial potential gradient and the conduction tensor, respectively. $\hat{\mathbf{D}}(\mathbf{g}; \mathbf{F})$ is a second-order tensor field that controls the conduction speed of the excitation waves. In our model, we decompose it to account for the isotropic and anisotropic conduction of the depolarization waves as

$$\mathbf{D} = d_{\text{iso}} \mathbf{g}^{-1} + d_{\text{ani}} \mathbf{m} \tag{2.22}$$

with d_{iso} and d_{ani} , the scalar conduction coefficients, where the latter accounts for the faster conduction along the myofiber directions.

2.3.3 Electrical Source Term

Referring to the FitzHugh-Nagumo model [30, 63], the term $\hat{I}^\phi$ is the current source responsible for the evolution of the electrical field with the recovery variable r during a complete cardiac cycle. In our model, the current source term depends solely on the electrical field when the primary fields are considered, meaning that the deformation-induced current generation [53, 65, 36] is not taken into account. Moreover, the dependency of $\hat{I}^\phi$ on r characterizes the properties of the action potential during repolarization of the cardiac cells. As proposed in the recent work by Göktepe & Kuhl [35], owing to the change in the

repolarization response throughout the heart, the recovery variable is considered to be a local variable specific to each cardiac cell. The evolution of the recovery variable is described by the first order differential equation (2.23)₂. In this thesis, we based our model on one of the two-variable phenomenological models, namely the Aliev-Panfilov model [11] whose equations are given in terms of one fast and one slow variable as follows

$$\begin{aligned}\partial_\tau \phi &= \hat{i}^\phi(\phi, r) = c\phi(\phi - a)(1 - \phi) - r\phi, \\ \partial_\tau r &= \hat{i}^r(\phi, r) = \hat{\epsilon}(\phi, r)[-r - c\phi(\phi - b - 1)].\end{aligned}\tag{2.23}$$

where a, b , and c denotes the material parameters and $\hat{\epsilon}(\phi, r)$ controls the restitution properties of the action potential depending on the variables γ, μ_1 and μ_2 through the equation $\hat{\epsilon}(\phi, r) := \gamma + \mu_1 r / (\mu_2 + \phi)$. In these equations the transmembrane potential Φ and the time, t , are introduced to be dimensionless as ϕ and τ , respectively. The conversion between the dimensionless potential and the physical potential is provided by the factor β_ϕ and potential difference δ_ϕ that are in units of millivolts. Similarly, the physical time t is obtained by multiplying the dimensionless time τ by the factor β_t .

$$\Phi = \beta_\phi \phi - \delta_\phi \quad \text{and} \quad t = \beta_t \tau.\tag{2.24}$$

$$\hat{I}^\phi = \frac{\beta_\phi}{\beta_t} \hat{i}^\phi.\tag{2.25}$$

Moreover, the relation between the normalized source term $\hat{i}^\phi$ and the physical source term $\hat{I}^\phi$ is given in (2.25).

As explained in Chapter 1, the main advantage of a two-variable model is to be able to analyze the behavior of the system on the phase plane. Having the system of equations (2.23) dependent on the dimensionless transmembrane potential ϕ and the recovery variable r the particular solutions are depicted in the two dimensional phase space in Figure 2.4. The distinct initial values of ϕ_0 and r_0 are shown with the filled circles and the dashed lines denote the nullclines for $\hat{i}^\phi = 0$ or $\hat{i}^r = 0$. As shown on the phase diagram, it is observed that the

solution converges to the stable equilibrium point although it is perturbed from the steady state.

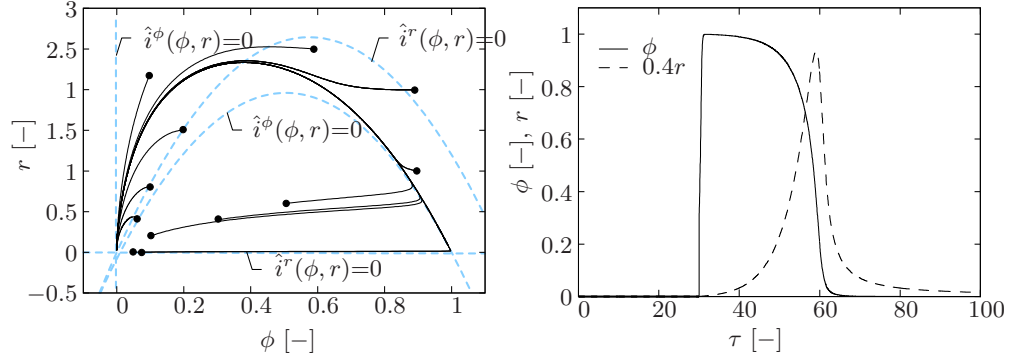


Figure 2.4: The Aliev-Panfilov model with $\alpha = 0.01, \gamma = 0.002, b = 0.15, c = 8, \mu_1 = 0.2, \mu_2 = 0.3$. The phase portrait depicts trajectories for distinct initial values ϕ_0 and r_0 (filled circles) converging to a stable equilibrium point (left). Non-oscillatory normalized time plot of the non-dimensional action potential ϕ and the recovery variable r (right).

CHAPTER 3

FINITE ELEMENT FORMULATION

In this chapter, continuous forms obtained for the governing differential equations of the cardiac electromechanics (2.4) and (2.6) are transformed into their discretized forms. For this purpose, the weak forms of these equations are obtained by following the conventional Galerkin procedure. Then, these weak integral forms are consistently linearized to be monolithically solved for the nodal degrees of freedom after they are discretized spatio-temporally.

3.1 Weak Formulation of the Field Equations

It is aimed to introduce the weak integral forms of the primary field equations in this section. For this purpose, the conventional Galerkin method is utilized to convert the differential forms into their weak integral counterparts. The first step is to write the residual form of the balance of linear momentum equation that is called as the strong form, given as follows

$$\mathbf{R}^\varphi = -J \operatorname{div}(J^{-1}\boldsymbol{\tau}) - \mathbf{B}. \quad (3.1)$$

Multiplying the residual equation by a square integrable weight function, satisfying (2.5)₁, gives the weak formulation of the residual as

$$G^\varphi(\delta\boldsymbol{\varphi}, \boldsymbol{\varphi}, \phi) = \int_{\mathcal{B}} \delta\boldsymbol{\varphi} \cdot (-J \operatorname{div}(J^{-1}\boldsymbol{\tau}) - \mathbf{B}) dV \quad (3.2)$$

The weighted residual equation found above is integrated over the solid volume to obtain the following weak form

$$G^\varphi(\delta\varphi, \varphi, \Phi) = G_{int}^\varphi(\delta\varphi, \varphi, \Phi) - G_{ext}^\varphi(\delta\varphi) = 0 \quad (3.3)$$

Using the integration by parts, $G^\varphi(\delta\varphi, \varphi, \Phi)$ can be written as

$$\begin{aligned} G^\varphi(\delta\varphi, \varphi, \Phi) &= \int_{\mathcal{B}} \delta\varphi \cdot (-J \operatorname{div}(J^{-1}\boldsymbol{\tau})) dV - \int_{\mathcal{B}} \delta\varphi \cdot \mathbf{B} dV \\ &= \int_{\mathcal{B}} \delta\varphi \cdot (-J \operatorname{div}(\boldsymbol{\sigma})) dV - \int_{\mathcal{B}} \delta\varphi \cdot \mathbf{B} dV \\ &= \int_{\mathcal{S}} \delta\varphi \cdot (-\operatorname{div}(\boldsymbol{\sigma})) dv - \int_{\mathcal{B}} \delta\varphi \cdot \mathbf{B} dV \\ &= \int_{\mathcal{S}} (-\operatorname{div}(\delta\varphi \cdot \boldsymbol{\sigma})) dv + \int_{\mathcal{S}} \operatorname{grad}(\delta\varphi) : \boldsymbol{\tau} dv - \int_{\mathcal{B}} \delta\varphi \cdot \mathbf{B} dV \\ &= - \int_{\partial\mathcal{S}_t} \delta\varphi \cdot \bar{\mathbf{t}} da + \int_{\mathcal{B}} \operatorname{grad}(\delta\varphi) : \boldsymbol{\tau} dV - \int_{\mathcal{B}} \delta\varphi \cdot \mathbf{B} dV \end{aligned} \quad (3.4)$$

where

$$\begin{aligned} G_{int}^\varphi(\delta\varphi, \varphi, \Phi) &:= \int_{\mathcal{B}} \operatorname{grad}(\delta\varphi) : \boldsymbol{\tau} dV, \\ G_{ext}^\varphi(\delta\varphi) &:= \int_{\mathcal{B}} \operatorname{grad}(\delta\varphi) \cdot \mathbf{B} dV + \int_{\partial\mathcal{S}_t} \delta\varphi \cdot \bar{\mathbf{t}} da \end{aligned} \quad (3.5)$$

and the operator $\operatorname{grad}[\bullet]$ is defined as the gradient with respect to spatial coordinates $\mathbf{x}$. Following the above described procedure for the electric field, the strong form of the residual for the reaction-diffusion type equation of excitation is given as

$$\mathbf{R}^\phi = \dot{\Phi} - J \operatorname{div}(J^{-1}\mathbf{q}) - \hat{I}^\phi. \quad (3.6)$$

Multiplication of the residual equation by a square-integrable weight function satisfying (2.7)₁ gives the weak formulation of the residual as

$$G^\phi(\delta\Phi, \boldsymbol{\varphi}, \Phi) = \int_{\mathcal{B}} \delta\Phi(\dot{\Phi} - J \operatorname{div}(J^{-1}\mathbf{q}) - \hat{I}^\phi) dV. \quad (3.7)$$

Again, (3.7) is integrated over the same domain to be written in the following form

$$G^\phi(\delta\Phi, \boldsymbol{\varphi}, \Phi) = G_{int}^\phi(\delta\Phi, \boldsymbol{\varphi}, \Phi) - G_{ext}^\phi(\delta\Phi, \boldsymbol{\varphi}, \Phi) = 0 \quad (3.8)$$

Integrating by parts, $G^\phi(\delta\Phi, \boldsymbol{\varphi}, \Phi)$ can be written as

$$\begin{aligned} G^\phi(\delta\Phi, \boldsymbol{\varphi}, \Phi) &= \int_{\mathcal{B}} \delta\Phi \dot{\Phi} dV - \int_{\mathcal{B}} \delta\Phi J \operatorname{div}[J^{-1}\mathbf{q}] dV - \int_{\mathcal{B}} \delta\Phi \hat{I}^\phi dV \\ &= \int_{\mathcal{B}} \delta\Phi \dot{\Phi} dV - \int_{\mathcal{S}} \delta\Phi \operatorname{div}[J^{-1}\mathbf{q}] dv - \int_{\mathcal{B}} \delta\Phi \hat{I}^\phi dV \\ &= \int_{\mathcal{B}} \delta\Phi \dot{\Phi} dV - \int_{\mathcal{S}} \operatorname{div}(\delta\Phi J^{-1}\mathbf{q}) dv - \int_{\mathcal{S}} \operatorname{grad}(\delta\Phi) \cdot J^{-1}\mathbf{q} dv - \int_{\mathcal{B}} \delta\Phi \hat{I}^\phi dV \\ &= \int_{\mathcal{B}} \delta\Phi \dot{\Phi} dV - \int_{\partial\mathcal{S}_h} \delta\Phi \bar{h} da - \int_{\mathcal{B}} \operatorname{grad} \delta\Phi \cdot \mathbf{q} dV - \int_{\mathcal{B}} \operatorname{grad} \Phi \hat{I}^\phi dV \end{aligned} \quad (3.9)$$

where

$$\begin{aligned} G_{int}^\phi(\delta\Phi, \boldsymbol{\varphi}, \Phi) &:= \int_{\mathcal{B}} \delta\Phi \dot{\Phi} + \operatorname{grad}(\delta\Phi) \cdot \bar{\mathbf{q}} dV, \\ G_{ext}^\phi(\delta\Phi) &:= \int_{\mathcal{B}} \delta\Phi \hat{I}^\phi dV + \int_{\partial\mathcal{S}_h} \delta\Phi \bar{h} da \end{aligned} \quad (3.10)$$

Having the weak forms of the weighted residual equations at hand, these equations can be solved for the primary field variables. However, the nonlinear terms due to spatial gradient operators and the constitutive equations, present in the weak formulation makes it is necessary to linearize the weighted residuals about $\boldsymbol{\varphi} = \tilde{\boldsymbol{\varphi}}$ and $\Phi = \tilde{\Phi}$.

$$\begin{aligned} \operatorname{Lin} G^\varphi(\delta\boldsymbol{\varphi}, \boldsymbol{\varphi}, \Phi) |_{\tilde{\boldsymbol{\varphi}}, \tilde{\Phi}} &:= G^\varphi(\delta\boldsymbol{\varphi}, \tilde{\boldsymbol{\varphi}}, \tilde{\Phi}) + \Delta G^\varphi(\delta\boldsymbol{\varphi}, \tilde{\boldsymbol{\varphi}}, \tilde{\Phi}; \Delta\boldsymbol{\varphi}, \Delta\Phi) \\ &:= G^\varphi(\delta\boldsymbol{\varphi}, \tilde{\boldsymbol{\varphi}}, \tilde{\Phi}) + \Delta G_{int}^\varphi - \Delta G_{ext}^\varphi \end{aligned} \quad (3.11)$$

$$\begin{aligned}
\Delta G_{int}^{\varphi}(\delta\varphi, \varphi, \Phi) &= \int_{\mathcal{B}} \Delta(\text{grad } \delta\varphi) : \boldsymbol{\tau} dV + \int_{\mathcal{B}} \text{grad}(\delta\varphi) : \Delta\boldsymbol{\tau} dV \\
&= \int_{\mathcal{B}} \text{grad}(\delta\varphi) : \mathbb{C}^{\varphi\varphi} : (\mathbf{g} \text{grad}(\Delta\varphi)) dV \\
&\quad + \int_{\mathcal{B}} \text{grad}(\delta\varphi) : (\text{grad}(\Delta\varphi)\tilde{\boldsymbol{\tau}}) dV + \int_{\mathcal{B}} \text{grad}(\delta\varphi) : \mathbf{C}^{\varphi\phi} \Delta\Phi dV.
\end{aligned} \tag{3.12}$$

where $\mathbb{C}^{\varphi\varphi} := 2\partial_{\mathbf{g}}\boldsymbol{\tau}(\mathbf{g}; \mathbf{F}, \Phi)$ and $\mathbf{C}^{\varphi\phi} := \partial_{\Phi}\boldsymbol{\tau}(\mathbf{g}; \mathbf{F}, \Phi)$. In (3.12), some of the terms may be further explained as

$$\begin{aligned}
\Delta(\text{grad}(\delta\varphi)) &= \text{Grad}(\delta\varphi)\delta_{\varphi}\mathbf{F}^{-1} = \text{Grad}(\delta\varphi)(-\mathbf{F}^{-1} \text{grad } \delta\varphi) \\
&= -\text{grad}(\delta\varphi) \cdot \text{grad}(\Delta\varphi)
\end{aligned} \tag{3.13}$$

where the operator $\text{Grad}[\bullet]$ stands for the gradient with respect to material coordinates $\mathbf{X}$. Assuming that the Kirchhoff stress tensor $\boldsymbol{\tau}$ depends both on the deformation and the action potential fields, it is linearized with respect to these two variables. Linearization of the electrical internal term, ΔG_{int}^{ϕ} yields

$$\Delta G_{int}^{\phi} := \int_{\mathcal{B}} \left(\delta\Phi \frac{1}{\Delta t} \Delta\Phi + \Delta(\text{grad}(\delta\Phi)) \cdot \mathbf{q} + \text{grad}(\delta\Phi) \cdot \mathbf{q} \right) dV \tag{3.14}$$

Substituting

$$\begin{aligned}
\Delta(\text{grad}(\delta\Phi)) &= -\text{grad}(\delta\Phi) \text{grad}(\Delta\varphi), \\
\Delta(\text{grad } \Phi) &= \text{grad}(\Delta\Phi) - \text{grad } \Phi \text{grad}(\Delta\varphi)
\end{aligned}$$

and

$$\begin{aligned}
\Delta\mathbf{q} &= \mathcal{L}_{\Delta\varphi}\mathbf{q} + \text{grad}(\Delta\varphi)\mathbf{q} + \partial_{\text{grad } \Phi}\mathbf{q} \text{grad}(\Delta\Phi) \\
&= \mathbf{C}^{\phi\varphi} : (\mathbf{q} \text{grad}(\Delta\varphi)) + \mathbf{C}^{\phi\phi} \text{grad}(\Delta\Phi) + \text{grad}(\Delta\varphi)\mathbf{q}
\end{aligned}$$

into (3.14) gives the following form of the linearized internal electrical term

$$\begin{aligned}
\Delta G_{int}^{\phi} &= \int_{\mathcal{B}} \left(\delta\Phi \frac{1}{\Delta t} \Delta\Phi + \text{grad}(\delta\Phi) \cdot \mathbf{C}^{\phi\phi} \cdot \text{grad}(\Delta\Phi) \right) dV \\
&\quad + \int_{\mathcal{B}} \text{grad}(\delta\Phi) \cdot \mathbf{C}^{\phi\varphi} : (\mathbf{g} \text{grad}(\Delta\varphi)) dV.
\end{aligned} \tag{3.15}$$

where $\mathbf{C}^{\phi\varphi} := 2\partial_{\mathbf{g}}\mathbf{q}(\mathbf{g}; \mathbf{F}, \Phi)$ and $\mathbf{C}^{\phi\phi} := \partial_{\text{grad } \Phi}\mathbf{q}(\mathbf{g}; \mathbf{F}, \Phi)$.

Linearization of the external current, that depends on both the primary fields, φ and Φ is as follows

$$\Delta G_{ext}^{\phi} := \int_{\mathcal{B}} \delta\Phi \Delta \hat{I}^{\phi} dV. \quad (3.16)$$

Substituting $\Delta \hat{I}^{\phi} = 2\partial_{\mathbf{g}}\hat{I}^{\phi} : (\mathbf{g} \text{ grad}(\Delta\varphi)) + \partial_{\Phi}\hat{I}^{\phi} \Delta\Phi$ yields

$$\Delta G_{ext}^{\phi} := \int_{\mathcal{B}} \delta\Phi \partial_{\Phi}\hat{I}^{\phi} \Delta\Phi dV + \int_{\mathcal{B}} \delta\Phi 2\partial_{\mathbf{g}}\hat{I}^{\phi} : (\mathbf{g} \text{ grad}(\Delta\varphi)) dV. \quad (3.17)$$

3.2 Spatial Discretization

In this section, the field variables, φ and Φ and the related weight functions, $\delta\varphi$ and $\delta\Phi$ are converted into their discretized forms. For this purpose, conventional isoparametric Galerkin procedure is utilized to find an approximate solution in the solution domain B discretized into subdomains B_e^h for each element, satisfying the relation $B = \bigcup_{e=1}^{n_{el}} B_e^h$ where n_{el} stands for the number of elements. Following relations are used for discretization

$$\begin{aligned} \varphi_e^h &= \sum_{i=1}^{n_{en}} N^i \mathbf{x}_i^e, \\ \Phi_e^h &= \sum_{j=1}^{n_{en}} N^j \Phi_j^e \\ \delta\varphi_e^h &= \sum_{k=1}^{n_{en}} N^k \delta\mathbf{x}_k^e, \\ \delta\Phi_e^h &= \sum_{l=1}^{n_{en}} N^l \delta\Phi_l^e. \end{aligned} \quad (3.18)$$

where N^{α} for $\alpha = i, j, k, l$ are C^0 shape functions and n_{en} represents the number of nodes per elements. It is also necessary to introduce the spatial gradient of

the weight functions and the incremental fields

$$\begin{aligned}
\text{grad}(\delta\boldsymbol{\varphi}_e^h) &= \sum_{i=1}^{n_{en}} \delta\mathbf{x}_i^e \otimes \text{grad } N^i, \\
\text{grad}(\delta\Phi_e^h) &= \sum_{j=1}^{n_{en}} \delta\Phi_j^e \otimes \text{grad } N^j, \\
\text{grad}(\Delta\boldsymbol{\varphi}_e^h) &= \sum_{k=1}^{n_{en}} \Delta\mathbf{x}_k^e \otimes \text{grad } N^k, \\
\text{grad}(\Delta\Phi_e^h) &= \sum_{l=1}^{n_{en}} \Delta\Phi_l^e \otimes \text{grad } N^l.
\end{aligned} \tag{3.19}$$

Discretization of (3.3) and (3.8) is found by substituting the appropriate definitions above

$$\mathbf{R}_I^\varphi = \mathbf{A}_{e=1}^{n_{el}} \left\{ \int_{\mathcal{B}_e^h} \text{grad } N^i \cdot \boldsymbol{\tau} dV - \int_{\mathcal{B}_e^h} N^i \mathbf{B} dV - \int_{\partial\mathcal{S}_t^e} N^i \bar{\mathbf{t}} da \right\} = \mathbf{0}, \tag{3.20}$$

$$\mathbf{R}_J^\phi = \mathbf{A}_{e=1}^{n_{el}} \left\{ \int_{\mathcal{B}_e^h} \left(N^j \frac{\Phi - \Phi_n}{\Delta t} + \text{grad } N^j \cdot \mathbf{q} \right) dV - \int_{\mathcal{B}_e^h} N^j \hat{I}^\phi dV - \int_{\partial\mathcal{S}_h^e} N^j \bar{h} da \right\} = \mathbf{0}. \tag{3.21}$$

The set of coupled equations obtained through the discretization of the primary fields, placement $\boldsymbol{\varphi}(\mathbf{X}, t)$ and electrical potential $\Phi(\mathbf{X}, t)$, is solved monolithically.

CHAPTER 4

MODELING OF PRESSURE-VOLUME CURVES

This chapter outlines the mathematical model utilized in the left ventricular pressure-volume curve simulation. After introducing the equations describing the pressure-volume relation within the left ventricle, their physiological interpretations are briefly discussed.

4.1 Left Ventricular Pressure Calculation

As explained before, a cardiac cycle is composed of four different phases. More detailed information about these phases is introduced in Section 1.5, however, they are briefly recalled here to understand the physiological meaning of the models used. As shown in Figure 1.10, the cardiac cycle starts with the isovolumic contraction phase and continues in the counter-clockwise direction in the order of ejection, isovolumic relaxation, and filling phases. The mechanical properties of the ventricular muscle cells change continuously during a cycle, resulting in an alternating pressure-volume relationship within the ventricle. Assuming that $V(t)$ represents the ventricular cavity volume at time t and $q(t) = \dot{V}(t)$ is the blood flow, it can be said that $\dot{V}(t) = 0$ for the isovolumic phases, where the ventricular volume is unaltered. Mathematical models used to simulate the pressure-volume relation are chosen to be different for ejection and the other phases. In order to obtain more accurate results for the ejection phase, an iterative approach is followed to calculate the ventricular pressure. In the literature, Windkessel-type models are widely used to represent the ventricular pressure in the ejection phase, see [77, 27, 28]. In this thesis, three-element Windkessel

model is utilized for the ejection phase while isovolumic relaxation, isovolumic contraction and filling phases are simulated by using the Signorini model [77].

4.1.1 Windkessel-Type Models

A Windkessel-type model, a kind of lumped parameter model, was introduced by the German physiologist Otto Frank in 1899 [31]. However, the origin of the lumped models goes back to 1700s [39]. He proposed to model the heart and the systemic arterial system analogous to a hydraulic circuit composed of a water pump and a chamber which contains water and an air pocket. The pumping of water into the chamber not only cause the water to move outwards but it also applies a pressure on the air pocket. Using the hydraulic circuit analogy, the physiological terms, arterial compliance and peripheral resistance can be explained. The behavior of the air pocket when squeezed by the water represents the elasticity of the arteries as the blood is ejected out of the heart; that is, the arterial compliance. Moreover, the force applied to the water while moving through the circuit is similar to the blood movement through the veins. The blood flow encounters resistive forces appearing due to the geometrical changes in the veins, called the peripheral resistance. The most basic form of the Windkessel model can be defined through the two-element model whose electrical circuit analog is depicted in Figure 4.1. Following Kirchhoff's Laws, the circuit in Figure 4.1 (left) can be described through the first order differential equation

$$I(t) = \frac{P(t)}{R} + C \frac{dP(t)}{dt}, \quad (4.1)$$

where $I(t)$, $P(t)$, C and R are the time-dependent current, electrical potential, capacitance and the resistance, respectively. In physiological terms, the associated circuit is given in Figure 4.1 (right) where $q(t)$ represents the blood flow into the arteries, $p_{lv}(t)$ is the blood pressure, C_{ap} is the arterial compliance and R_p is the peripheral resistance. The differential equation describing the relation

between the blood pressure and flow is

$$q(t) = \frac{p_{lv}(t)}{R_p} + C_{ap} \frac{dp_{lv}(t)}{dt}. \quad (4.2)$$

The two-element Windkessel model can be modified to include the contribution of other factors such as the valve resistances and inertia of the blood. The three-element Windkessel model is obtained by adding one more resistive element into the circuit to represent the resistance due to valves. In this thesis, the left ventricular pressure in the ejection phase is simulated using a three-element model. Thus, it is discussed in detail in the next section. Besides the resistive element, an inductor can be added to the three-element Windkessel model to consider the effect of the inertia of blood in the simulation. The reader is referred to [79] for further information on 4-element Windkessel models.

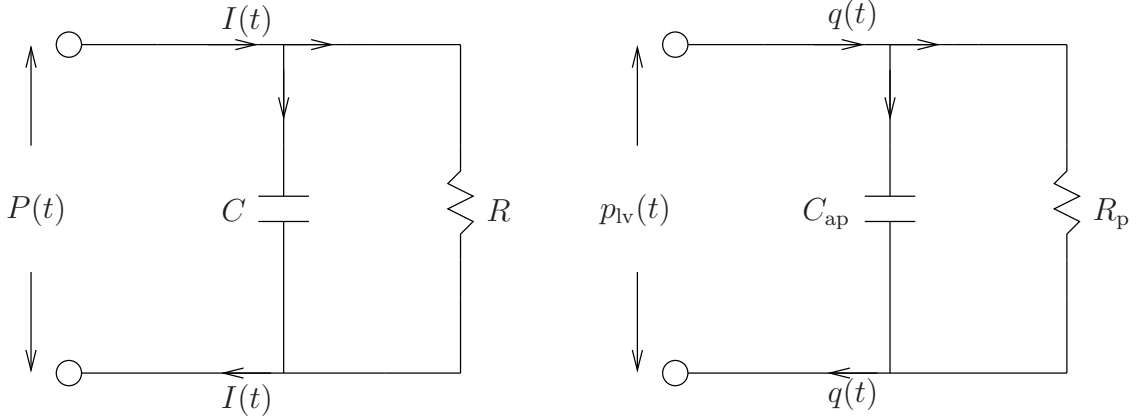


Figure 4.1: Electrical Circuit Analog for the Two-Element Windkessel Model with the time dependent current $I(t)$, electrical potential $P(t)$, capacitance C , and resistance R (left) while the same circuit is drawn with the physiological parameters; blood flow $q(t)$, blood pressure $p_{lv}(t)$, arterial compliance C_{ap} , and peripheral resistance R_p (right).

4.2 Three-Element Windkessel Model

Three-element Windkessel model is an improved version of the two-element Windkessel model to simulate the blood pressure more accurately. It is de-

scribed in the article written by Ph. Broemser and Otto Frank in 1930 [18]. The electrical circuit analog for the 3-element Windkessel model is depicted in Figure 4.2. It is an RCR circuit that includes one more resistance compared to the two-element one. Kirchhoff's Laws yields the following relation to describe the electrical circuit depicted in Figure 4.2 (left)

$$\left(1 + \frac{R_1}{R_2}\right) I(t) + CR_1 \frac{dI(t)}{dt} = \frac{P(t)}{R_2} + C \frac{dP(t)}{dt} \quad (4.3)$$

where the terms $P(t)$, $I(t)$, and C have the same meaning as in the two-element model while R_1 and R_2 are the resistive terms. Figure 4.2 (right) represents the same electrical circuit with the physiological terms $p_{lv}(t)$, $q(t)$, and C_{ap} defined for the two-element model. R_c and R_p stand for the resistance to blood flow due to the aortic or pulmonary valve and the peripheral resistance, respectively.

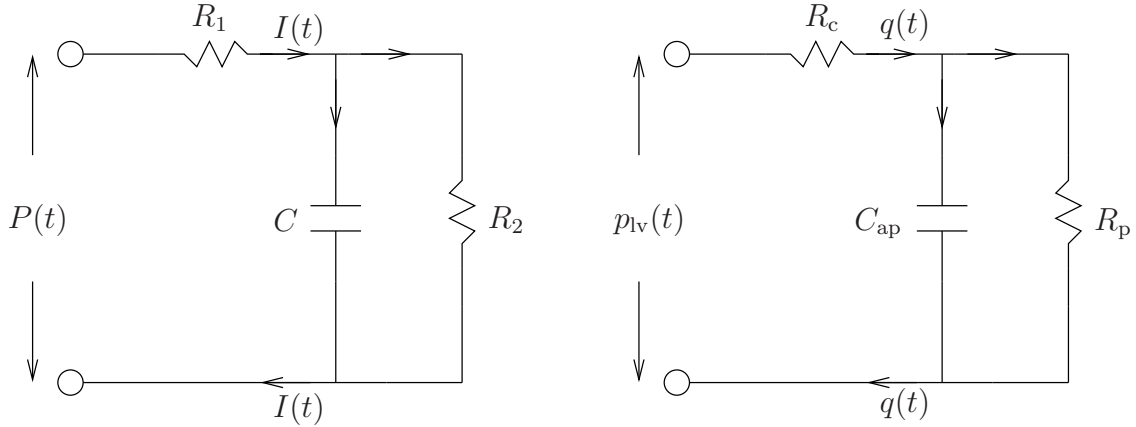


Figure 4.2: Electrical Circuit Analog for the Three-Element Windkessel Model with the time dependent current $I(t)$, electrical potential $P(t)$, capacitance C , and resistances R_1 and R_2 (left) while the same circuit is drawn with the physiological parameters; blood flow $q(t)$, blood pressure $p_{lv}(t)$, arterial compliance C_{ap} , peripheral resistance R_p , and resistance due to aortic or pulmonary valves R_c (right).

The blood pressure and flow relation for the three-element model is described through the relation

$$\left(1 + \frac{R_c}{R_p}\right) q(t) + C_{ap} R_c \frac{dq(t)}{dt} = \frac{p_{lv}(t)}{R_p} + C_{ap} \frac{dp_{lv}(t)}{dt}. \quad (4.4)$$

The reader is referred to [89, 83] for the studies on three-element Windkessel model to simulate the pressure.

In our model, following update equation is utilized to find the current pressure

$$\begin{aligned} p_{lv}(t+1) &= p_{lv}(t) + \Delta t \dot{p}_{lv}(t) \\ &= p_{lv}(t) + \Delta t \left[\frac{1}{C_{ap}} \left(1 + \frac{R_c}{R_p} \right) q(t) + R_c \dot{q}(t) - \frac{p_{lv}(t)}{C_{ap} R_p} \right]. \end{aligned} \quad (4.5)$$

The numerical values used for the parameters, R_c , R_p , and C_{ap} are introduced in Table 5.2.

4.3 Signorini Model

In this study, blood pressure for isovolumic relaxation, isovolumic contraction, and filling phases are simulated using the Signorini model. In the isovolumic phases, the left ventricular pressure lies between the atrial and arterial pressures because both the mitral and aortic valves are closed. Therefore, there is no change in the ventricular volume, that is $\dot{V} = 0$. However, in the filling phase, left ventricular pressure becomes equal to the atrial pressure as the mitral valve opens and the ventricular volume starts to increase, thereby, $\dot{V} \geq 0$. Referring to [77], the change in ventricular volume q is written as a function of pressure. Following relations are satisfied for the cardiac phases, assuming that the relation $q = -V\dot{V}(t)$ holds.

$$q = \begin{cases} \frac{1}{m_{at}}(p_{lv} - p_{at}), & \text{if } p_{lv} \leq p_{at} \\ \frac{1}{m_p}(p_{lv} - p_{at}), & \text{if } p_{at} \leq p_{lv} \leq p_{ar} \\ \frac{1}{m_{ar}}(p_{lv} - p_{ar}) + \frac{1}{m_p}(p_{ar} - p_{at}), & \text{if } p_{lv} \geq p_{ar} \end{cases} \quad (4.6)$$

In (4.6), p_{at} , p_{ar} , and p_{lv} are the atrial, arterial and left ventricular pressures, respectively. The blood flow $q(t)$ is a linear function of p_{lv} and depends on the variables m_{at} , m_{ar} and m_p that represent the valve properties. m_{at} and m_{ar} are physiologically related to the functioning of valves whose states change in the

filling and ejection phases. The numerical values assigned to m_{at} and m_{ar} are given in Table 5.2. m_p is chosen to be a very large number to satisfy the relation $q = 0$ in isovolumic phases.

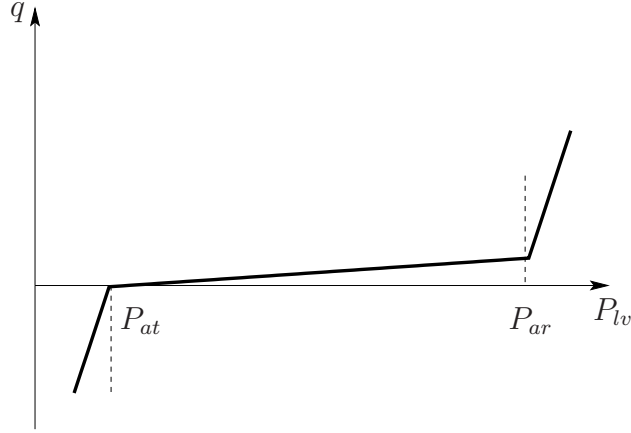


Figure 4.3: Blood Flow as a Function of Pressure.

In (4.6), flux is calculated for a known ventricular pressure, however, for the purpose of pressure simulation, flux must be known to calculate the pressure. Therefore, an inverse relation for (4.6) should be considered. The equation proposed for the Signorini model to simulate the ventricular pressure is as follows

$$p_{lv} := \hat{p}_0 + (\hat{p}_\infty - \hat{p}_0) \exp[-\exp(-\chi \tilde{q})] \quad (4.7)$$

where p_0 and p_∞ are linear functions of the flux given as

$$\hat{p}_0(\tilde{q}) := p_{at} + m_{at} \tilde{q} \quad \text{and} \quad \hat{p}_\infty(\tilde{q}) := p_{ar} + m_{ar} \tilde{q}, \quad (4.8)$$

While p_0 is found just inverting the corresponding equation in (4.6), in the derivation of p_∞ , the term m_p^{-1} is neglected and its contribution is modeled by the variable ξ that behaves like a switching term. As depicted in Figure 4.4, it provides an abrupt pressure change in isovolumic phases. In Figure 4.4, the behavior of the Signorini model (4.7) is depicted using the same values with the material parameters introduced in Table 5.2.

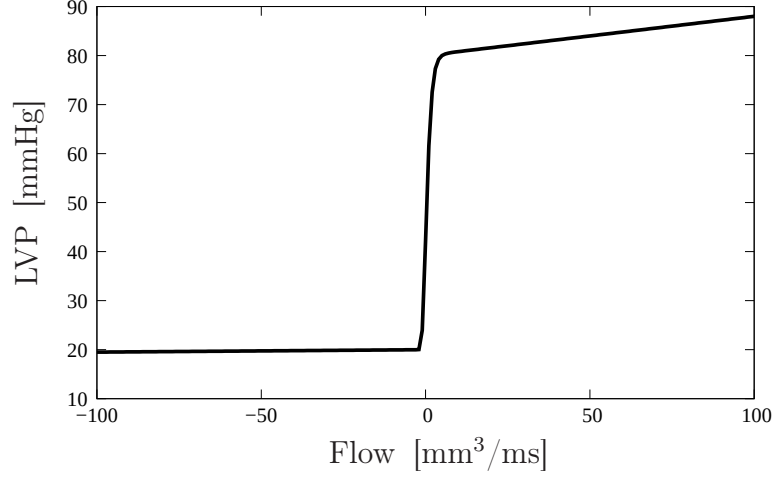


Figure 4.4: Left ventricular pressure as a function of blood flow, simulated using the Signorini Model (4.7)

An inverse procedure can be followed just for the purpose of showing the potential of the Signorini model to simulate the ventricular pressure. Medical tools used today allow to measure the ventricular pressure. Having the clinical pressure data at hand, if our model is correct, we can find the corresponding fluxes, thereby, the ventricular volume. However, the calculation procedure gets more complex due to the nonlinearity involved in finding the root of (4.7), necessitating an iterative solver, namely the Newton-Raphson method.

The first step is to write the residual as

$$R := p_{lv} - [\hat{p}_0 + (\hat{p}_\infty - \hat{p}_0) \exp(-\exp(-\chi\tilde{q}))]. \quad (4.9)$$

Linearization of (4.9) yields the following

$$\text{Lin } R|_{q=q_i} = R(q_i) + \frac{\partial r}{\partial q}(q - q_i). \quad (4.10)$$

Then, the flux term is updated to find its current value using the equation

$$q_{i+1} = q_i - \left(\frac{\partial r}{\partial q}\right)^{-1} R. \quad (4.11)$$

If the norm of the residual is found to be greater than a pre-defined tolerance, these steps are repeated from (4.9). However, if the convergence criterion is satisfied, using the updated value of the flux, volume change is computed and the ventricular volume is updated, that is mathematically shown as follows

$$V_{i+1} = V_i - q\Delta t. \quad (4.12)$$

For the clinical pressure data, depicted in Figure 4.5, associated pressure-volume curve is given in Figure 4.6 using the Newton-Raphson algorithm. By the way, it is important to mention that, for the both models, the ventricular volume is computed by generating tetrahedrons inside the ventricles. Knowing the position of each node and their connectivities, the total ventricular volume is the summation of the tetrahedron volumes having one of their vertexes at the origin of the coordinate system.

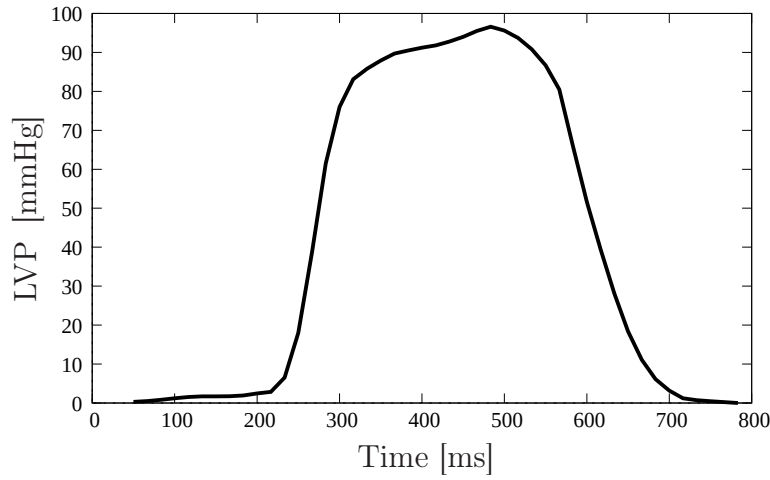


Figure 4.5: Clinical pressure data plotted with respect to time.

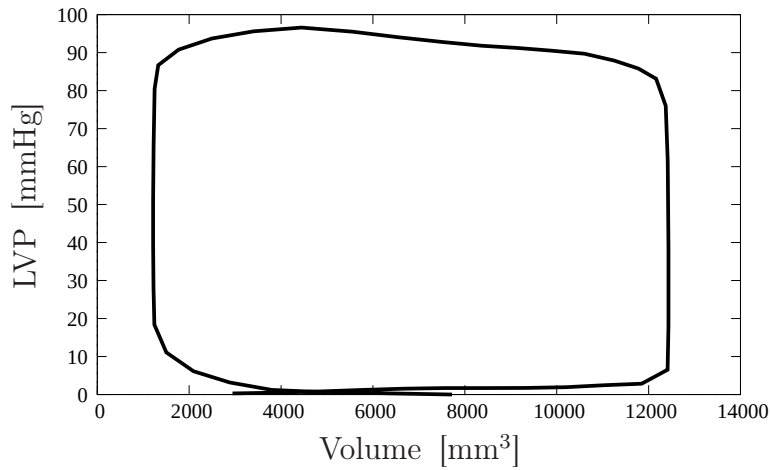


Figure 4.6: Pressure-volume loop for the real pressure data.

CHAPTER 5

VIRTUAL HEART MODELS INCORPORATING SELECTED CARDIAC DYSFUNCTIONS

This chapter is devoted to the numerical examples demonstrating the capability of our model in simulating the left ventricular pressure-volume relationship for the healthy and dysfunctional cases. First, the general properties of the proposed heart model are introduced. Then, the simulation of the pressure-volume curves for the healthy heart is explained along with the modeling approach followed. Additionally, three dysfunctional cases; myocardial infarction, concentric hypertrophy, and eccentric hypertrophy are investigated. Before introducing the numerical examples related to these three cases, the modeling of the related disorder is explained in detail. In addition to the pressure-volume curves, the cross-sectional snapshots taken during the contraction and relaxation of the heart are presented. These illustrative examples provide a way to observe the geometrical changes within the ventricles during a cardiac cycle. They also give a chance to appreciate the difference in the deformation patterns between healthy and dysfunctional models. Finally, the performance of our model is demonstrated by comparing the analysis results with the clinical findings.

5.1 General Properties of the Heart Model

For the analysis of the coupled problem of cardiac electromechanics, a generic three-dimensional heart model is utilized. In Figure 5.1 (top), the mathematical heart model is shown. The left and right ventricles can be considered as two

truncated ellipsoids whose geometrical properties are different from each other. Assuming that a, b , and c are the dimensions corresponding to x, y , and z axes in the Cartesian coordinate system, these ellipsoids are constructed in accordance with the standard ellipsoid equation given below.

$$\frac{x^2}{a^2} + \frac{y^2}{b^2} + \frac{z^2}{c^2} = 0. \quad (5.1)$$

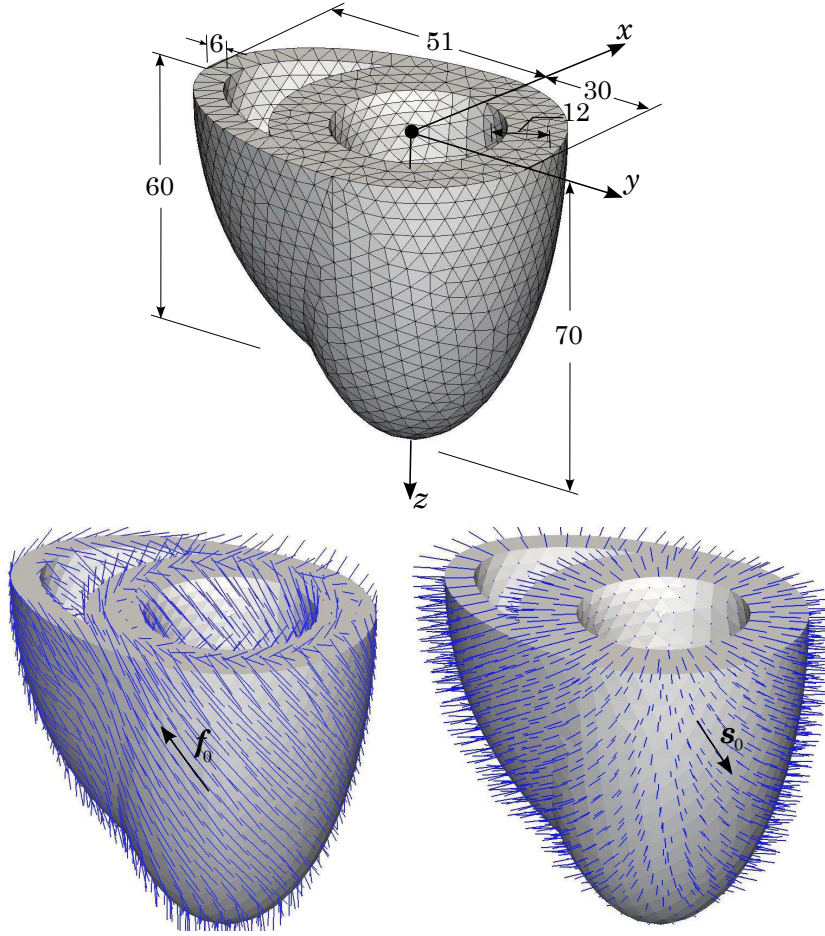


Figure 5.1: The geometry and discretization of a generic heart model generated by truncated ellipsoids. All dimensions are in millimeters (top). The position-dependent orientation of the myofibers $\mathbf{f}_0(\mathbf{X})$ (bottom left) and the sheets $\mathbf{s}_0(\mathbf{X})$ (bottom right) in $\mathcal{B}$.

The heart model is discretized into 13348 four-node tetrahedral elements connected at 3059 nodes. The geometrical properties of the both ventricles are clearly depicted in Figure 5.1 (top). Although they do not exactly reflect the

real heart dimensions, the model proposed here is sufficient to demonstrate its capability in simulating the pressure volume curves. The left ventricle has a wall thickness of 12 mm and a height of 70 mm while the ventricular cavity has a height of 58 mm and a radius of 18 mm. However, the right ventricle has a more complex geometry, that is not like an ellipsoid, but has a crescent-like shape when looked at transversely. Also it has smaller dimensions that are physiological when compared to the left ventricle. The right ventricle has a wall thickness of 6 mm, that is half of the thickness of the left ventricle, and a height of 60 mm. The mechanical and electrophysiological natural and essential boundary conditions are described in Figure 2.2. The displacements at the top surface of the heart are restrained to prevent the heart from moving in all directions. Also, the outer surface of the heart is assumed to be electrically flux-free. As it is stated in Chapter 2, the transient term involved in the formulation of the electrophysiological model necessitates an initial boundary condition. At the beginning, the transmembrane potential at all the nodes is assigned to the resting potential $\Phi_0 = -80$ mV except for the ones at the top of the septum. These nodes are set to a potential of $\Phi_0 = -10$ mV to initiate the electrical excitation. In order to achieve the dimensionless conversion introduced in (2.24) and (2.25), the conversion factors are assigned as follows: $\beta_\phi = 100$ mV, $\delta_\phi = -80$ mV and $\beta_t = 12.9$ ms. Distribution of the myofiber and sheet directions are worth to mentioning due to the dependence of our model on the anisotropic structure of the heart. In Figure 5.1 (left) and (right), myofiber directions $\mathbf{f}_0$ and sheet directions $\mathbf{s}_0$ are depicted. They agree with the distribution of the myofiber and sheet orientation in the real human heart. The fiber direction ranges from -70° in the epicardium to $+70^\circ$ in the endocardium.

5.2 Healthy Heart Model

Using the model described above, the coupled problem of cardiac electromechanics is solved for the healthy heart with the material parameters described in Table 5.1. Their numerical values can be found in Table 5.2 . The pressure-volume curve obtained after the finite element analysis is shown in Figure 5.2.

As it is seen, pressure-volume curve obtained after we run the simulation has a similar shape with the one introduced as a generic pressure-volume curve in Figure 1.10. The simulated pressure-volume curve clearly indicates the four cardiac phases. Starting from Point A, it goes in the counter-clockwise direction. At first, the left ventricular pressure is about 20 mmHg, that is the end-diastolic pressure where the ventricular volume is the largest. As the ventricles contract, the pressure inside increases and an abrupt jump is observed at this point, that is the isovolumic contraction phase. As it is explained previously, there is no volume change during this phase. When the ventricular pressure reaches the aortic pressure, Point B, that is about $p_{ar} = 80$ mmHg, the ejection phase begins. Modeling this phase with three-element Windkessel model gives a smooth curve that is important while observing the changes in case of a dysfunction. At Point C, the end-systolic pressure-volume relationship is reached, meaning that the ventricular volume has its smallest value here. Then, the ventricles relax while the volume is kept constant and the filling phase begins at Point D. One cardiac cycle is completed at Point A as the ventricular volume resumes its initial value.

Table5.1: Material parameters of the specific model

Parameter	Description	Equation
a_1, b_1	Isotropic passive stress response	(2.12)
$a_m, b_m, a_n, b_n, a_k, b_k$	Anisotropic passive stress response	(2.12)
η	Active stress response	(2.18)
$q, k, \beta, \lambda_{\max}^a$	Evolution of active contraction	(2.19, 2.20)
α, b, c	Dynamics of the AP model	(2.23)
γ, μ_1, μ_2	Restitution properties	(2.23)
d_{iso}, d_{ani}	Conduction speed	(2.22)
$\bar{q}, m_{at}, m_{ar}, \chi, p_{at}, p_{ar}$	Pressure evolution (Signorini)	(4.7, 4.8)
C_{ap}, R_c, R_p	Pressure evolution (Windkessel)	(4.5)

Having the pressure-volume curve simulated, we can discuss some of the physiological metrics that are commonly used to assess the performance of the heart. Because our model has not the geometrical properties of a real heart, it is not

Table5.2: Values of the material parameters used for the healthy heart

Stress response	$a_1 = 0.496 \text{ kPa}, b_1 = 7.209 [-]$ $a_m = 15.193 \text{ kPa}, b_m = 20.417 [-]$ $a_n = 3.283 \text{ kPa}, b_n = 11.176 [-]$ $a_k = 0.662 \text{ kPa}, b_k = 9.466 [-]$ $\eta = 100 \text{ kPa}$
Active Contraction	$q = 0.1 [-], k = 0.07 [-]$ $\beta = 3 [-], \lambda_{\max}^a = 0.4 [-]$
Excitation	$\alpha = 0.01 [-], b = 0.15 [-], c = 8 [-]$ $\gamma = 0.002 [-], \mu_1 = 0.2 [-], \mu_2 = 0.3 [-]$
Conduction	$d_{\text{iso}} = 1 \text{ mm}^2/\text{ms}, d_{\text{ani}} = 0.1 \text{ mm}^2/\text{ms}$
Pressure Evolution (Signorini)	$\bar{q} = 228 \text{ mm}^3/\text{s}, \chi = 1 \text{ ms}/\text{mm}^3$ $p_{\text{at}} = 20 \text{ mmHg}, p_{\text{ar}} = 80 \text{ mmHg}$ $m_{\text{at}} = 5 \cdot 10^{-3} \text{ mmHg} \cdot \text{ms}/\text{mm}^3$ $m_{\text{ar}} = 8 \cdot 10^{-2} \text{ mmHg} \cdot \text{ms}/\text{mm}^3$
Pressure Evolution (Windkessel)	$C_{\text{ap}} = 950 \text{ mm}^3/\text{mmHg}$ $R_c = 10^{-3} \text{ mmHg} \cdot \text{ms}/\text{mm}^3$ $R_p = 1 \text{ mmHg} \cdot \text{ms}/\text{mm}^3$

meaningful to compare the end-systolic and end-diastolic volumes with the clinical findings although they are utilized as an indicator to know about the ventricular functioning. However, they are proportionally in good agreement with each other, meaning that their proportion can be compared with the clinical data. The most commonly used metric for this purpose is the ejection fraction (EF), that is the division of the difference between the end-diastolic volume (EDV) and the end-systolic volume (ESV) by the end-diastolic volume. A physiological value for the ejection fraction measured for the healthy heart is greater than or equal to 55% [52].

For our simulation, the ejection fraction for the healthy heart is found as follows,

$$EF = \frac{EDV - ESV}{EDV} = \frac{0.34083 \cdot 10^5 - 0.18332 \cdot 10^5}{0.34083 \cdot 10^5} = 46\%. \quad (5.2)$$

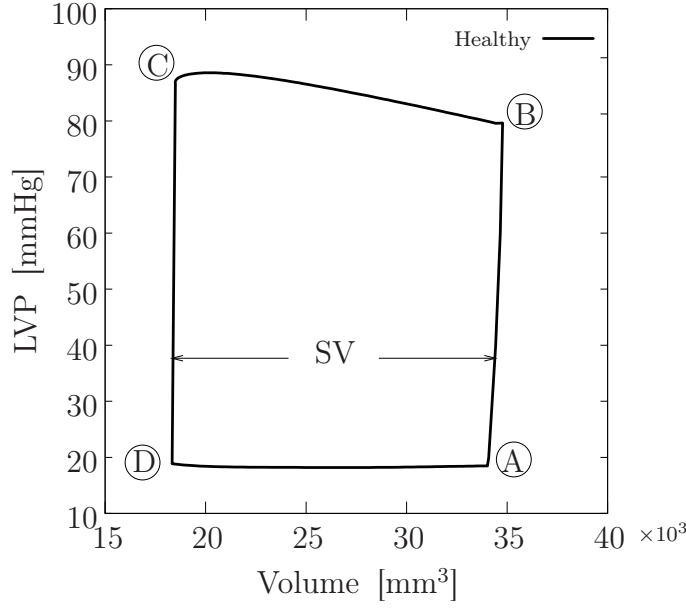


Figure 5.2: The simulated left ventricular pressure-volume curve of the generic heart model for the healthy heart.

5.3 Modeling of Cardiac Diseases

Cardiovascular diseases are the leading cause of death in industrialized nations. According to 2011 statistics published by WHO [9], the first two causes of death are cardiac-related disorders, see Figure 5.3. Over the last five decades, there have been a significant development in the clinical research carried on the cardiovascular system, resulting in a noticeable decrease in the death rate and an improvement in the diagnostic and therapeutic techniques. In addition, people are informed about the prevention methods and the importance of early action in case of a disease indicator.

Moreover, the existing medical technology has the capability to treat both the electrophysiological and mechanical disorders with less effort and in a shorter time. For example, in case of a heart rhythm disorder, the infarcted region of the heart can be ablated to prevent the uncoordinated contraction of the heart or the negative effects of the tachycardia. If the patient has a serious life-threatening rhythm disturbance and he/she does not respond to existing medical options, the cardiac resynchronization therapy (CRT) can be applied.

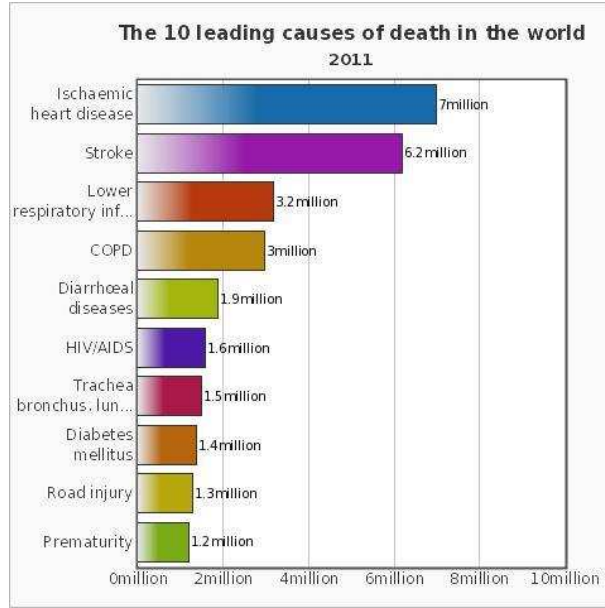


Figure 5.3: Top 10 leading causes of the death in 2011 according to WHO statistics [9].

In CRT, the simultaneous contraction of the ventricles is provided by the implantation of a small electronic device with a surgical operation. Furthermore, when there is a problem with the pumping ability of the heart, a mechanical assist device may be implanted to sustain the blood circulation and restore the mechanical performance of the ventricles. For further information on treatment options, the reader is referred to [10].

Although these techniques are currently in use and look promising as different treatment options, they are not completely reliable. To exemplify, in the ablation procedure, several problems may be faced, such as damaging the healthy tissue, stroke, pulmonary vein stenosis, even the death of the patient [90]. Moreover, CRT may have some complications, in particular concerning the device implementations that necessitate a careful monitoring period after the operation [80]. Mechanical assist devices, similar to the others, may cause serious complications. These may include the rejection of the device, bleeding, formation of blood clots, and heart stroke [44]. Among the others, the heart transplantation is considered to be a long-term solution for the patients whose diseases are almost at the end-stage. Although it saves the life of the patient, it is known that it may

result in early morbidity and mortality [62]. Perhaps, the biggest problem with the heart transplantation is the difficulty in finding the appropriate donor for the transplantation. Even it is found, there may be several complications during the post-transplantation period [21].

Although it is important to improve and widen the usage of the clinical tools used in the diagnosis and treatment of cardiovascular diseases, it is apparent that there will be several risks involved in these procedures. These may result from the insufficiency of the medical technology concerning the measurement of relevant quantities and the stresses developed in the cardiac tissue that play a crucial role in the determination of cardiac disorders [77]. At this stage, computational modeling provides a way to understand the mechanical changes in case of pathologies and to test and develop novel therapeutic methods and new drugs.

In the literature, there is an extensive research on cardiac disorders related with electrophysiological problems. These studies generally include the simulation of the action potentials and the electrocardiogram, used as an indicator for the rhythm disorders, myocardial infarction, and electrical conduction problems [16]. For the modeling of ECGs for healthy and pathological cases, we refer to [54, 43]. Moreover, there are several models on fibrillation for both the atria and the ventricles [38, 84], rhythm disorders [87, 73, 74], left bundle block [51], cardiac ischemia [75], and defibrillation [85, 24]. Compared the electrophysiological models, there is a limited number of studies on the coupled electromechanical behavior of the diseased heart. For the simulation of the pressure-volume curves incorporating the cardiac dysfunctions, the reader is referred to [50, 51].

5.3.1 Myocardial Infarction

Myocardial infarction (MI), commonly known as the heart attack, is the primary cause of the mortality and morbidity in the world [82]. It is the reason for the death of more than a million people in the U.S. each year [6]. The primary reason for the MI is the blockage of the blood flow in the heart that is caused generally by a blood clot. Cardiac muscle cells, similar to the skeletal and smooth muscles,

need oxygen and nutrients for proper functioning. In the heart, the main blood supplier is the aorta, that is the main artery in the body. It branches into the right and left coronary arteries that are composed of a network of smaller arteries, carrying oxygen-rich blood. In case of a blockage, the heart cannot be supplied with the enough oxygen and nutrients, resulting in the death of the cardiac cells. In Figure 5.4, the infarcted tissue is shown with the brownish region on a lateral slice of the ventricle. In order to prevent the possibility of the disability



Figure 5.4: The transverse heart section with the infarcted region shown in brownish color [3].

or death of the patient, it should be treated immediately. If the signs of the disease are not taken seriously, the healthy cells may be damaged because they have to work much more to maintain the normal functioning of the heart. One of the diagnostic tools, commonly used for the diagnosis of MI, is the pressure-volume curves. As indicated in Section 1.6, pressure-volume curves inform about the hemodynamic parameters, used as clinical metrics to determine the abnormality in the cardiac functioning. These are end-diastolic pressure-volume relationship, end-systolic pressure-volume relationship, and stroke volume, shown in Figure 1.10. In case of MI, the end-systolic pressure value becomes smaller during the ejection phase because the amount of blood ejected into the aorta decreases. In the pressure-volume curves, this symptom can be observed as a reduced SV and a more compliant ESPVR.

In this thesis, to model the MI, two different models with different sizes of infarcted regions are considered, so that, the effect of the infarction size on the

cardiac electromechanical activity can be observed. In Figure 5.5, the infarcted hearts (bottom) and slices are shown. The infarcted regions are shown in red, while the healthy one is represented in the blue color. The small-sized infarction extends from $\theta = 120^\circ$ to $\theta = 150^\circ$, while it is from $\theta = 110^\circ$ to $\theta = 160^\circ$ for the model with the larger infarcted region. For both cases, the height of the infarcted region is 30 mm.

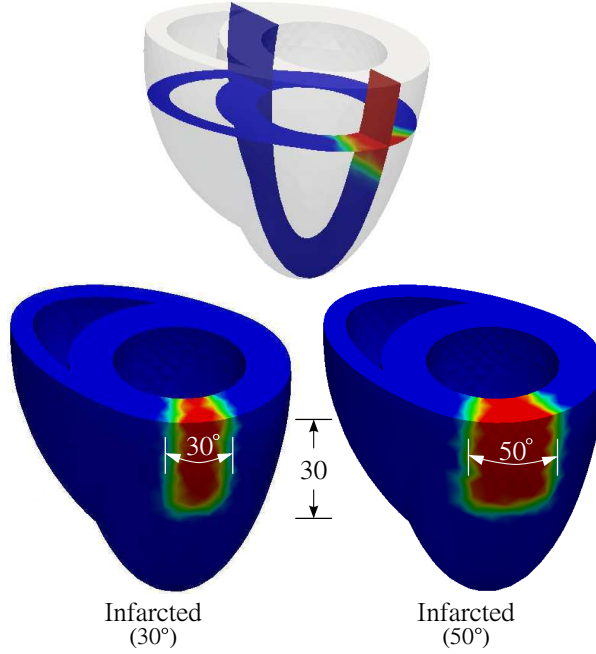


Figure 5.5: The locations of the lateral and longitudinal cross-sectional slices, used to generate the snapshots in Figures 5.6 and 5.7. The positions and dimensions of the infarcted regions (bottom). Two sizes of infarction have been considered. The smaller infarction (30°) extends from $\theta=120^\circ$ to $\theta=150^\circ$ and the large one (50°) is situated between $\theta=110^\circ$ and $\theta=160^\circ$. The height of both measures 30 mm.

In order to model the infarction, some of the material parameters given in Table 5.2 are modified to simulate the effect of MI; that is, to have the infarcted region stiffer. Therefore, the bulk modulus is multiplied by ten, and the values of the isotropic modulus a_1 and the maximum contraction $\lambda_{\max}^a$ are assigned to be $a_1 = 496kPa$ and $\lambda_{\max}^a = 1$. After the electromechanical finite element analysis of the healthy and infarcted heart models, the effect of the decreased

contractility is observed in both the cross-sectional slices of the heart models and the pressure-volume curves obtained [15].

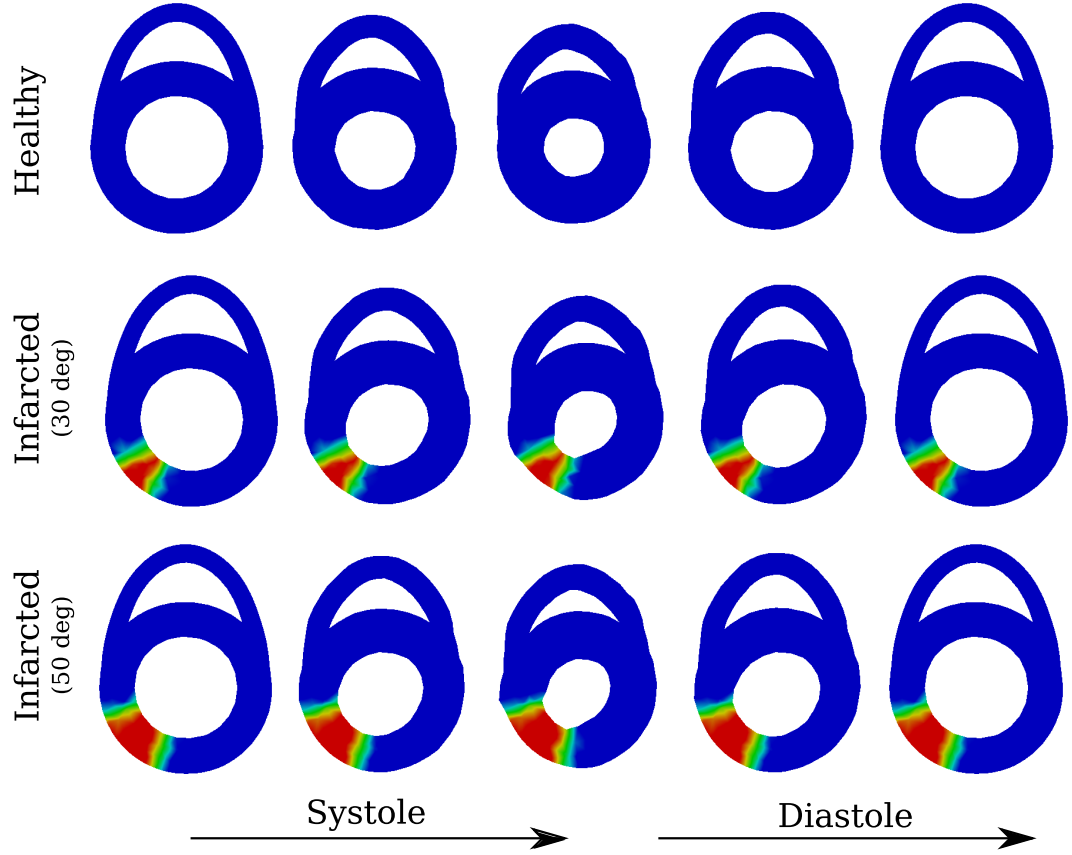


Figure 5.6: The lateral snapshots taken during a cardiac cycle for the healthy and infarcted hearts. The first row is for the demonstration of the change in the cross-sectional slice of a healthy heart during systolic and diastolic phases while the second and third ones represent the models with the small and large infarcted regions, respectively.

In Figures 5.6 and 5.7, the lateral and longitudinal snapshots are introduced for different phases of a cardiac cycle. The location of the longitudinal and lateral slices are introduced in Figure 5.5. In Figures 5.6 and 5.7, the first row stands for the healthy heart while the second and third rows represent the snapshots of the infarcted hearts with the infarcted regions of angle $\theta = 30^\circ$ and $\theta = 50^\circ$, respectively. In Figure 5.6, the physiological thickening of the ventricular walls and the twisting motion of the heart can be observed during the systolic phase (columns 1-3). The resulting decrease in the ventricular cavity volume and

the upward motion of the apex can be clearly observed in the snapshots taken longitudinally in Figure 5.7. For both Figure 5.6 and Figure 5.7 (columns 3-6), the heart is in the diastolic phase and ventricular volume continues increasing while the apex moves downward until it reaches its initial state again. The cross-sectional snapshots of the infarcted hearts are given in the second and third rows of Figures 5.6 and 5.7. Compared to the healthy heart, it is apparent that the contractile ability of the cardiac tissue is decreased for the infarcted case. Therefore, ventricular walls thicken less, thereby decreasing the pumping efficiency of the heart. In the most contracted state (Figures 5.6 and 5.7, Column 3), sharp strain gradients are observed at the tissues between the healthy and infarcted regions.

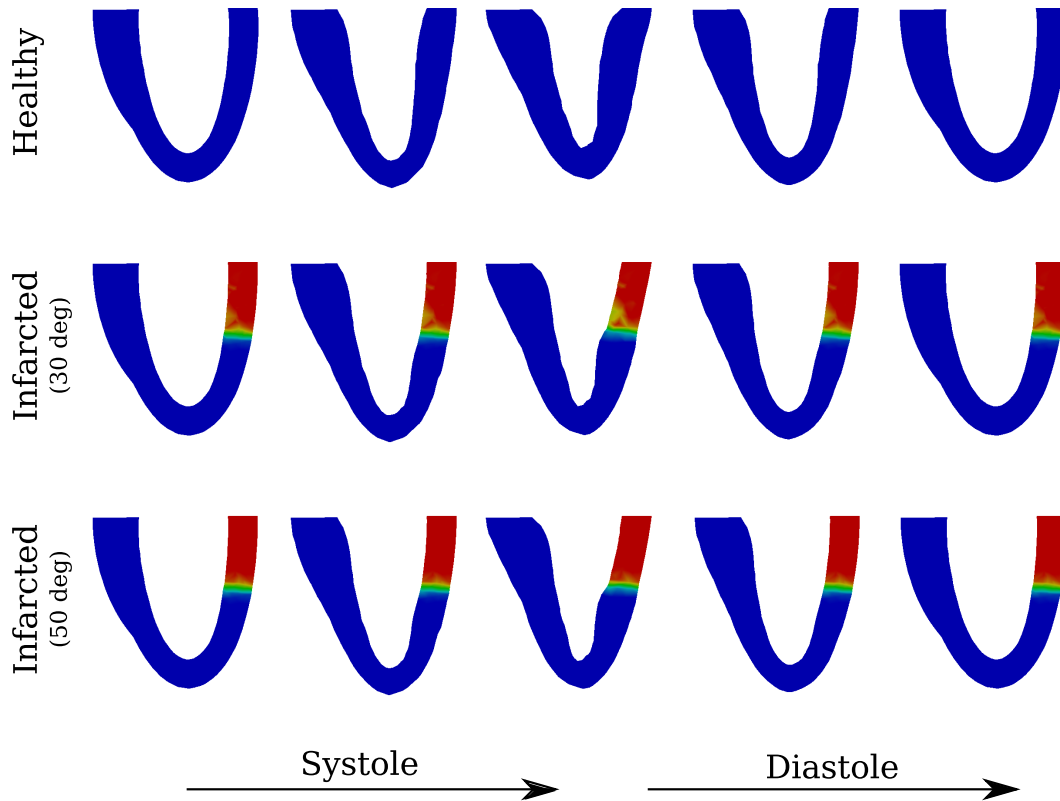


Figure 5.7: The longitudinal snapshots taken during a cardiac cycle for the healthy and infarcted hearts. The first row is for the demonstration of the change in the cross-sectional slice of a healthy heart during systolic and diastolic phases while the second and third ones represent the models with the small and large infarcted regions, respectively.

Although the effect of the infarction size on the pumping efficiency can be qualitatively observed on the cross-sectional slices given in Figures 5.6 and 5.7, this effect is better emphasized in the pressure-volume curves plotted in Figure 5.8 (left). For the modeling purposes, the value of the switch flow parameter $\bar{q}$ is changed for the infarcted hearts to calculate the left ventricular pressure. It is assigned to $\bar{q} = 198 \text{ mm}^3/\text{ms}$ for the model with small infarction (30° infarction) and $\bar{q} = 191 \text{ mm}^3/\text{ms}$ for the model with large infarction (50° infarction). This modification on the flow parameter is needed to model the sudden pressure change in isovolumic phases. When the pressure-volume curves for the infarcted cases are compared to the healthy one, it is clear that as the infarcted region size gets larger, ESPVR becomes more compliant and the ventricular pressure becomes smaller in the ejection phase. Thereby, the pumping efficiency of the heart is decreased, that is seen as a reduction in SV in the pressure-volume curves. In these cases, in addition to the effects of infarction on pressure-volume curves, the relation between the size of the infarcted region and the pumping capability of the heart is also demonstrated. The simulated pressure-volume curves (Figure 5.8, left) are shown to demonstrate the expected changes in case of an infarction (Figure 5.8, right).

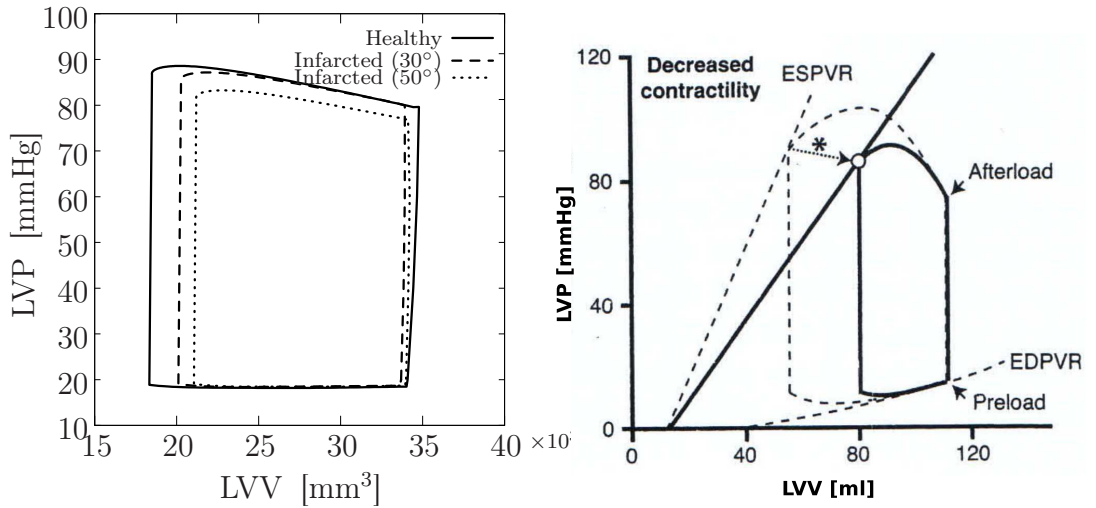


Figure 5.8: Left ventricular pressure-volume curves of the generic heart model for healthy and infarcted cases. The curve on the left is obtained through the electromechanical analysis of the infarcted heart. The expected pressure-volume curves for the healthy and infarcted hearts are shown on the right with the dashed and solid lines, respectively [45].

5.4 Concentric and Eccentric Hypertrophy

5.4.1 Generation of Hypertrophied Heart Models

Before the electromechanical finite element analysis, the concentrically and eccentrically hypertrophied heart models are generated for simulating the pressure-volume curves to observe the effects of maladaptive cardiac growth. Referring to [33] and [34], in our formulation, the deformation gradient $\mathbf{F}$ is decomposed into the elastic deformation gradient $\mathbf{F}^e$ and the growth tensor $\mathbf{F}^g$, multiplicatively. Then, $\mathbf{F}$ is written as

$$\mathbf{F} = \mathbf{F}^e \mathbf{F}^g. \quad (5.3)$$

The growth tensor $\mathbf{F}^g$ is represented by the equation

$$\mathbf{F}^g = \mathbf{1} + (\vartheta_g - 1) \boldsymbol{\alpha}_0 \otimes \boldsymbol{\alpha}_0 \quad (5.4)$$

where ϑ_g is the scalar growth field and $\boldsymbol{\alpha}_0 \in T_X \mathcal{B}$ stands for the sheet direction $\mathbf{s}_0$ in modeling concentric hypertrophy, while it represents the fiber direction $\mathbf{f}_0$ in eccentric hypertrophy. The elastic part of the deformation gradient $\mathbf{F}^e$ is obtained as

$$\mathbf{F}^e = \mathbf{F} - (1 - 1/\vartheta_g) \boldsymbol{\alpha} \otimes \boldsymbol{\alpha}_0 \quad (5.5)$$

in terms of $\boldsymbol{\alpha} := \mathbf{F} \boldsymbol{\alpha}_0$. Following orthotropic free energy function is utilized to model the passive response

$$\hat{\Psi}^g(\mathbf{g}; \mathbf{F}^e) = U^g(J^e) + \tilde{\Psi}^g(I_1^e, I_{4m}^e, I_{4n}^e, I_{4k}^e) \quad (5.6)$$

in terms of the volumetric part $U^g(J^e)$ and the orthotropic part $\tilde{\Psi}^g(I_1^e, I_{4m}^e, I_{4n}^e, I_{4k}^e)$, where $J^e := \det(\mathbf{F}^e)$ and $I_1^e, I_{4m}^e, I_{4n}^e, I_{4k}^e$ are the invariants in terms of the preferred directions that are mapped by the elastic part of the deformation gradient $\mathbf{F}^e$. The growth variable ϑ_g is considered to be a local variable and its evolution

is governed by the first order differential equation

$$\dot{\vartheta}_g = \hat{g}(\vartheta_g) \zeta, \quad (5.7)$$

where the growth limit and the speed of the growth evolution are controlled by the function

$$\hat{g}(\vartheta_g) = \frac{1}{\tau} \left[\frac{\vartheta_{\max} - \vartheta_g}{\vartheta_{\max} - 1} \right]^\nu. \quad (5.8)$$

In this equation, $\vartheta_{\max}$ is the steady-state growth. Moreover, the rate and nonlinearity of the evolution of the growth variable ϑ_g are governed by the parameters τ and ν , respectively. In Equation (5.7), the term ζ determines if the growth parameter evolves or not, meaning that if $\zeta > 0$, the growth variable evolves. In modeling of the maladaptive growth in the heart, we consider two different cases in this thesis. There are the pressure overload-driven concentric growth and the volume overload-driven eccentric growth. We incorporate them into the model through the variable ζ , given as

$$\zeta = \hat{\zeta}(\boldsymbol{\tau}) = \text{tr}(\boldsymbol{\tau}) - \pi^{\text{crt}}, \quad \zeta = \tilde{\zeta}(\lambda^e) = \lambda^e - \lambda^{\text{crt}}, \quad (5.9)$$

where the stress dependent growth criterion $\zeta = \hat{\zeta}(\boldsymbol{\tau})$ is used to model the concentric growth through the parameters $\text{tr}(\boldsymbol{\tau}) = \boldsymbol{\tau} : \mathbf{g}$, the weighted pressure, and the critical weighted pressure π^{crt} that determines the activation of the growth. The stretch-dependent growth criterion $\zeta = \tilde{\zeta}(\lambda^e)$ accounts for the overstretching of myofibers to model the eccentric growth. In this equation, $\lambda^e := \sqrt{I_{4f}^e}$ and λ^{crt} are the elastic fiber stretch and the critical elastic fiber stretch, respectively. Similar to the former one, λ^{crt} controls the growth activation in modeling the eccentric growth.

The concentrically grown heart model is generated by replacing the parameter $\boldsymbol{\alpha}_0$ with $\mathbf{s}_0$ given in Equation (5.4) and the growth parameters are assigned to $\tau = 0.1 \text{ MPa/s}$, $\nu = 2$, $\vartheta_{\max} = 1.5$ and $\pi^{\text{crt}} = 0.012 \text{ MPa}$. For the eccentrically grown model, we set $\boldsymbol{\alpha}_0 = \mathbf{f}_0$ with the growth parameters $\tau = 0.1 \text{ s}^{-1}$, $\nu = 2$, $\vartheta_{\max} = 1.2$ and $\lambda^{\text{crt}} = 1.001$. The parameters of the free energy function

used in (5.6) are chosen to be the same for the both models and given in Table 5.2. Then, the left ventricles of the hypertrophied hearts are subjected to a one-cycle pressure transient, as depicted in Figure 6 of [33]. Simulating the real case, one-fifth of the pressure is applied to the right ventricle. In Figure 5.9, the hypertrophied heart models (bottom) are introduced with the healthy one (top), indicating the contour plots of the growth variable ϑ_g . Looking at this figure, the geometrical changes in case of a maladaptive growth can be clearly observed. Figure 5.10 shows the transverse sections for the healthy and hypertrophies hearts. For the concentric growth (Figure 5.10 right), in accordance with the clinical findings, the ventricular walls are relatively thickened and the ventricular volume is decreased. For the eccentric growth (Figure 5.10 center), there is almost no change in the ventricular wall thickness while the ventricular volume is significantly increased, see also Figure 5.12.

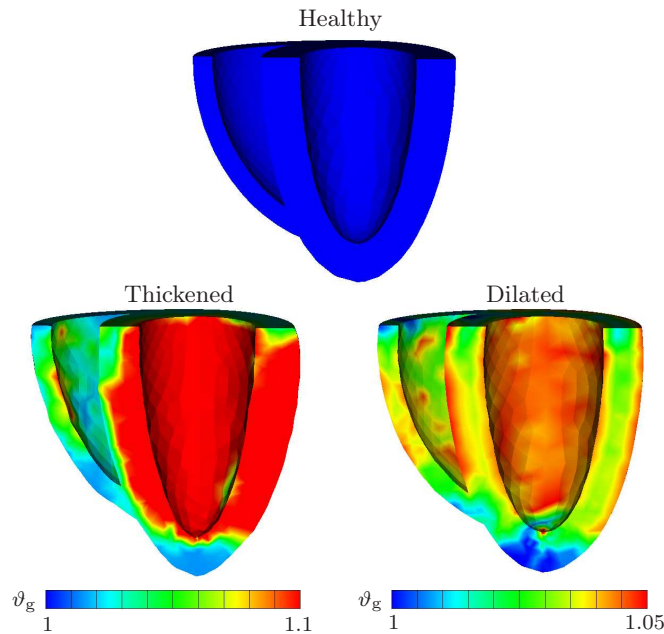


Figure 5.9: The healthy (top), concentrically hypertrophied (bottom left), and eccentrically hypertrophied (bottom right) heart models. The contour plots of the growth variable ϑ_g illustrate the distribution of the concentric and eccentric hypertrophy throughout the heart.

5.4.2 Pressure-Volume Curve Simulations for the Hypertrophied Heart Models

The effects of the concentric and eccentric hypertrophy on the cardiac pumping efficiency is shown by running the fully coupled cardiac electromechanical analysis and obtaining the related pressure-volume curves [15]. The heart models, generated to simulate the concentric and eccentric growth, have their compressibility decreased about 33% while all the other parameters given for the healthy in Table 5.2 heart remain unchanged.

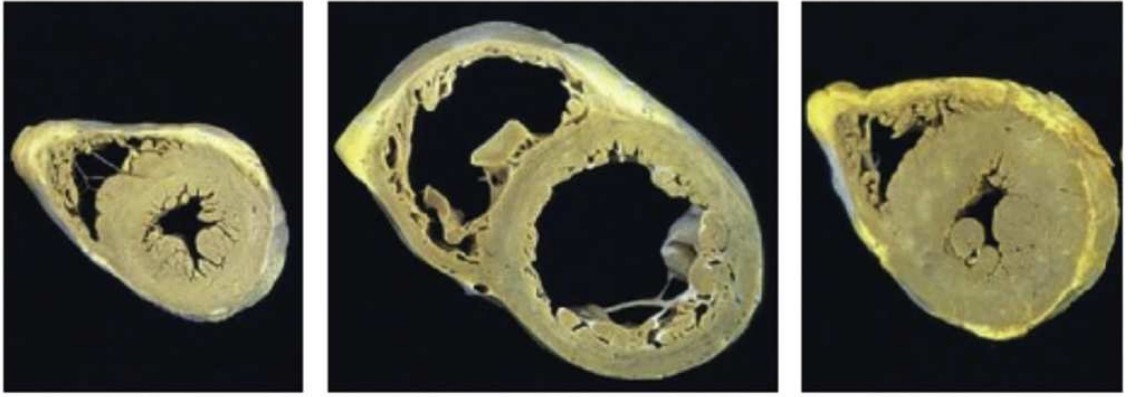


Figure 5.10: Transverse heart sections showing the maladaptive growth of the heart [12, 55]. The eccentric hypertrophy (center) is the dilation of the ventricles due to volume overload, while the concentric hypertrophy (right) is the ventricular wall thickening due to pressure overload. The geometrical changes in the ventricles for both cases can be compared with the normal heart (left).

In Figure 5.11, the lateral cross-sectional slices are shown for the healthy and the grown heart models. The first row represents the healthy heart while the second and third rows demonstrate the concentrically and eccentrically grown hearts, respectively, for a complete heart cycle. When the healthy heart model is compared to the thickened one, the difference in their initial volumes (EDV) can be realized. Moreover, the end-systolic volume (ESV) of the thickened heart is larger than the healthy one. The eccentrically grown heart model, given in row 3, has its end-diastolic volume (EDV) relatively larger than the healthy one while its ESV is the greatest one among the others.

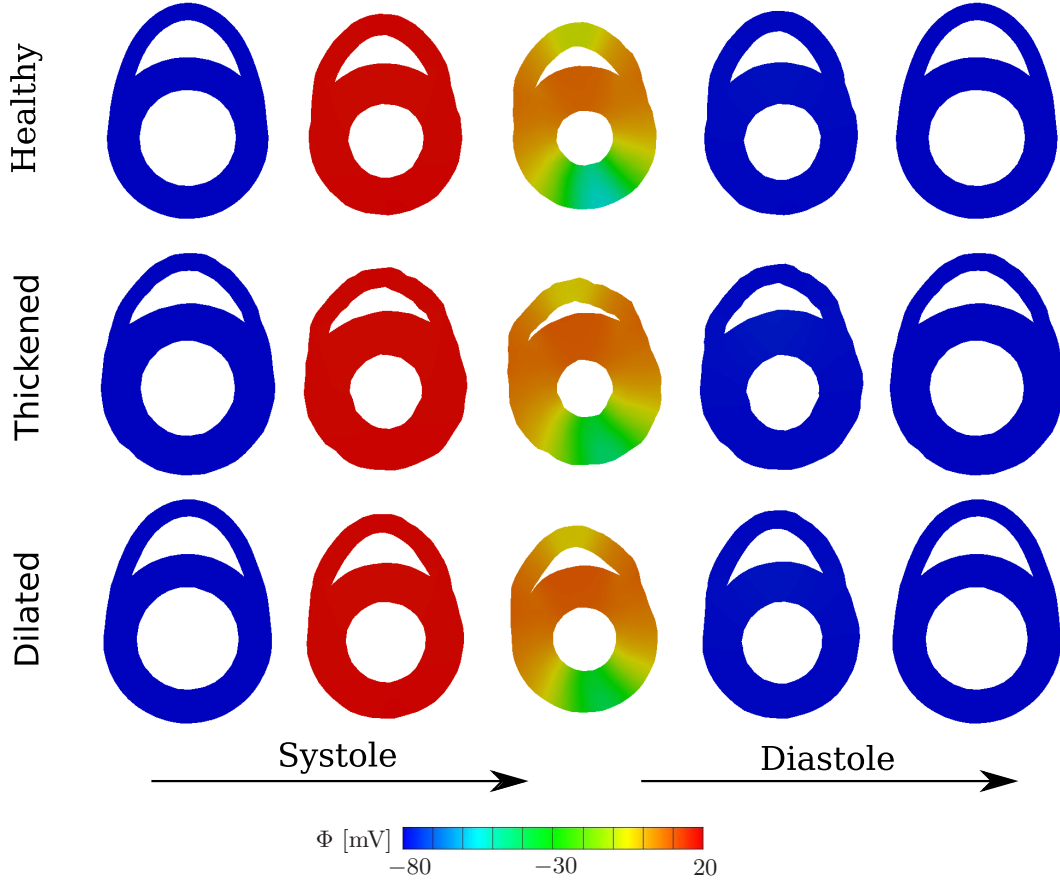


Figure 5.11: The snapshots of the lateral slices at different phases of the cardiac cycle are generated by the electromechanical finite element analyses of the normal heart (first row), the thickened heart (second row), and the dilated heart (third row). The lateral cross-section is located at $z=20$ mm as depicted in Figure 5.5 (top). The contour plots demonstrate the distribution of the trans-membrane potential Φ throughout the lateral slices.

The pressure-volume curves shown in Figure 5.12 are generated for the healthy and the hypertrophied heart models. The pressure-volume curve obtained for the thickened heart shows that the ventricular pressure during the ejection phase takes higher values and end-systolic pressure is considerably higher compared to the healthy one. On the other hand, ESV and EDV in the dilated heart model differs significantly from the healthy one.

The analysis results, shown in Figures 5.11 and 5.12, agree with the clinical observations on the wall thickening (Figure 5.10, right) and the dilation (Figure 5.10, left), see [52, 45].

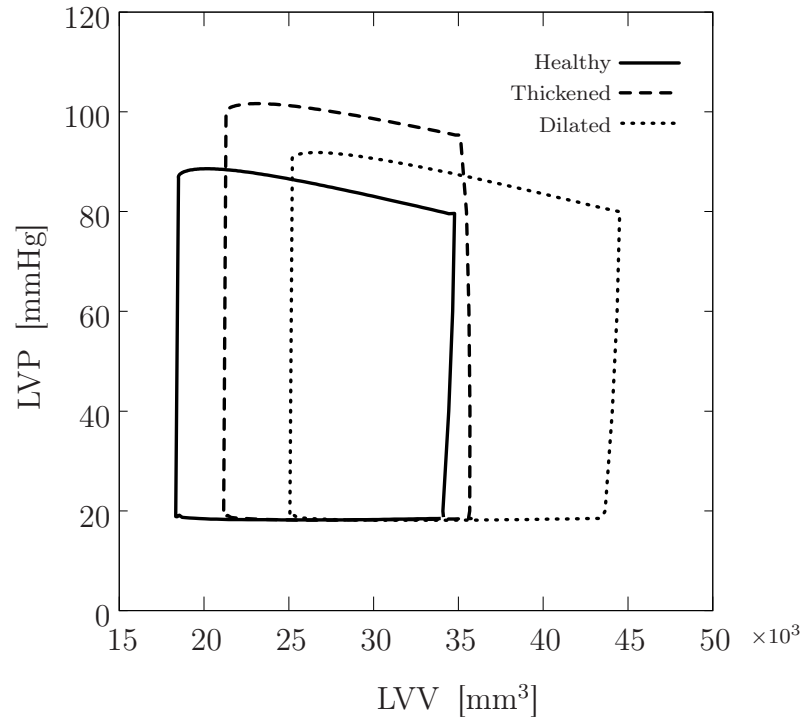


Figure 5.12: Left ventricular pressure-volume curves obtained through the electromechanical finite element analyses of the normal, thickened, and dilated heart models.

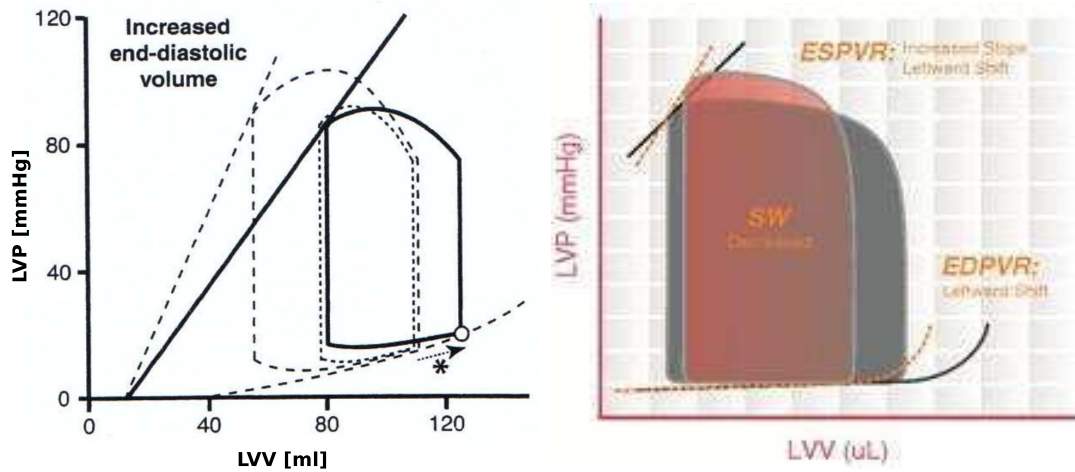


Figure 5.13: Expected clinical observations on the left ventricular pressure-volume curves for eccentric hypertrophy (left) and concentric hypertrophy (right). The curve shown with the dashed line represents the pressure-volume relation for the healthy heart while the solid line stands for the eccentrically grown heart model [45].

CHAPTER 6

CONCLUDING REMARKS

In this thesis, we have presented the computational three-dimensional heart models generated to simulate the left ventricular pressure-volume curve for the healthy and dysfunctional cases, namely the myocardial infarction, concentric hypertrophy, and eccentric hypertrophy. The simulation results are shown to agree with the clinical observations for these pathological cases.

Computational modeling of the cardiovascular system contributes to both the development of new therapeutic strategies and improvement of the existing methods, especially for the treatment of cardiac arrhythmias and pump dysfunctions [86]. The success of the computational cardiac modeling in developing novel approaches for the diagnosis and therapy of the diseases depends primarily on the individualization of the heart models. The advances in the imaging technology provides the researchers with more realistic heart geometries. Modeling of the complex physiological processes within the cardiovascular system with a detailed heart model reveals more about the cardiovascular dysfunctions compared to the clinical observations. For the current studies on the causes and termination of the cardiac arrhythmias and the analysis of drug interactions, the reader is referred to [4]. The success of computational heart models in modeling the improvement of the ventricular functioning using artificial pacemakers are also promising. The studies on the optimization of cardiac resynchronization therapy (CRT) aim to decrease the number of clinical trials for the lead positioning and to avoid the time-consuming procedures. For the related literature, we refer to [48, 49, 67, 22]. Also, incorporation of the fluid mechanics of heart valves into

the cardiac models allows the researchers to optimize the design of heart valves. This provides the most mechanically appropriate valve design with less number of in vitro or animal tests [61].

This study has demonstrated the capacity of our models to model the left ventricular pressure for the healthy heart and the change in the ventricular mechanics in case of a dysfunction through the pressure-volume curve simulations. In the literature, there are numerous studies on modeling both the electrophysiological and coupled behavior of the healthy heart. Additionally, the dysfunctions related with the electrical conduction problems within the heart have been investigated by several researchers. However, there are only few studies on modeling the pressure-volume loops for the myocardial infarction and hypertrophied heart models utilizing an electromechanically coupled model. Our work can be further extended to model several cardiac diseases, that also include the electrophysiological disorders. The pressure-volume curves obtained in this thesis may be supported by the another common diagnostic tool, the electrocardiogram. In order to achieve more realistic results and use our model to test and develop new therapies, the next step is to make our model to have the realistic heart dimensions. Then, it would also be possible to compare several hemodynamic parameters to show the performance of our model.

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