Computational Simulation of an Electrophysiological Human Heart Failure Model with an Early AfterDepolarization Arrhythmia Application

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Computational Simulation of an Electrophysiological Human Heart Failure Model with an Early AfterDepolarization Arrhythmia Application

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A dissertation submitted to the School of Graduate Studies in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

August 17th 2015
During my graduate study, after Allah’s support, guidance, and inspiration, I have received unlimited support on the personal level from countless individuals.

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Computational Simulation of an Electrophysiological Human Heart Failure Model with an Early AfterDepolarization Arrhythmia Application

by Mohamed Elshrif

Committee Approval: We, the undersigned committee members, certify that we have advised and/or supervised the candidate on the work described in this dissertation. We further certify that we have reviewed the dissertation manuscript and approve it in partial fulfillment of the requirements of the degree of Doctor of Philosophy in Computing and Information Sciences.

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Abstract

The main purpose of this thesis is to develop a population-based cellular model of remodeled electrophysiological properties in a single cell of a human ventricle under heart failure conditions. The developed model is used to study ventricular arrhythmia (VA) applications under heart failure (HF) conditions, such as inducing early afterdepolarizations (EADs) in single cells and initiating spiral waves in tissue. Early afterdepolarizations as well as reentrant waves are an important cause of ventricular arrhythmias in heart failure. However, the underlying transmural distribution of alterations in currents is unknown. Therefore, it is important to study the impact of remodeled transmural currents on inducibility of early afterdepolarization in heart failure across population-level variability. We seek to develop a population-based transmural heart failure electrophysiological model and assess the relative contribution of each ionic current in early afterdepolarization development during HF. We developed an electrophysiological model that incorporates HF-induced remodeling of related currents, pumps and exchangers as documented in the literature, by modifying a recently published model of human ventricular cell electrophysiology, namely the O’Hara, Virág, Varró, and Rudy (OVVR) model. To do so, we broke down our work into the following categories: First, we analyzed healthy human models where we implemented six cellular models under normal conditions in tissue to validate the behavior of these models. Second, we developed and analyzed a human heart failure model, where we developed a general HF model in an isolated myocyte and characterized the difference between normal and HF electrophysiological properties in a single myocyte (0D). The analysis included action potential (AP) properties, sodium concentration and
calcium dynamics. We used steady-state and S1-S2 protocols to assess the dynamics of the developed HF model. In addition, we built a more human-specific HF model and introduced population-based remodeling variability on the developed human-specific HF model for three cell types as observed experimentally. Then, the developed HF models were extended to include the analysis of a one-dimensional cable (1D) where we measured the conduction velocity (CV) under HF conditions and compared it with the normal case. Since arrhythmia can be caused by abnormal formation and/or propagation of the excitation wave, it is important to investigate the behavior of our developed models under this scenario. Therefore, we induced arrhythmia in a two-dimensional (2D) tissue by initiating spiral waves using a cross-field stimulation protocol. Then, we measured the vulnerability window, stability of reentrant waves, spiral tip trajectory, duration of induced arrhythmias, dominant action potential duration (APD) and rotation period in the myocytes that constituted the tissue during reentry. Third, we assessed the inducibility of EAD for the general HF model as well as the human-specific HF model across population-level remodeling variability for all types of human ventricular cells. Our thesis should help to elucidate the roles of alterations in electrophysiology on ventricular arrhythmia properties during HF.
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Chapter 1

Introduction

More than 15 million Americans suffer from coronary heart disease (CHD) in the United States. One-third of them suffer from heart failure (HF) and ~280,000 die yearly [71]. HF is characterized by decreased contractility and an inability of the ventricles to pump enough blood to the body.

At the cellular level, HF is accompanied by remodeling of the ion channels that govern the electrical activity of the heart. During HF, the electrophysiology and the associated arrhythmogenesis mechanisms are altered and this alteration depends on the etiology that led to HF [38]. Therefore, HF cannot be represented by a single set of electrophysiological changes. However, there are a number of consistent findings thought to be important for arrhythmogenesis. These include ion channel remodeling, altered calcium homeostasis, and increased accumulated sodium concentration [38; 70]. Many experimental studies observed altered ionic currents and exchangers in failing human ventricular myocytes [38; 40; 70; 141; 144; 174]. Moreover, non-invasive measurements have confirmed differences in membrane potential and calcium dynamics between failing and non-failing human hearts [139; 144], with potentially pro-arrhythmic implications [40; 174].

Therefore, understanding the impact of HF remodeling at the cellular level on the dynamics of cardiac electrical activity and ventricular arrhythmia properties necessitates investigating how a remodeled transmural human heart failure cellular model and its variability for each ventricular cell type affects the cellular electrophysiological properties and contributes to inducing early afterdepolarizations. This will help elucidate how the alteration of ionic channels on a single cell
could impact the related action potential properties and induce the incidence of ventricular arrhythmias. In the meantime, many researchers have studied the abnormalities at sub-cellular and cellular levels for many years on a single myocyte. However, these studies did not investigate how the heterogeneous remodeling under HF modulates the electrophysiological properties that may lead to arrhythmias considering all remodeled currents. In addition, previous studies did not introduce uncertainties in their HF models explicitly. These uncertainties may represent the averages from different HF causes or the variability between isolated myocyte samples from the investigated subject. Therefore, we constructed an HF population-based model by incorporating the upregulation and downregulation of transmembrane current conductances as observed in experiments.

1.1 Thesis Contribution

This dissertation develops a new heart failure model considering uncertainties of remodeling ionic channels. In addition, it assesses the roles of electrophysiological remodeling in ventricular arrhythmia (VA) development, e.g. early afterdepolarizations (EADs) during heart failure (HF). The main components of the thesis contribution can be summarized as follows:

1. Assessment of the behavior of human ventricular cell models in tissue level to ease selecting an appropriate model for a target application.

2. Development of an electrophysiological heart failure (HF) model, based on recent human ventricular experiments, by proposing real and precise alterations of ionic currents, permeabilities, and exchangers that may lead to one form of cardiac arrhythmia such as alternans (ALTs), or early afterdepolarizations (EADs) in an isolated myocyte.

3. Introduction of uncertainties to the developed HF model through generating a population of remodeling ionic currents based on experimental observations for different cell types.

4. Investigation of the properties such as the conduction velocity (CV) in a 1D cable of HF-remodeled cells.
5. Investigation of the properties such as the initiation and dynamics of reentry in a 2D tissue of HF-remodeled cells.

6. Prediction of the formation of early afterdepolarization (EAD) formation across population-level variability in ion channel expression for all human ventricular cells under normal and HF conditions.

1.2 Thesis Overview

This dissertation is organized into seven chapters and these chapters can be described as follows:

**Chapter 1:** Introduces the thesis contribution and reviews the structure of the whole thesis.

**Chapter 2:** Presents a background on the cardiac anatomy discipline, followed by an explanation of the types of ventricular remodeling. Then, an overview of the previous observations of anatomy remodeling for patients with HF is discussed. After that, it reviews background on the cardiac electrophysiology discipline with preceding findings on the main ionic currents and exchanger dynamics under HF conditions in lab experiments and simulation studies. Finally, a literature review for previous heart failure models is discussed.

**Chapter 3:** Presents the methods that have been used throughout the thesis. The measurement of restitution curves and accommodation is explained. Then, the spiral wave dynamics and tip trajectory methods are stated. After that, the cardiac electrical modeling in single cells and tissue is presented. The numerical methods, including the spatio-temporal discretization and boundary conditions handling are explained. In addition, the implementation tactics for efficient computation gain, which include constructing lookup tables, parallelization, and operator splitting are described.

**Chapter 4:** Presents a quantitative analysis of the behavior of human ventricular cardiac electrophysiology models in tissue under normal conditions. It
begins with describing the model formulation of the chosen ventricular cell models. Then, a comparison of the action potential shape, main transmembrane currents, and calcium transient dynamics in single cells is presented. After that, transmural variations in action potentials are mentioned. Lastly, a tissue level analysis is conducted.

Chapter 5: Presents the developed HF electrophysiological cell model with a detailed explanation of each altered ionic current and pump and how each affects the shape of an action potential (AP). Then, we present a quantitative analysis of the HF model properties in a single myocyte (0D) along with a comparison of the original undiseased model. The analysis of 0D properties includes the AP morphology, the rate dependence of an AP and the major currents and exchangers. Steady-state (S-S), S1-S2, and abrupt change restitution curves of an APD are used to assess the behavior of the developed HF model in single cells. Also, the dynamics of alternans in an isolated myocyte are investigated. The HF model properties in a single myocyte are compared with the experimental observations from the documented literature of human species when applicable. In addition, a comparison with previous HF model findings is conducted. After that, we present a quantitative analysis of the HF model in a 1D cable. The analysis of 1D cable properties includes the rate dependence of an AP and the major currents. Steady-state (S-S), S1-S2, and abrupt change restitution curves of an APD and CV were used to assess the behavior of the developed model in tissue. In addition, the dynamics of alternans in 1D tissue is characterized. Then, the HF model properties in a 1D cable are compared with experimental observations from the documented literature of human species when applicable. Finally, a quantitative analysis of the HF model in a 2D tissue is presented. The analysis of the 2D sheet includes the tip trajectory patterns of the spiral wave, dominant APD and rotation period.

Chapter 6: Presents an application of the developed HF model in single cells. An assessment of the induction of early afterdepolarization (EAD) formation for the general HF model and human-specific model across population-level variability in ion channel expression for transmural human ventricular
cells is conducted. The simulations involve varying ten ionic current parameters one at a time with fixing all other nine parameters. The assessment of inducing EADs is based on three different quantitative measurements: the onset of EAD cycle length (CL), the range of CLs for which EADs can be induced, and the number of additional peaks (upstrokes) during the induction of EADs. Lastly, a comparison with the original model is conducted, in terms of inducing EADs.

Chapter 7: Presents the conclusion, limitations, and future research directions.
Chapter 2

Background and Related Work

The heart is an important organ of the cardiovascular system and its anatomical structure is very complicated [68]. It is a synchronized muscular pump that is responsible for circulating the blood; it supplies approximately 8,000 liters of blood [155] and beats 100,000 times each day [155]. The heart contracts with each beat to circulate the blood through every part of the body, and the contraction of the heart is stimulated by the electrical activity which is known as an action potential (AP), or transmembrane potential (TMP).

2.1 Cardiac Anatomy

The heart is situated close to the anterior chest wall, directly behind the sternum, which resembles a pyramid in shape. The inferior pointed tip of the heart muscle is known as the apex and the other end of the heart, which is located posterior to the sternum, is known as the base. A common human heart measures approximately 12.5 cm between the base and apex [155]. The heart is a hollow muscular organ that consists of four chambers. They are connected vertically in pairs as the right atrium (RA) and right ventricle (RV), along with the left atrium (LA) and left ventricle (LV), as indicated in Fig. 2.1. Each pair is separated by an atrioventricular valve to prevent the back-flow of blood into the atrium, where the tricuspid valve separates the RA and RV and the mitral valve separates the LA and LV. A normal human heart is encompassed by a double-walled sac known as
the pericardium. This wall can be categorized into three layers: the epicardium layer, which is the visceral pericardium that constitutes the exterior surface of the heart, the midmyocardium layer, which is the muscular wall that constitutes both the atria and ventricles, and the endocardium layer, which covers the heart valves and forms the inner surface of the heart [155].

The primary function of the heart muscle is to pump the oxygenated blood to the whole body and the deoxygenated blood to the lungs. The oxygenated blood starts from the lungs and then travels through the pulmonary veins to the LA, after which it discharges into the LV through the mitral valve. When the LV contracts, it discharges the oxygenated blood to the whole body through the aorta. Deoxygenated blood returns to the heart from the whole body to the RA through the inferior and superior vena cava and it discharges into the RV through the tricuspid valve. When the RV contracts, it discharges the deoxygenated blood to the lungs through the pulmonary artery. The LV muscular wall is thicker than the RV muscular wall, as depicted in Fig. 2.1, because the systemic circulation, which is the general circulation of the blood through the body, has four times
higher pressure than the pressure in the pulmonary circulation, which represents
the blood flow from the heart muscle to the lungs and vice versa [53].

Each cardiac beat could be separated into two phases: systolic phase and
diastolic phase. Atria store the blood in the diastolic phase to ensure that the
ventricles are emptying the blood, while the ventricles contract in the systolic
phase. Then, the atria contract to fill the ventricles with the blood.

2.2 Heart failure progression and ventricular re-
modeling:

Heart failure is a clinical syndrome resulting from structural (anatomical) and/or
functional (electrophysiological) disorders. Under HF conditions, the muscle of
the heart wall begins gradually to weaken and enlarge. This prevents the heart
muscle from pumping enough blood to the body.

Ventricular, or cardiac, remodeling can be defined as an alteration in the
structure of the heart muscle, function of the heart muscle, or both together as a
result of hemodynamic load and/or cardiac injury. The remodeling development
could include molecular, cellular, structural, or functional alterations. During this
development process many elements are involved such as fibroblasts. However,
the main element involved in this development process is a cardiac myocyte.
Patients who had severe cardiac remodeling manifested these changes over a long
period of time [66; 206]. However, mechanisms other than remodeling also can
affect the evolution of heart disease. In addition, the heart disease progression
may develop without remodeling.

Heart failure is commonly verified by changes in cardiac dimensions and pres-
sure, and it is projected as a degradation in cardiac performance. The anatomy
remodeling could cause an increase in the ratio of chamber diameter-to-wall
thickness that is associated with elevated wall stress and ventricular dysfunction
[48; 110]. Some reports [67; 217], indicate that the chamber dilated in patients
with HF is due to excessive myocyte lengthening. Data from animal models with
HF support the concept that myocyte elongation without concomitant transverse
growth may be a hallmark of ventricular dilation and HF [127; 275]. Myocyte
length-to-width ratio increases in humans with HF from ischemic and dilated cardiomyopathy [67; 217].

2.3 Cardiac Electrophysiology

2.3.1 Action Potential Generation

The heart muscle regularly and continuously contracts without resting. Each cardiac contraction undergoes a series of electrical and mechanical events that leads to a cardiac cycle, which is the duration that the heart needs to complete all mechanical and electrical events for one period. Each cardiac cell is surrounded by an insulating thin membrane that consists of two layers of lipid molecules and whose thickness is about 7.5-10 nm, [148]. This membrane regulates the flow of ions between inner and outer space of the cell and isolates the inside of each cell from the surrounding environment. The membrane behaves as a capacitor because it stores energy in the electric field created between the inside and the outside of the cell membrane and then discharges it. However, most of the ions can travel across the cell membrane through voltage sensitive channels that are species-specific. The most important ions that pass through the membrane are sodium (Na$^+$), calcium (Ca$^{2+}$), and potassium (K$^+$). The difference in intracellular and extracellular potentials is called the transmembrane potential (TMP) or simply action potential (AP). The electrical potential across the cell membrane changes transiently as a consequence of the flow of different ions through the cell membrane. When a cardiac cell is at rest, the intracellular sodium concentration (Na$^+$) is $\sim 10mM$ compared to $\sim 145mM$ extracellularly. This means that the concentration gradient of Na$^+$ ions favors inward diffusion [62]. Likewise, the Ca$^{2+}$ concentration also diffuses inwardly because the extracellular concentration, between 1 – 2mM at rest, is much higher than the intracellular concentration, which is in the range of $\sim 50 – 300nM$. Conversely, the extracellular concentration of K$^+$, $\sim 4mM$, is less than the intracellular concentration, $\sim 135mM$, which causes the K$^+$ ions to diffuse outside the cell.

In addition, it depends on the Nernst potential (which is the voltage for which there is no net diffusion across the membrane for a given ion species in the absence
of other ions) of each channel that carries specific ions across the cell membrane. When a cell membrane is at rest, the main ion species that contributes to the membrane permeability is $K^+$, through the inward rectifying potassium current ($I_{K1}$), which will close at the Nernst potential for $K^+$ ($E_K$) at about $-96mV$. Therefore, the TMP of a cardiac cell, which is approximately between $-90mV$ and $-70mV$, is near the equilibrium potential of the $K^+$ ions [200]. At the $K^+$ equilibrium potential the outward $K^+$ ion flux from diffusion due to the concentration gradient exactly matches the inward $K^+$ ion flux, due to electrical gradient. As a result of applying an external stimulus current directly to the cell, and/or implicitly through the diffusive current from the adjacent cells via gap junctions, the TMP potential will rapidly increase and trigger cellular activation when the TMP reaches $\sim -50mV$. This activates the voltage-dependent fast sodium channels, which permit the influx of sodium ions and depolarize the cell membrane, as depicted in Fig. 2.2. The permeability of $Na^+$ channels permit $Na^+$ ions to flow inside the cell until the transmembrane potential reaches the Nernst potential of $Na^+$, which is $\sim 20mV$. This depolarization phase is maintained only for a few milliseconds because it is derived from the fast sodium current ($I_{Na}$), which inactivates quickly. These $Na^+$ ion channels remain inactivated until the TMP repolarizes below $\sim -50mV$, when the cardiac myocyte is in the absolute refractory period, which means that the cell cannot be activated during this period. During the depolarization phase, the permeability of $K^+$ ion channels is reduced. However, partial repolarization occurs due to the outflow of the $K^+$ ions, primarily through the transient outward current ($I_{to}$).

In the meantime, the late calcium current ($I_{CaL}$) is activated because the voltage increases enough during the depolarization. Therefore, the $Ca^{2+}$ channels voltage-dependence will be activated. Calcium-induced calcium release (CICR) will activate the intracellular release of calcium channels from the sarcoplasmic reticulum (SR) that causes the cell to contract. As a consequence of the relative equilibrium between the flux of calcium ions toward inside of the cell membrane and the flux of potassium ions toward outside of the cell membrane, the TMP maintained without change during the plateau phase. Through both the delayed rectifier potassium ($I_K$) and the inward potassium ($I_{K1}$) currents, additional $K^+$ channels will open and the TMP will begin to repolarize. This will cause the TMP
Figure 2.2: Ventricular action potential with a schematic of the ionic currents flowing during the phases of an action potential. The potassium current $I_{K1}$ is the principal current during phase 4, and it determines the resting membrane potential of the myocyte. The sodium current generates the upstroke of the action potential (phase 0); activation of $I_{to}$ with inactivation of $I_{Na}$ inscribing early repolarization (phase 1). The plateau (phase 2) is generated by a balance of repolarizing potassium currents and depolarizing calcium current. Inactivation of the calcium current with persistent activation of potassium currents (predominantly $I_{Kr}$ and $I_{Ks}$) causes phase 3 repolarization. Reproduced from [236]

to return close to the Nernst potential of $K^+$. During the repolarization phase, the sodium channels recover from inactivation, which allows the cardiac cell to activate again if stimulated. During this time, the cell is said to be in the relative refractory period [277]. The sodium-calcium exchanger $I_{NaCa}$ current is important for $Ca^{2+}$ handling, but it does not affect the plateau phase with its contribution during the late phase of an AP. Similarly, the sodium-potassium exchanger $I_{NaK}$ current plays a minor role in the plateau phase. Both exchangers mainly function to create and maintain the $Na^+$, $K^+$, and $Ca^{2+}$ gradients balanced across the cell membrane.
2.3.2 Action Potential Propagation

One study [277], indicated that under normal circumstances, the human heart beats \( \sim 70 \) times a minute with the timing of the heart beat cycle governed by the electrical signals. These electrical signals are driven by a small group of self-excitatory cardiac cells, known as pacemaker cells, that usually reside in the right atrium (RA). This cluster of cells is known as sino-atrial (SA) node. These specialized cells depolarize spontaneously during diastole, as a result of interaction between an inward leak of sodium ions via the \( I_f \) current, activation of T-type \( Ca^{2+} \) channels, and/or the net inward current from the \( I_{NaCa} \) current [136]. These pacemaker cells are spontaneously excited when a certain \( Na^+ \) activation threshold is reached and the L-type calcium channels are opened.

Propagation of this transmembrane potential spreads from cell to cell via gap junctions, which directly couple and allow ion diffusion between cells, throughout the RA and LA to the insulating barrier between the atria and ventricles, atrio-ventricular (AV) node. The AV node slows conduction velocity from 0.5-1 m/s to 0.05-0.1 m/s to ensure that there is a gap of time allowing the ventricles to be filled with the blood before contracting sequentially after the atria. Normally, the AV node is less driven by the SA node rhythm, which prevents automaticity of the AV node [4; 148]. Following the activation of the AV node, the ventricles activate swiftly through a specialized conduction system. This system includes the bundle of HIS, which is a group of specialized heart cells and part of the cardiac conduction system, the right and left bundle branches, and the Purkinje network, which has a rapid conduction speed about 3-5 times faster than the speed of propagation through the ventricular muscle. The bundle of HIS and the right and left bundle branches reside in the interventricular septum, whereas the Purkinje system resides on the endocardial surfaces, in humans and some animals, such as canines. The process of ventricular activation begins at the inter-ventricular septum and then propagates swiftly to the endocardial surfaces of the RV and LV, spreading to the epicardium, and from the apex to the base: see Fig. 2.3.
2.3.3 Ventricular Arrhythmia and Heart Failure

When the pathways that convey the electrical activity become structurally damaged, the normal pattern of this electrical activity gets disturbed, a phenomenon known as arrhythmia. Generally, we can classify cardiac arrhythmias into two classes, tachycardia, where the heart rate increases, and bradycardia, where the heart rate decreases. The mechanisms underlying these types of arrhythmias generally are different. It could be organized such as stable monomorphic ventricular tachycardia (VT), or disorganized electrical activity such as sinus tachycardia. Cardiac arrhythmias can be confined to the atria or to the ventricles. Atrial arrhythmias include atrial tachycardia (AT), atrial fibrillation (AF), and supraventricular arrhythmias (SVT). Ventricular arrhythmias (VA) include ventricular fibrillation (VF), ventricular tachycardia (VT), and premature ventricular contraction (PVC). VF is more severe than AF because AF causes rapid and irregular ventricular rate as well as an increased risk of stroke, whereas VF compromises the heart’s ability to pump blood, which may lead to sudden cardiac death (SCD) [95]. Mortality in the USA alone from the SCD ranges between
300,000 and 400,000 deaths annually [202; 276]. Most of these deaths, $\sim 84\%$, are caused by VT [42] because the currently available treatment is insufficient to prevent SCD, as ventricular arrhythmias degenerate quickly in a way that do not leave time to diagnose VF before it is life-threatening [89; 95; 276]. Usually, VT easily degenerates into VF [17; 226] and quickly leads to SCD.

Figure 2.4 shows the general classification of cardiac arrhythmia mechanisms. The dysfunction of cardiac electrical activity may arise either as impulse generation abnormalities, impulse propagation abnormalities, or both together [89; 90; 226; 277]. On the one hand, the abnormality occurs from the generation of the action potential and can be categorized into two main classes: spontaneous activity and triggered activity. In spontaneous activity, the rhythms can be normal or abnormal in which case other cells, besides the SA node, initiate APs (ectopic focus). In triggered activity, there are two kinds of rhythms: early afterdepolarizations (EADs), which happen with extra depolarization during either plateau phase, or repolarization phase of APs and delay afterdepolarizations (DADs), which occur with abnormal stimulation during late repolarization phase, or early resting phase of an AP.

On the other hand, the abnormality that occurs in the propagation patterns of the AP can be classified as conduction block and reentry. Block within the conduction system can occur at the SA node, AV node, or bundle of HIS, as well as in normal atrial or ventricular myocardium. The propagation of a wavefront as a spiral or scroll wave, where the electrical activation continually reenters previously excited tissue, is known as reentrant electrical activation, or simply reentry. The wave may circulate around an obstacle that is associated with anatomical structure, such as blood vessels, infarct scars, or branches of the Purkinje network where this kind of reentry is known as anatomical reentry. Alternatively, the reentry may not be associated with anatomical structure and is said to be functional reentry where the wavefront propagates around the central area of unexcited tissue [240]. In this case, refractory tissue functions the same as the anatomical structure obstacle by blocking the propagation of the electrical wavefront. Functional reentry is more common in ventricles [240] because they have fewer tissue ridges and large vessels than the atria. Reentry is considered to be an essential cause of many cardiac arrhythmias [5; 58; 75] and it may lead
to sustained tachycardia and fibrillation.

There are complicated interwoven factors that predispose patients with ventricular arrhythmias to congestive heart failure and vice versa. Also, HF could be caused by other diseases such as myocardial infarction, and cardiomyopathy.

2.3.4 Computational Modeling

Traditional experiments and mathematical models can be complementary. Ideally, researchers use experimental observations to propose an appropriate framework for mathematical models and benefit from the results of these models to improve future experiments. In this way, it is possible to verify simulation results and to make predictions for situations that are difficult to implement in the lab.

Therefore, for the last two decades, there has been a paradigm shift from experiments to computer simulations that model the electrophysiological conditions of the heart [35; 83; 122]. The reasons to use computational methods can be classified into three categories. First, often it is difficult to control the experimental environment, and it is difficult to record experimental observations without altering the physiological processes that are under investigation, because it is not always possible to isolate one component from many variables present in a heart tissue. Second, advances in computer power, speed, and capacity allow researchers to simulate electrical propagation of the heart within an anatomically realistic geometry in three dimensions. Third, advanced knowledge in understanding physiological properties of the heart at microscopic levels has allowed the advancement of more sophisticated mathematical computational models.

Cardiac electrophysiology modeling has many advantages over experiments. First, with computational models, any variable can be easily viewed at any time step in the solution domain. Second, we can create different scenarios that represent different pathophysiological cardiac conditions, through adjusting the input model parameters, and examining the effect of this adjustment on the results of the model. We can benefit from these results to forecast the behavior of new cardiac diseases and suggest suitable therapies.

Fundamentally, many models of cardiac physiology [35] are dependent on the principle of the reaction-diffusion equation [57]. However, we can classify these
Figure 2.4: General Classification of Cardiac Arrhythmias Mechanisms.
models depending on the scale of how it represents the diffusion term (simulates the propagation of the electrical wave that triggers the cardiac contraction) namely, Eikonal Models (EM), Phenomenological Models (PM) and Ionic Models (IM). EM models \cite{37, 119, 218} calculate only the time of depolarization of the electrical wave at specific spatial positions of cardiac tissue. They can be very fast to compute \cite{32}, almost in real time \cite{186} using a fast marching method \cite{54}. This type of model has one or two parameters that can control the whole model. However, it cannot be used to simulate complex arrhythmias because of the complexity of the wavefront curvature as well as its refractoriness. PM models \cite{3, 18, 60, 166} are based on partial differential equations (PDEs) in simulating the diffusion of the electrical wave at the tissue level. The PM models are more complex than EM, because the PM model can be controlled using two or three parameters, but it needs more computational resources. IM models \cite{176, 177, 232} are based on ordinary differential equations (ODEs) to simulate the propagation of the electrical waves at the cellular level including ionic interactions within the cell. These models are very complex because it has more than fifty parameters and it is very slow to compute due to the high computational cost demands. However, they are the most realistic models because they have the ability to simulate ionic currents and concentration dynamics simultaneously inside the cell. Also, we can use IM models to construct larger tissues and investigate the tissue properties, rather than investigating the single cell properties.

2.3.5 Reentry waves in a 2-dimensional sheet

One of the fastest communication systems available within the human body is the signaling information that propagates through the myocardium in the form of electrical waves. Under normal circumstances, these electrical waves stimulate the cardiac muscle to contract in a controlled and organized rhythm. Any depolarization or repolarization disturbance that occurs to these electrical excitation waves may give rise to cardiac arrhythmias. One of the most dangerous cardiac arrhythmia classes is known as reentrant ventricular arrhythmias, or simply reentry. Reentry has two forms: ventricular tachycardia and ventricular fibrillation. For ventricular tachycardia, the heart rate is increased substantially and for the ven-
tricular fibrillation, the heart rate becomes disorganized. In reentrant ventricular arrhythmias, the wavefront periodically reenters previously excited tissue where in many cases it degenerates to ventricular tachycardia, or ventricular fibrillation, which may lead to sudden cardiac death (SCD).

2.3.5.1 Reentry wave types

There is consensus among scientists that many life threatening arrhythmias begin with reentry [117; 146; 196]. For ventricular reentry to happen, two tissue conditions are required for an excitation wavefront: the excitable and unexcitable (obstacle) tissue. Based on continuing research, people classify the formation of reentrant excitation waves based on how this obstacle is formed. The reentry waves can be classified as follows:

- **Anatomical reentry**
  
The idea of reentrant activation is always associated with the wavefront propagating around an obstacle, which in this case could be infarct scars, blood vessels, or branches of the Purkinje network. When reentry is facilitated by anatomic structure, there will be a clear reentry path in the underlying structure of the tissue.

- **Functional reentry**
  
  When there is no clear path in the underlying tissue structure during reentry, it is classified as functional reentry and it is always associated with the ionic kinetics in a single myocyte.

2.4 Literature review of electrophysiological remodeling in human HF

One of the prominent hallmarks of heart failure is the prolongation of action potential duration (APD) of a failed ventricular myocyte. This APD prolongation could be caused by many underlying remodeled ionic current mechanisms such as
the decrease of an outward current \[114; 115\], the increase of an inward current \[243\], or the inactivation alteration of the calcium current \[93; 182; 256\].

Although characterizing the cellular electrical activity under heart failure conditions is essential to the electrophysiological community, few studies address this problem at the biophysical level of probing the effect of the electrical propagation on the whole myocardium. Our aim is to remodel ionic currents and exchangers on a single myocyte depending on experimental observations and investigate the effects of this remodeling on the whole myocardium. The related previous experimental observations can be classified based on the alteration (up/down-regulation) of each current and pump, which is under HF conditions compared to the control heart conditions.

2.4.1 Alterations in sodium (Na\(^+\)) currents

Generally, (Na\(^+\)) currents can be classified into two categories: fast and slow (or late). Neither the fast sodium (\(I_{Na}\)) nor the late sodium (\(I_{NaL}\)) currents, are well studied in heart failure myocytes. However, recently some research and experiments have been done to elucidate the effects of these depolarization currents on heart failure.

- Fast sodium (Na\(^+\)) current

It is widely accepted that the \(I_{Na}\) current is responsible for rapid activation (depolarization phase) of an action potential (AP) \[214; 243\] and it is the main contributing factor in determining the conduction speed at the whole myocardium level, because it provides energy to a cardiac cell that stimulates electrical propagation. Therefore, any reduction in the \(I_{Na}\) current will contribute to slowing the conduction velocity (CV) in HF \[149\], which favors reentry \[172\]. In addition, the inactivation of the \(I_{Na}\) current is important in repolarizing an AP \[210; 242\]. Accordingly, slow rates of inactivation in the \(I_{Na}\) current, which is one of the observations that accompanied cardiac arrhythmias in HF, will produce a large inward \(I_{Na}\) current during the plateau phase causing failure to repolarize the AP \[24; 241\], increasing the propensity for EADs \[241\], and tendency for life-threatening VAs \[169\].
The majority of the studies suggest that the peak of \( I_{Na} \) current is reduced under HF conditions \([65; 221; 246]\). However, these studies tested different species and have different percentages of this reduction ranging between \( \downarrow 39.3\pm6.5\% - \downarrow 91.1\pm9.3\% \). On the contrary, one study reported that the peak of the \( I_{Na} \) current is unchanged \([211]\). The findings of all these studies are summarized in Appendix B Table A.1 in chronological order with consensus studies first, followed by dissenter studies.

- Late sodium (\( Na^+ \)) current

A late sodium current is an ultraslow inactivation and reactivation current, which participates in both the plateau and repolarization phases of an AP \([120; 150; 249]\), which means that an alteration of this current will prolong or reduce an action potential duration (APD). Also, it has been reported that this current contributes to generating arrhythmias \([246]\). The \( I_{NaL} \) current is significant in maintaining the plateau phase of an AP as reported by \([150]\) in human ventricular myocytes. This means that this current can modulate the APD with a range of pacing rates, especially in HF \([150]\). In addition, this current also contributed to the repolarization phase of an AP in human and rabbit ventricular trabeculae \([249]\), which may prolong APD and participate in generating an arrhythmia in failing human and canine hearts \([246]\).

Most of the studies reported an increase in the \( I_{NaL} \) current in human and animal heart failure \([151; 152; 244; 246]\) with a wide range of enhancement \( \uparrow 30\pm0\% - \uparrow 238.5\pm1.3\% \), when compared to normal hearts. However one sole study \([150]\) observed the same maximum density of \( I_{NaL} \) current on both the normal and failing human ventricular cells. The more detailed observations of these studies are summarized in Appendix B Table A.2 in chronological order with consensus studies first, followed by dissenter studies.

2.4.2 Alterations in L-type Calcium (\( I_{CaL} \)) Current

The primary functions of this current are maintenance of the plateau period of an action potential, electromechanical coupling, automaticity, and conduction in
the SA and AV node [214]. It is also involved in the occurrence of EADs [243].

There is a massive amount of research that has been done towards the alterations of the $I_{CaL}$ current in human ventricular myocytes under HF conditions. Most of the experimental observations on HF support that the $I_{CaL}$ current is unchanged [9; 12; 14; 26; 47; 114; 133; 158; 198; 213; 215; 235]. However, a few studies found that the $I_{CaL}$ current is either down-regulated [231], or increased [188]. Table A.3 in Appendix B summarizes in chronological order the main findings of these studies in terms of species, protein, and mRNA levels.

### 2.4.3 Alterations in Potassium ($K^+$) Currents

Contrary to the sodium ($Na^+$) currents, potassium ($K^+$) currents are well established and studied in HF myocytes. These studies have linked ($K^+$) currents with heart failure.

- **Transient Outward Potassium ($I_{to}$) Current**

  This current affects the notch segment in the early phase of repolarization of an AP, especially in the epicardial cell types. Prominent $I_{to}$ current has been measured from epicardial ventricular cells isolated from different species [184]. The main contribution of the $I_{to}$ current is during the early repolarization phase of an action potential. Therefore, up- or down-regulation of this current will modulate the plateau and repolarization phases of an AP [255], as well as the other properties that are related to these phases of an AP.

  A considerable number of studies from heterogeneous transmural human cell types showed consistent findings where most of them agreed that the $I_{to}$ current is decreased on cardiac HF myocytes [13; 91; 114; 133; 164; 165; 235; 261; 274]. However, these studies differ in terms of amount of downregulation, which is ranging between $\downarrow26.4\pm1.3\% - \downarrow73.2\pm5.8\%$. In addition, some of these studies investigate the down-regulation difference in the transmural heterogeneity of the $I_{to}$ current density in normal and failing hearts [165; 261]. In contrast, a few studies [165; 261; 262] report an unchanged $I_{to}$ current density. These studies share many characteristics...
where all of these studies investigated myocytes that have been extracted from patients with end-stage HF. However, there are variabilities in cell types investigated that could explain the observation difference because within the same studies [165; 261] they observed a reduction in the $I_{to}$ current in both the sub-epicardial and sub-endocardial cell types, respectively. The observation discrepancy between these two studies could be related to the tissue sampling. In [261] study, it did not restrict their sampling tissue from a specific ventricular site. Instead, it segments a thick wall to obtain sub-epicardial and sub-endocardial myocytes. This allows large variability of the extracted myocytes that may influence the observations. In [165] study, it excised the tissue from the left ventricular anterior wall and both the sub-epicardial and sub-endocardial cells were obtained by removing the thin layer of both the sub-epicardial and sub-endocardial surface with a scalpel. Other studies have reported that the reduction in the $I_{to}$ current is accompanied by changes in the $I_{CaL}$ current, $Na^+/Ca^{2+}$ exchanger, and other currents [209; 251; 281] and it is very difficult to predict the exact changes in these currents that affect the APD and how it may degenerate to a heart failure. One study [1] observes that as a consequence of down regulating the $I_{to}$ current in HF myocytes, a prominent decrease in the spike-and-dome morphology is exhibited. The findings of all these studies are summarized in Appendix B Table A.4 in chronological order with consensus studies first followed by dissenter studies.

- **Inward Potassium ($I_{K1}$) Current**
  
  In the ventricular myocyte, the $I_{K1}$ current stabilizes the AP in resting state, and at the same time it participates in the terminal repolarization phase of an action potential [8; 114; 190; 203; 235; 236]. In addition, it contributes to forming delayed afterdepolarizations, simulating action potentials, and arrhythmogenesis in heart failure [190].

  There are many studies on ventricular myocytes that show a decrease of $I_{K1}$ current in HF hearts [2; 13; 114; 125; 132; 133; 231; 235], ranging between ↓40.0±0% - ↓64.0±2.2%. As a result of reducing $I_{K1}$, the likelihood of an arrhythmia in heart failure is increased as reported by [190]. However, there
is one investigator, Wang et al. [257] who demonstrates that the $I_{K1}$ current does not change under HF conditions. The findings of all these studies are summarized in Appendix B Table A.5 in chronological order with consensus studies first, followed by dissenter studies.

- **Rapid Delayed Rectifier Potassium ($I_{Kr}$) Current**

The ($I_{Kr}$) current contributes during the last portion of the repolarization phase of an AP. The $I_K$ current is mainly responsible for generating the repolarization phase of an action potential, controlling the duration of an action potential, as well as the refractoriness at the tissue level [255].

There are many studies on heterogeneous transmural ventricular myocytes that investigate the $I_{Kr}$ current in failing myocytes [13; 50; 114; 115; 133; 248; 258], but with controversial results. For example, one study, [133] reports that there is no change in the $I_{Kr}$ current in isolated epicardial myocytes. However, in a more recent study [50] it observes a reduction in the protein levels of $I_{Kr}$ current by ↓45.9±9.5% in single epicardial myocytes. The same observation occurs for endocardial myocytes where one study [258] found that the $I_{Kr}$ current levels do not change, while [50] observes a reduction of $I_{Kr}$ protein levels by ↓27.3±1.7%. Only one study [13], could not observe $I_K$ current in normal hearts. The variability in these findings regarding $I_{Kr}$ current may be due to the differences in the stage of HF, or the difference in isolation region as happens between [50; 258] where the first study isolates the endocardial myocytes from RV while the second study extracted it from LV. Also, most of the dissenters’ studies investigate the mRNA or protein expressions that underlie the $I_{Kr}$ current, not the density of the $I_{Kr}$ current itself, which means that this reduction may be compensated by other expressions and preserves the density of the $I_{Kr}$ current. All of the findings from these studies are summarized in Appendix B Table A.6 in chronological order with consensus studies first followed by dissenter studies.

- **Slow Delayed Rectifier Potassium ($I_{Ks}$) Current**

This current affects an AP during the late period of the repolarization phase
and more greatly when blocking $I_{Kr}$ current. At fast rates, the $I_{Ks}$ current is the important factor that contributes to the repolarization phase of an AP \cite{111}, leading the reverse use-dependence of $I_{Kr}$ blockers. However, other studies suggest that $I_{Ks}$ possesses a limited contribution during the repolarization phase of an AP. In one study \cite{130}, reports that blocking $I_{Ks}$ results in small or no effect on the duration of an AP in ventricles under normal conditions in spite of the pacing frequency. In another study \cite{247}, it shows that the $I_{Ks}$ contributes to repolarization of an AP only when the AP is abnormally prolonged. Another study \cite{255}, claims that the $I_{Ks}$ serves mainly to inhibit extreme prolongation of APD. Also, blocking $I_{Ks}$ may remove this protection process and consequently contributes to initiating such arrhythmias.

Several studies investigated the $I_{Ks}$ current under HF conditions from ventricular cells that were isolated from humans as well as from canines \cite{2; 13; 132; 133; 258}. Most of these studies agreed that the $I_{Ks}$ current is decreased in the range $\downarrow49.5\pm1.6\%$ - $\downarrow61.7\pm1.4\%$; except for two studies where this current is either not observed \cite{13}, or the mRNA is increased \cite{258}. Discrepancies between these studies could be associated with the severity level of HF, or with the underlying heart disease. For \cite{258} study, it did not observe the same levels of the $I_{Ks}$ current density. Instead, it analyzed the underlying transcripts of the $I_{Ks}$ current, which does not necessarily directly reflect the density itself. All of the findings from these studies are summarized in Appendix B Table A.7 in chronological order with consensus studies first, followed by dissenter studies.

### 2.4.4 Alterations in Sodium/Calcium ($Na^+/Ca^{2+}$) Exchanger

$I_{NaCa}$ helps to regulate intracellular $Ca^{2+}$ and it is affected by $[Ca^{2+}]_i$ and $[Na^+]_i$, concentrations as well as the transmembrane potential, where all of which are modified during HF. This means that an alteration in the $I_{NaCa}$ function will contribute to abnormally regulate intracellular $Ca^{2+}$ and $Na^+$ dynamics, and consequently the AP morphology. The sodium-calcium current is a surface membrane protein, which transfers sole calcium ions in exchange for three sodium
ions. The \( (Na^+/Ca^{2+}) \) exchanger contributes in shaping the AP profile. This exchanger current has two modes; during the forward mode, in which the \( Na^+ \) ions are transported into the cell, it initiates an inward current causing prolongation of the APD. During the reverse mode, in which \( Na^+ \) ions are transported outside of the cell, it contributes to the early plateau phase and causes shortening of an APD. However, some experimental data reports that the combination of both the forward mode and the late \( I_{CaL} \) inactivation may contribute to increase the APD [266]. In the existence of large \([Na^+]_i\) levels and small \([Ca^{2+}]_i\) levels, as observed in HF, there is an abundant \( Na^+/Ca^{2+} \)-dependent calcium inward flux during the AP [191], which eventually necessitates removing these excessive calcium ions during the diastolic phase. This makes the \( Na^+/Ca^{2+} \) exchanger an essential efflux pathway, which could facilitate a maintained inward current during the diastolic interval. The sodium-calcium exchanger prolongs an APD, causes fluctuation of the RMP, and initiates abnormal impulses [224].

The \( I_{NaCa} \) can be arrhythmogenic, due to sustained inward current simultaneous with the removal of calcium, which can initiate DADs. As a consequence of increasing the \( Na^+/Ca^{2+} \) exchanger and decreasing \( I_{K1} \) current, the likelihood of an arrhythmia in heart failure is increased, as suggested by [190]. The functional rule of this current under HF conditions is more important to calcium dynamics than in normal conditions because of changed sarcoplasmic reticulum (SR) function [45].

Direct studies of \( Na^+/Ca^{2+} \) exchanger activity under HF conditions are limited [45; 229; 235], and many studies demonstrate an increase in the \( Na^+/Ca^{2+} \) exchanger activity as well as the mRNA and protein levels ranging between \( \uparrow 80.0\pm0\%-\uparrow 200.0\pm0\% \) [61; 81; 199; 228; 229]. Generally, \( Na^+/Ca^{2+} \) exchanger mRNA and protein levels are increased under pressure overload ventricular hypertrophy. However, explicit recordings of \( Na^+/Ca^{2+} \) exchanger activity \( I_{NaCa} \) revealed significant reduction that could represent related disease remodeling in the specified \( Na^+/Ca^{2+} \) exchanger protein to the SR [212]. However, the alterations of this current under HF conditions are controversial. The same protein levels of \( Na^+/Ca^{2+} \) in human HF have been disclosed [45; 81; 215; 216; 235]. All of the findings from these studies are summarized in Appendix B Table A.8 in chronological order with consensus studies first, followed by dissenter studies.
2.4.5 Alterations in Sodium/Potassium \((Na^+/K^+)\) Exchanger

The sodium-potassium exchanger transports potassium ions inside the cell and sodium ions outside the cell according to stoichiometry of 2:3. Accordingly, it generates an outward repolarizing current. It establishes and stabilizes most of the ionic gradients that cause transport through the cell membrane [8]. Also, it maintains cell homeostasis and the excitation-contraction mechanism [227].

The majority of experimental observations claim that the expression as well as the function of \(I_{NaCa}\) current are reduced in failing hearts within a range between ↓36.0±0% - ↓56.0±0%, [22; 106; 113; 121; 145; 216; 219; 253], compared with control hearts. All of the detailed findings from these studies are summarized in Appendix B Table A.9 in chronological order with consensus studies first, followed by dissenter studies.

2.4.6 Alterations in the Intracellular Calcium \([Ca^{2+}]_i\) Handling

One prominent mechanism that occurs inside the cell is that the dynamics of \([Ca^{2+}]_i\) is found to be altered in failing cells when compared to normal cells. There is no agreement upon the direction of alteration of \([Ca^{2+}]_i\) because many currents and exchanger activities are involved in this alteration such as: \(I_{NaCa}\), \(I_{CaL}\), Sarcoplasmic Reticulum \(Ca^{2+}\) pump (\(SERCA\)), and ryanodine receptor (\(RyR\)).

In this thesis, we will focus on the SR \(Ca^{2+}\) because most of the experimental observations report that an alteration of the intracellular \([Ca^{2+}]_i\) concentration on failing human and animal myocytes is profoundly based on the contents of SR \(Ca^{2+}\).

There are two opinions about what causes the content of SR \(Ca^{2+}\) to reduce, which is either the reduction of \(Ca^{2+}\) uptake via \(SERCA\) [7; 41; 46; 79; 80; 81; 86; 107; 121; 135; 139; 144; 157; 187; 192; 268], or regulation of the efflux of \(Ca^{2+}\) via \(RyR\), [153; 154; 156]. These studies agreed on a reduction of the \(SERCA\) activity of failing myocytes within a range between ↓15.4±10.0% - ↓65.0±7%, [7; 46; 79; 81; 121; 139; 144; 157; 192; 268]. All of the detailed findings from these studies are summarized in Appendix B Table A.10 in chronological order with consensus studies first, followed by dissenter studies.
2.5 Previous HF Simulation Models

In addition to the experimental observations that prove alterations to many currents and concentrations, there are several simulation studies [72; 94; 143; 160; 161; 170; 193; 195; 222; 237; 254; 266; 267; 272; 273; 278] that aimed to simulate the remodeled AP properties during heart failure. The adapted alterations of the transmembrane currents from these simulation studies are summarized in Table 2.1. We will explain the remodeled currents of these HF models and the impact of each altered current on the HF model. In this section we focus ourselves to investigate how these models remodel their currents and exchangers. In chapter 5, subsection 5.4.6, we will compare our results with their simulation results.

For the fast sodium current $I_{Na}$, most previous HF simulation studies on a single myocyte [72; 160; 161; 193; 195; 222; 237; 254; 266; 267; 272] did not consider remodeling $I_{Na}$ in their HF models, except a few studies that consider a reduction of $I_{Na}$ [143; 273; 278] by ↓57%, 34%, and 40%, respectively. In addition, one study [170] considered scaling $I_{Na}$ by 25% - 200% from the control value. Reducing $I_{Na}$ will affect the amplitude as well as the upstroke velocity of an action potential.

Regarding the late sodium current $I_{NaL}$, previous simulation studies [143; 160; 193; 195; 222; 254; 266; 267; 278] did not consider remodeling $I_{NaL}$ in their HF models. However, more recent HF simulation studies [237; 272; 273] [72; 161; 170] believed that remodeling the $I_{NaL}$ plays a dominant role in changing AP characteristics during the plateau and repolarization phases, and as a consequence this current could alter the duration of an AP. $I_{NaL}$ is remodeled in these simulation studies through increasing the peak current density 12-fold in [273], 2-fold in [237], 6.7-fold in [272], 0.25-2-fold in [170], 2-fold in [72], and 10-fold in [161].

The former simulations of HF cell models did not consider altering the L-type calcium current $I_{CaL}$ [72; 143; 161; 170; 193; 195; 222; 237; 266; 267; 272; 278], except three studies [160; 254; 273] that remodeled $I_{CaL}$ by ↑200%, ↑↓30%, and ↑150%, respectively.

Previous HF simulation studies show agreement regarding the transient outward current $I_o$. Most of these studies reduced $I_o$ in human by ↓33% [222], ↓36% [160; 161; 273; 278], ↓40% [72], ↓60% [237], and ↓64% [143]. For animal species,
$I_{to}$ is reduced by ↓36% [195] in rabbit, ↓66% and ↓84% in canine [266; 272], and ↓66% in guinea pig [267] myocytes. Two HF models did not change $I_{to}$ [170; 193]. One study [254] perturbed $I_{to}$ in both directions by ↑↓30%.

Most of the existing simulation studies follow the findings that show downregulation of the inward rectifier potassium current $I_{K1}$ by implementing a reduction of $I_{K1}$ density between ↓25% and 68% in their HF models [193; 237; 266; 267; 272; 273] [72; 143; 160; 161; 195; 222; 278]. Two HF studies [170; 254] used the same $I_{K1}$ as in normal conditions.

Surprisingly, none of the previous simulation studies [72; 143; 160; 161; 170; 193; 195; 222; 237; 266; 267; 272; 273; 278] considered remodeling the rapid delayed rectifier potassium current $I_{Kr}$ in their HF cellular models to investigate the effects of this current on AP characteristics. Only one study [254] considered investigating the effect of $I_{Kr}$ by ↑↓30%.

Similarly, most of the previous HF simulation models [72; 160; 161; 170; 193; 195; 237; 266; 267] did not investigate remodeling the slow delayed rectifier potassium current $I_{Ks}$. However, there are a few studies [143; 222; 254; 272; 273; 278] that integrated a reduction of $I_{Ks}$ within the range ↓30% - 50%. One study [273] did not specify the percentage reduction in $I_{Ks}$ density used in the paper.

In addition, many HF studies [72; 143; 160; 161; 195; 222; 237; 266; 267; 272; 278] remodeled the sarcoplasmic reticulum calcium SERCA activity ranging from ↓24% to 85%, along with one study [273] which did not specify the percentage of reduction. One study [170] scaled SERCA by 25% - 200% from the original value. In addition, one study [254] considered perturbing SERCA activity by ↑↓30%. One sole study [193] did not consider remodeling SERCA.

On the contrary, most of the preceding HF simulation models realized the importance of incorporating remodeling of the sodium calcium exchanger $I_{NaCa}$. Therefore, an upregulation was incorporated with a broad range of ↑36% to 200% in these HF models [72; 143; 160; 193; 195; 222; 237; 266; 267; 272; 273; 278]. One study [254] perturbed $I_{NaCa}$ by ↑↓30%. Also, two studies [161; 170] did not consider remodeling this current in their HF models.

For the sodium-potassium pump $Na^+/K^+$, some of the HF cellular models incorporated remodeling $I_{NaK}$ through reducing its conductance ($G_{NaK}$) by ↓10% [193] and ↓42% [237; 273] [143]. One study [161] chose to use the range of these
<table>
<thead>
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<th>Model</th>
<th>Species</th>
<th>$I_{to}$</th>
<th>$I_{Na}$</th>
<th>$I_{Ca}$</th>
<th>$I_{Kt}$</th>
<th>$I_{Ks}$</th>
<th>SERCA</th>
<th>$I_{Na,Ca}$</th>
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<th>$I_{leak}$</th>
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<td>human</td>
<td>-</td>
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<td>↓(42%)</td>
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<td>Zhang et al. [273]</td>
<td>human</td>
<td>↓(57%)</td>
<td>↑(1200%)</td>
<td>↓(36%)</td>
<td>↑(200%)</td>
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<tr>
<td>Trenor et al. [237]</td>
<td>human</td>
<td>-</td>
<td>↑(200%)</td>
<td>-</td>
<td>↓(36%)</td>
<td>↑(25%)</td>
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<tr>
<td>Winslow et al. [266]</td>
<td>canine</td>
<td>-</td>
<td>↓(66%)</td>
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<td>↓(32%)</td>
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<tr>
<td>Zang et al. [272]</td>
<td>human</td>
<td>-</td>
<td>↑(670%)</td>
<td>-</td>
<td>↓(84%)</td>
<td>↓(35%)</td>
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<td>T(220%)</td>
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<tr>
<td>Walmsley et al. [254]</td>
<td>human</td>
<td>-</td>
<td>-</td>
<td>$I_{Na,Ca}$ $I_{Na,K}$ $I_{leak}$</td>
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<tr>
<td>Shannon et al. [222]</td>
<td>human</td>
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<td>$I_{Na,Ca}$ $I_{Na,K}$ $I_{leak}$</td>
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<tr>
<td>Moreno et al. [160]</td>
<td>human</td>
<td>-</td>
<td>↑(150%)</td>
<td>-</td>
<td>↓(36%)</td>
<td>↑(65%)</td>
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<tr>
<td>Winslow et al. [267]</td>
<td>guinea pig</td>
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<tr>
<td>Zlochiver [278]</td>
<td>human</td>
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<td>$I_{Na,Ca}$ $I_{Na,K}$ $I_{leak}$</td>
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<td>Shannon et al. [222]</td>
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<tr>
<td>Moreno et al. [161]</td>
<td>human</td>
<td>-</td>
<td>↑(1000%)</td>
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<td>↓(36%)</td>
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<tr>
<td>Buglisi et al. [195]</td>
<td>rabbit</td>
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<td>Narayan et al. [170]</td>
<td>human</td>
<td>-</td>
<td>↑(200%)</td>
<td>-</td>
<td>↓(40%)</td>
<td>$I_{to}$</td>
<td>-</td>
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<tr>
<td>Moren et al. [166]</td>
<td>human</td>
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<tr>
<td>Narayan et al. [170]</td>
<td>human</td>
<td>-</td>
<td>↑(200%)</td>
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<tr>
<td>Moreno et al. [161]</td>
<td>human</td>
<td>-</td>
<td>↑(1000%)</td>
<td>-</td>
<td>↓(40%)</td>
<td>$I_{to}$</td>
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<tr>
<td>Lu et al. [143]</td>
<td>human</td>
<td>↓(40%)</td>
<td>-</td>
<td>$I_{to}$</td>
<td>$I_{Na,Ca}$</td>
<td>$I_{leak}$</td>
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<tr>
<td>Moreno et al. [161]</td>
<td>human</td>
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</table>

Table 2.1: Summary of the changes in the main currents during HF as suggested by HF simulation studies. + Trenor et al. [237] $EC_{50,SR}$ ↓(11%). * Shannon et al. [222] $I_{to,slow}$ ↓(35%). # Lu et al. [143] ↑(23%). Gomez et al. [72] ** $\tau_{hL}$ ↑(200%).
previous studies, ↓10% - 42%. In addition, one study [72] remodeled $I_{NaK}$ by ↓90%, while the rest of the HF models [160; 170; 195; 222; 254; 266; 267; 272; 278] did not remodel this pump.

Regarding background currents, most of the previous HF models did not change the sodium background current $I_{Nab}$, except one study [161], which increased $I_{Nab}$ 16-fold. However, some of these HF studies [193; 218] altered the calcium background current $I_{Cab}$ by ↑25%, while [237] [72] altered this current by ↑153%. One study [143] did not specify the percentage of remodeling $I_{Cab}$.

For $I_{leak}$, many of the previous HF models [94; 143; 170; 193; 195; 254; 266; 267; 272; 273; 278] did not consider remodeling this current. However, a few studies [72; 160; 161; 222; 237] increased this current with disparate percentages of ↑500%, 300%, 30%, 300%, and 350%, respectively. In addition, two studies [143; 222] considered remodeling the ryanodine receptor (RyR), but with opposite direction of remodeling. One study [222] incorporated an increase of RyR activity by ↑300%, while [143] considered a reduction of RyR activity by ↓50%.

Concerning remodeling heterogeneous cell types, most of the previous HF models [143; 160; 161; 170; 193; 195; 222; 237; 254; 266; 267; 273; 278] remodeled a single cell type, except for two studies [72; 272], which considered remodeling three transmural types of cells. One of these studies [272] did not remodel the statistical difference between cell types during HF as observed experimentally, instead, it used the same remodeling parameters setting across all types of cells. In addition, the other [72] considered remodeling only two types of ionic currents, $I_{NaCa}$ and $I_{SERCA}$.

Most importantly, most of the previous HF models [72; 143; 160; 161; 193; 195; 222; 266; 267; 272; 273; 278] incorporated a fixed set of remodeled current, exchanger, and pump parameter values without introducing any kind of uncertainty to the remodeling parameters. However, a few studies [170; 237] considered different ways of including uncertainty. One study [170] scaled the sarcoplasmic reticulum calcium uptake current $I_{up}$ by 25% to 200% as well as the time constants of fast and slow sodium channel inactivation $\tau_{h,j}$ by the same scale. In addition, [237] performed a sensitivity analysis of ionic currents by ±15% to assess the sensitivity of electrophysiological biomarkers to changes in ionic current properties. Another study [254] generates a population for both normal and HF
Figure 2.5: Afterdepolarizations. Abnormal oscillations that occur either during (EAD) or following repolarization (DAD) of the action potential. Figure adapted from [82].

cellular models through perturbing the $G_{CaL}$, $G_{lo}$, $G_{K1}$, $G_{Kr}$, $G_{Ks}$, $G_{NaCa}$, and $J_{up}$ ionic parameters by ±30%.

2.6 Afterdepolarization proarhythmias

Generally, afterdepolarization arrhythmias [234] are irregular oscillations of the action potential, which occur either before or after full repolarization of the AP as depicted in Fig. 2.5. When the irregular oscillations occur prior to the AP repolarization phase, it is referred to as early afterdepolarization (EAD); whereas when the irregular oscillations occur following the AP repolarization phase, it is referred to as a delayed afterdepolarization (DAD). In tissue level, when these irregular oscillations propagate between cells as an excitation wave, it is referred to as triggered activity.

2.6.1 Early afterdepolarizations (EADs)

There are many possible mechanisms for setting the stage to induce EADs through prolonging an APD [25]. This prolongation could be a result of increasing the total inward currents over the total outward currents, or reactivating the L-type $Ca^{2+}$ current. While all these mechanisms for inducing an EAD are possible, they depend on magnitude rather than time. Therefore, these mechanisms can not explain precisely the induction of an EAD with multiple oscillations (see Fig.
Figure 2.6: EAD with multiple oscillations. Epicardial cell type of the HF-OVVR model with decreasing $I_{Kr}$ to 78%.

2.6.2 Delayed afterdepolarizations (DADs)

Although DAD is outside the scope of this chapter, it is important to mention it because its mechanism is involved in a subset of EADs, especially during the EAD phase 3, which occurs after the repolarization phase of an AP via the sodium-calcium exchanger (NCX) [25]. The process of reverse excitation-contraction coupling occurs through the calcium transient, which induces a voltage response as shown in Fig. 2.7. DADs occur when the intracellular $Ca^{2+}$ is sufficiently high to produce a significant enough NCX-mediated inward current to produce a bump in the membrane potential following repolarization [25]. In the case that this oscillation depolarizes with enough magnitude and rate to activate sodium channels, then either all-or-none AP is initiated. This abnormal AP could propagate through the whole myocardium and constitute what is known as an ectopic beat.
Figure 2.7: Delayed afterdepolarization (DAD). DADs that rise with sufficient rate and magnitude can trigger another action potential. Figure adapted from [25].
Chapter 3

Methods

The purpose of this chapter is to present the methods that have been used in this thesis. We begin with the procedure of measuring the restitution curves using steady-state and S1-S2 protocols and accommodation of action potential duration. Then, we explain the measurements used to assess the spiral wave dynamics, which include initiating spiral wave, tracking the tip trajectory, calculating dominant action potential duration and period, and assessing spiral wave motion. After that we explain the implemented numerical methods used to model cardiac cells and tissue. Then, we discuss some implementation tactics used to increase the computational efficiency. These strategies include creating lookup tables, parallelization, and operator splitting. Finally, we present the experimental data used in this thesis, which include data sources, measurement conditions, measuring variability, and calculating electrophysiological biomarkers.

3.1 Measurement of restitution curves and accommodation

In order to study how the cycle length (CL) perturbation affects the ventricular APD, two common protocols were implemented: steady-state restitution (S-S), and S1-S2 restitution, along with probing the accommodation of APD to a single change in CL for single cells (0D) and in one-dimensional (1D) cables. For every protocol, we generated APs using a current strength twice diastolic threshold at
a CL of 1000 ms; in the 1D case, the stimulus was applied only to one end of the cable. APDs were assessed by measuring the repolarization voltage thresholds corresponding to 90% ($APD_{90}$) and 50% ($APD_{50}$) after pacing for 1 min at the corresponding CL. APD measurements in 1D were taken from the middle of the cable to minimize the effects of current stimulation and the boundaries [30].

For the steady-state protocol, the targeted myocyte was stimulated for 1 min beginning from a CL of 1000 ms, after which the CL was decreased in steps until 2:1 block was observed. For every CL, the last APD and the prior diastolic interval (DI) pair were recorded. However, when the targeted myocyte exhibited alternans during pacing process, the last two DI and APD were registered. For the S1-S2 protocol, the intended myocyte was stimulated for 1 min with a constant CL, which is known as S1, after which a second stimulation (S2) was used after a variable DI. The last pair of DI and APD was recorded. The amplitude of short-term memory (STM) was computed as the variation between APD values for the maximum DI at the highest S1 CL, which is in our simulations 1000 ms, and the lowest S1 CL before block or alternans was noticed [29].

In addition, we adapted a protocol for measuring the accommodation of APD to an abrupt change in CL, since this protocol was recommended as a clinical marker for arrhythmia risk [194]. We follow the same procedure from the preceding studies [63; 128] to construct the accommodation curve by recording $APD_{90}$ at a CL of 1 s after pacing for 8 min, after which the CL was abruptly decreased to 600 ms for a similar pacing period (8 min). Then, the CL was restored to 1 s for another 8 min pacing period (for more details see [51; 52]).

Note that it was not always possible for the models to reach a stable steady state, even when assigning a charge carrier to the stimulus current and axial current in tissue [96]. For example, the difference between consecutive APDs after pacing single cells using the Grandi-Pasqualini-Bers (GPB) and O’Hara, Virág, Varró, and Rudy (OVVR) models at a constant CL for 5 minutes was on the order of $10^{-4}$ to $10^{-3}$ ms, as indicated in Table 3.1. Although the difference between successive APDs was decreasing, it did not appear to saturate.

We used the same steady-state and S1-S2 protocols to measure conduction velocity (CV) restitution curves in 1D cables. The CV was measured between two adjacent cells in the middle of the cable to minimize boundary effects. The
resulting CV values were plotted as a function of the preceding DIs recorded in each restitution protocol. S1-S2 CV restitution curves obtained using different S1 CL values were used to assess the presence of memory in CV [18].

### 3.2 Measurement of spiral wave

**Spiral wave dynamics** Many mechanisms for functional substrate to facilitate reentry have been proposed, but the current state of the art focuses on modeling spiral waves. Spiral waves are continuously rotating spirals around a distinct point. The center of spiral waves is known as the spiral core, or phase singularity [21; 43; 55]. In spite of the excitability of this region, it stays unexcited while the spiral waves rotate. This is due to the large curvature of the wavefronts at the spiral tip, which reduces the amount of current available to depolarize this region [10]. The reentrant wavefront that rotates around a phase singularity is known as a rotor [55].

- **Spiral wave initiation**
  
  Spiral waves were initiated in two-dimensional (2D) isotropic and homogeneous tissue sheets using a cross-field stimulation protocol [64].

- **Tracking the spiral wave tip trajectory**
  
  The spiral tip trajectory was tracked using the zero normal-velocity method [56] by detecting spiral tips as the intersections of the isopotential line $V = 260$ mV and the line $dV/dt = 0$ for all models except...
for the OVVR midmyocardial cell type, for which we used the isopotential line $V = 265 \, \text{mV}$.

- Dominant APD and period
One mechanism to obtain the valuable information for understanding arrhythmias is to investigate the distribution of action potentials over both the single cell and the entire tissue. Here, we extract the spatiotemporal distribution of the transmembrane potentials over the whole tissue used.

Histograms of APD, diastolic interval (DI), and cycle length (CL) values measured to the nearest 1 ms were developed from all points in the 2D sheet during the simulation and were used to calculate the dominant APD and dominant spiral wave period for each model.

- Spiral wave motion
Spiral waves may remain stationary in a small region, or they may jump and drift, giving rise to multiple dynamic reentrant pathways. We measured the movement of the tip trajectory.

### 3.3 Cardiac electrical modeling

In this part, we aim to explain how the numerical methods are implemented for modeling cellular models used in this thesis including our developed HF model in tissue. The numerical simulation of an evolving time and spatial extension system, like the reaction-diffusion system we have, which describes the propagation of electrical signals within the myocardium, requires both temporal and spatial discretization. In addition, it requires a computational algorithm that can handle and track model dynamics that evolve over time, especially with this nonlinear cellular model we use. The spatiotemporal coupling approach could lead to very different simulation results in terms of precision and the computational complexity (such as the time needed to run the simulation). However, based on the spatiotemporal discretization chosen, some schemes may be unsuccessful in reaching the solution because of a loss of the numerical stability as the simulation runs (such as capturing the upstroke velocity and calcium dynamics). In the case
of cardiac propagation involving two coupled subprocesses, one reactive and one diffusive, both are potential candidates for a loss of numerical stability. Their coupling could also potentially induce a loss of stability, even if each one of them taken individually leads to stable solutions.

3.3.1 Time discretization

Determining an optimal time step for a cardiac cellular model in tissue is a complex decision, which is based on many factors, including the chosen numerical approach and the used cellular model. In addition, it depends on the anatomy’s geometrical characteristics. The decision should not be to ensure the stability of the chosen numerical approach. However, it should consider that the outcome of the model fulfills the accuracy requirements. The purpose is to guarantee that fast mechanisms like the upstroke of an AP and the calcium dynamics are accurately resolved temporally. One approach to fulfill these requirements is to choose the time step depending on the dynamics of the reaction-diffusion characteristics. The speed of depolarized action potential could be used to measure the maximum temporal resolution limit. Simultaneously, there is no agreement on the exact value that should be used. Previous simulations on real geometries used temporal resolution within a range of 0.01 ms - 0.02 ms to consider the diffusion term of the cardiac cellular model, along with lower temporal resolution for the membrane dynamics of the cell.

There are three techniques that have been adapted to determine the time dependence of AP propagation: explicit, implicit, and semi-implicit techniques. The choice of any of these techniques will influence the aforementioned characteristics including the numerical stability of the model, the accuracy of the results, and the efficiency of the model implemented. One approach to overcome the numerical instability for the diffusion part of the model is to compute it explicitly for each time step. The ordinary differential equation (ODE) system of equations for membrane potential and ionic dynamics in all cellular models was calculated utilizing the forward Euler method. This was used because it has low computational cost to integrate temporally and because of the ease of implementation. However, it needs to have a small enough time step to ensure that the
cardiac tissue model is stable. In the case of implementing either semi-implicit, or implicit approaches, high temporal resolution can be implemented without worrying about the numerical instability. However, when a temporal resolution becomes very large, it can cause faults in conduction velocity, as mentioned in the preceding studies (Cherry et al., 2003; Courtemanche, 1996).

3.3.2 Spatial discretization

Finding an optimal space resolution for cardiac cellular models in tissue is nontrivial because it depends on many factors, including the chosen numerical approach and the cellular model used. In addition, it depends on the anatomy’s geometrical characteristics. This optimal space resolution should not be decided upon merely to ensure the stability of the chosen numerical approach. However, the outcome of the model does need to fulfill the accuracy requirements. The purpose is to guarantee that fast mechanisms like the sharpness of spatial gradients (propagating wavefront), are accurately resolved spatially. One approach to fulfill these requirements is to choose the space step size depending on the dynamics of the reaction-diffusion characteristics. The size of the wavefront could be used to measure the maximum spatial size limit. However, there is no agreement on the exact value that should be used. Previous simulations on real geometries used spatial resolution within a range of 0.1 mm - 0.2 mm. In higher dimensions such as 2D and 3D, space resolution can be an integral part for exploring the dynamics of the tissue model. Choosing inappropriate spatial resolution can cause curved wavefronts to develop corners, even with using finite difference methods on a uniform lattice. A previous study (Cherry 2010) shows that the corners could develop 45-degree angles. The spatial resolution required to prevent these diversions differ between models and depends on the steepness of the upstroke for the specific model. This type of distortion has greater effect on model kinetics that are under HF conditions due to more complicated model scenarios such as complex spiral wave trajectories, which may cause model instability. When anisotropy is considered, extra spatial resolution constraints should be considered. Also, choosing coarse spatial resolution may affect the fast sodium current as shown by Spaach and Kootsey, and Wu and Zipes with all related properties.
such as increasing upstroke velocity and decreasing CV.

In addition to the aforementioned electrophysiological properties in tissue such as the CV, shape of the wavefront, trajectory of the spiral wave, and reentrant rotation period, inappropriate space size could affect simulation results in many different ways. Choosing large spatial discretization could induce spiral wave breakup whilst small spatial discretization produces stable spiral waves (Fenton et al., 2002; Panfilov and Keener, 1995). In addition, the opposite may happen. For example, using large spatial discretization will cause stable tip trajectories. However, small spatial discretization produces spiral wave breakup (Bueno-Orovio et al., 2008; Panfilov, 2002). Therefore, one of the prominent electrophysiological properties in a 1D strand that should be considered is the conduction velocity. It was reported to be highly sensitive to the spatial discretization.

3.3.3 Single cells

Modeling cardiac electrophysiology can be classified into two processes: the reaction process that represents the simulation of an action potential in an isolated myocyte, and the diffusion process that represents the propagation of the current between cells. Generally, when modeling cardiac electrophysiology in tissue, there are two dominant approaches used, namely monodomain and bidomain. The monodomain approach represents the intracellular space of the tissue and it is sufficient to use in many applications, such as simulation of wave propagation. However, the bidomain approach represents both, intra- and extra-cellular spaces in the tissue. It is also beneficial if we need to consider extracellular conductivities or investigate the effects of stimuli bath, for example. The bidomain approach gives greater realism, but it comes at the cost of computational time.

In this work, the following differential equation was used to describe the time-dependent electrophysiological behavior of a single normal myocyte [181]:

\[
\frac{dV_m}{dt} = -\frac{(I_{\text{ion}} + I_{\text{stim}})}{C_m}
\]

where \(V_m\) is the transmembrane voltage; \(t\) is time; \(I_{\text{ion}}\) is the total of all transmembrane ionic currents, pumps, and exchangers; \(I_{\text{stim}}\) is an external stimulus current; and \(C_m\) is the cell membrane capacitance.
Time derivatives were integrated uniformly using the explicit Euler method to solve the ordinary differential equations (ODEs) of the AP and concentration dynamics of the cellular model. The integration of the ionic gating variables was implemented using the Rush and Larson method [207]. The time resolution used for all models were 0.02 ms, except the calcium equations of the OVVR model were integrated with a smaller time step of 0.001 ms. All single-variable functions were pre-computed and saved in lookup tables [87] to reduce the computational time. Action potentials were stimulated using a transmembrane stimulus current 32.0 µA/µF for 2.0 ms.

All simulations were written in Fortran 95, visualized using MATLAB, and run on a MAC Pro 2×2.8 GHz Quad-Core Intel Xeon CPU with 32 GB 800 MHz DDR2 FB-DIMM RAM. It took 1.3 minutes to simulate 60 seconds of physical time and performing the whole simulation for each cell type under one set of conditions took 2.2 hours.

### 3.3.4 One-dimensional cables

In all cases, we solved the following monodomain representation of cardiac tissue:

\[
\partial_t V_m = D \partial^2_x V_m - I_{ion}/C_m
\]  

(3.2)

Where \(V_m\) is the membrane potential, \(D\) is the diffusion constant, \(I_{ion}\) is the sum of the ionic currents given by the model formulation used in each case, and \(C_m\) is the membrane capacitance (set to 1 mF/cm² in all cases). All models were integrated using the explicit Euler method with uniform spatial and temporal resolutions. The Rush and Larsen method [207] was used to integrate the Hodgkin-Huxley-type equations of the gating variables in all models. Some variables were integrated semi-implicitly to extend the range of time steps for which the method was stable. In 1D strand, the time step used for all models was 0.02 ms and the spatial resolution used in all tissue simulations was 0.015 cm. For the OVVR model, we also used operator splitting to integrate the calcium concentration equations with a smaller time step of 0.001 ms, which was necessary to accurately capture the fast dynamics of these equations. To increase efficiency, pre-computed lookup tables were used to calculate single-variable computationally intensive functions, such as
The cable equation is applied to a 1-D isotropic strand of cardiac tissue with the assumption that there is no-flux boundary conditions. With adequate spatial discretization of $\Delta x=0.015$ cm, the evolution of the transmembrane potential at any myocyte $i$ can be explicitly updated from a specific time at $t$ to the subsequent time that can be expressed as $t + \Delta t$ by:

$$V_{t,i}^{m+\Delta t,i} = V_{t,i}^{m} + \frac{\Delta t}{C_m \Delta x^2}(V_{t,i}^{m-1} - 2V_{t,i}^{m} + V_{t,i}^{m+1}) + \frac{\Delta t}{C_m}(I_{ion}^{t,i} - I_{stim}^{t,i})$$

Which is the generalized Laplacian current with a finite difference centered scheme for the evaluation of the second spatial derivative, computed at node $i$ using $(V_{t,i}^{m-1} - 2V_{t,i}^{m} + V_{t,i}^{m+1})$.

### 3.3.5 Two-dimensional tissue

In all 2D sheets, we solved the following partial differential equation of cardiac tissue:

$$\frac{\partial V}{\partial t} = D(\frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 V}{\partial y^2}) - \frac{I_{ion}}{C_m}$$

Where $V_m$ is the membrane potential, $D$ is the diffusion constant, $I_{ion}$ is the sum of the ionic currents given by the model formulation used in each case, and $C_m$. 

exponentials [88]. The diffusion coefficient used in all cases was $0.001171 \text{ cm}^2/\text{ms}$, as calculated for human ventricular tissue [18]. No-flux boundary conditions were used in all tissue simulations and initial conditions were as specified in the publications of the original models [18; 74; 99; 181; 193; 232; 233]. The length of the cables in 1D for all models was 1.5 cm. We used the same temporal and spatial resolution for previously published models except the time resolution of the Iyer-Mazhari-Winslow (IMW) model, where we used 0.01 ms. Our codes are consistent with the implementations for the models available at www.cellml.org (GPB model) and http://rudylab.wustl.edu/research/cell/code/AllCodes.html (OVVR model) with the exception that for the GPB model we set the coefficient in the equation for $I_{K1}$ to 0.35, as in the original paper, rather than to 10.35, as in the CellML code. All other parameters are as specified in the original papers.
is the membrane capacitance (set to 1 $mF/cm^2$ in all cases). In the 2D sheet, we utilized the Laplacian method which approximates each point by calculating the averages of the four neighboring points. All cells of different models were integrated using the explicit Euler method with uniform spatial and temporal resolutions, which facilitated parallelization in 2D. The time step used for all cell models was 0.02 ms and the spatial resolution used in all 2D simulation domains was 0.015 cm. No-flux boundary conditions were used in all tissue simulations. For all 2D tissue, we used a square domain of size 14.4 cm $\times$ 14.4 cm, which represents a grid with 960 cell $\times$ 960 cells, except for the epicardial cell type of the OVVR model, where the 2D sheet size was 18.0 cm $\times$ 18.0 cm, which represents a grid with 1,200 cells $\times$ 1,200 cells. In addition, we used isotropic diffusion for both directions with a diffusion coefficient used in all 2D domains of 0.001171 cm2/ms, as calculated for human ventricular tissue [18].

3.4 Computationally Efficient Implementation

Since simulating electrophysiological properties such as the electrical wave propagation within the ventricles will be computationally very intensive, we incorporated some strategies in our implementation of cardiac electrophysiological cell models besides the chosen numerical approaches itself. For example, to accurately simulate the OVVR biophysical membrane model for each time step, a large number of ordinary differential equations need to be solved. Furthermore, there is a diffusion term that must be evaluated for each time step. Without making some useful strategies, the simulation for one cardiac cycle in 3D may take days. This is based on the computational resources devoted to perform the simulation. Therefore, efficient implementation in solving the monodomain equation is necessary using some specific tactics. These tactics are aimed at reducing the computational time when running the simulations of the cardiac electrophysiological cell models, especially when it is implemented in higher dimensions such as simulating a cellular model on real 3D anatomy. These strategies can be summarized as follows:
3.4.1 Lookup tables

Most cardiac electrophysiology cell models have highly computational functions such as logarithms, divisions, and exponentials that need to be solved. For single variable functions, such as membrane voltage and sodium concentration, pre-calculated lookup tables were generated because this increases computational efficiency. These precomputed values can subsequently be beneficial when solving cellular models.

3.4.2 Parallelization

There are many solvers for parallel implementations. These solvers were evolved and applied to simulate cardiac tissue electrophysiological models such as open multi-processing (OpenMP). These solvers were evolved and applied to simulate cardiac tissue electrophysiological models such as open multi-processing (OpenMP) and Message Passing Interface (MPI) http://www.mpi-forum.org/. In MPI, a message with required information is passing between an application programming interface which permits codes that run on multi-processors to interact with each other. There are many advantages of using an MPI technique such as ease of implementation and achieving high scalability. In addition, codes that are based on the MPI approach can be executed on either distributed, or shared memory architectures.

In our case, we developed a specific code to accommodate an MPI approach, where we divided the heart geometry into x subdomains/subregions. Each processor can solve a separate subdomain of the tissue/myocardium in conjunction with other processors that lie within the boundaries of the subdomain. This means that there are messages passing between the nodes that lie on the boundaries on adjacent subdomains. For example, the membrane potentials at these nodes must be explicitly passed between processors. Adapting this approach should decrease the computational time by a factor of x, theoretically.
3.4.3 Operator Splitting

The aim of using an operator splitting technique on a system that has either ordinary differential equations (ODEs), or partial differential equations (PDEs), is to split the model, cardiac cellular models in our case, into a set of sub-equations either to ensure model stability, improve the computational efficiency, ease analyzing the model numerically, and/or reduce the dependency between the variables. In our case, we used an operator splitting technique in the OVVR model to integrate the calcium concentration equations with a smaller time step, which is necessary to accurately capture the fast dynamics of these equations. Without incorporating this technique, the calcium dynamics will be unstable.

3.5 Developed HF-OVVR model description (experimental data):

Certain ionic exchanger and pump currents were investigated with their corresponding experimental human HF data published and remodeled based on these observations. We used the same equations of the normal OVVR model [181] and reformulated the maximum current conductances for major currents of the undiseased OVVR model [181], while other values remained unchanged, such as the background currents. We took the first steps toward developing a meaningful representation of population variability through calculating the mean and the standard deviation for each ionic current across experimental observations found in the literature. Tables 5.1 and 5.2 summarize the heterogeneous remodeled ionic currents used in our HF-OVVR model along with the data sources. The details of HF remodeling for each current are discussed below.

- Data sources: In this thesis, we developed two heart failure models where for both models the underlying model is human. However, the HF remodeling is either general without considering any differences between species type, or is more human-specific where it is mainly based on humans, except when there is scarcity of data on humans. For some currents during heart failure, we benefit from the existence of data from other animal species found in the
literature. Therefore, we incorporated canine [2; 115; 132] and rabbit [203; 238; 280] data. So, for the general heart failure model, we considered all the HF-remodeled experimental data available in the literature. However, for the more human-specific model, most of the sources of experimental data used to construct and simulate human HF myocytes are based mainly on human species.

- Measurement conditions: For all simulations used in this thesis, we stimulated each ventricular cell type until it reached steady-state with cycle length 1000 ms. However, for assessing EADs, we used three different pacing protocols beginning at CL=2000 ms, CL=4000 ms, and CL=10000 ms. Then, we calculated the biomarkers.

- Data variability: Data for the HF-OVVR model are presented as the mean ± standard deviation (\( \mu \pm SD \)). We calculated the SD in this manuscript based on the formula \( \sqrt{\sigma_1^2 + \sigma_2^2 + \ldots + \sigma_n^2} \), where \( \sigma_i^2 \) is the variance of the instance (myocyte) \( i \) and \( n \) is the number of experiments involved in the calculations of the specified remodeling current.

- Biomarkers calculation: We varied each modified parameter from \((\mu + 2SD)\) to \((\mu - 2SD)\) in increments of 1 SD and calculated the biomarkers for each varied parameter value. For each biomarker, the minimum and maximum biomarker values obtained over all parameter variations and over all currents are given as the range in Table 5.8.
Chapter 4

A Quantitative Comparison of the Behavior of Non-Failing Human Ventricular Cardiac Electrophysiology Models in Tissue

The purpose of this chapter is to analyze quantitatively the human ventricular cell models [18; 74; 99; 181; 193; 232; 233] with an emphasis on rate-dependent properties associated with tachyarrhythmias and compare the dynamics of these models with each other. In this chapter, we start by introducing the available ventricular cell models and explaining why analyzing these models in tissue is important. Then, we describe the formulation of these electrophysiological models. After that, we introduce the restitution protocols, which are used to assess the behavior of these models in a 1-dimensional cable, followed by an explanation of the extracted properties, which are useful in characterizing these models in 2-dimensional tissue. Then, we present the action potentials, transmembrane currents, and calcium dynamics results with declaration of transmural variations in action potentials for each model. This is followed by an exhibition of the rate dependence of action potential duration (APD) and conduction velocity (CV)
4.1 Introduction

Over the last several decades, mathematical models of the electrophysiology of cardiac cells have become an important resource for studying the mechanisms underlying cardiac arrhythmias. These models generally use systems of coupled ordinary differential equations to describe the movement of sodium, calcium, and potassium ions across the cell membrane through different ion channels and the changes in membrane potential during an action potential. Many models also represent sub-cellular processes, such as cycling in intracellular calcium that is responsible for contraction at the cellular level. Tissue-level phenomena can be studied by including cell-to-cell coupling, normally through a diffusion term, to allow for propagation of electrical waves. The models can be used to study the normal electrical state of the heart, in which electrical waves remain coherent to stimulate a coordinated contraction, and arrhythmic states, in which electrical wave disturbances, such as reentry and fractionation, compromise the heart’s ability to pump blood.

The advantages models provide include reproducibility, the ability to vary parameters systematically, and ready access to all simulation results at high spatial and temporal resolution, serve as a useful complement to traditional biological experiments and can be used to develop and to perform preliminary tests of hypotheses. As modeling cardiac electrophysiology has become a more important investigative tool, models have grown in number, specificity, and complexity [57; 59]. For example, models have been developed to describe different regions of the heart, including atria, ventricles, sinoatrial node, atrioventricular node, and Purkinje network, and in many cases are designed to reproduce the behavior of cells of particular species, sometimes under various disease conditions. Models may be developed to incorporate new experimental data on ion channels or

and short-term memory (STM). In addition, an alternans in a 1D cable is illustrated by showing the dynamics of each model after initiating spiral waves. Then, there is a discussion of the observed results and we close this chapter with an explanation of the candidate model, which will be developed to a heart failure (HF) model.
other intracellular processes, to address limitations of previous models, or to represent a specific system or mechanism not previously modeled. The availability of a large number of mathematical models of cardiac cells leads to challenges in selecting an appropriate model. Even when a particular species and region of the heart are identified, it is often the case that several models are available [20; 27; 29; 31; 180; 233; 263]. The choice of model becomes especially challenging for simulations in tissue, where electronic coupling can cause the emergent properties in higher spatial dimensions to differ from the characteristics of isolated cells [28; 33]. For example, important properties of alternans in tissue, such as alternans magnitude, range of cycle lengths (CL) exhibiting alternans, and even whether alternans occurs at all, can differ significantly from what is observed in single cells [29]. In addition, some tissue behavior, such as reentrant wave dynamics, currently cannot be predicted from the properties of isolated cells.

Models of human cells and tissue are of particular importance because of their potential for clinical relevance. A number of mathematical descriptions of human ventricular cells have been published over the past decade and a half [11; 18; 99; 193; 232; 233]. More recently, two new models were developed: the Grandi-Pasqualini-Bers (GPB) model [74] and the O’Hara-Virág-Varró-Rudy (OVVR) model [181]. These models incorporated more detailed physiological data concerning intracellular calcium dynamics and transmembrane currents. Although the authors established model behavior in isolated cells and for some conditions in tissue, important dynamical properties, including the behavior of reentrant waves, have not been shown previously.

4.2 Model descriptions

4.2.1 Electrophysiological model formulations

In this study, we focus on two recently published models of human ventricular cells derived from different experimental data: the Grandi-Pasqualini-Bers (GPB) model [74] and the O’Hara-Virág-Varró-Rudy (OVVR) model [181]. The models have different formulations: the GPB model uses 38 state variables and 14 transmembrane currents, whereas the OVVR model has 41 state variables and 12
transmembrane currents. Eleven currents are common to both models: the fast Na\(^+\) (\(I_{Na}\)), L-type \(Ca^{2+}\) (\(I_{CaL}\)), transient outward \(K^+\) (\(I_{to}\)), rapidly and slowly activating delayed rectifier \(K^+\) (\(I_{Kr}\) and \(I_{Ks}\), respectively), inward rectifier \(K^+\) (\(I_{K1}\)), \(Na^+/Ca^{2+}\) exchanger (\(I_{NaCa}\)), \(Na^+/K^+\) pump (\(I_{NaK}\)), sarcolemmal \(Ca^{2+}\) pump (\(I_{pCa}\)), background \(Na^+\) (\(I_{bNa}\)), and background \(Ca^{2+}\) (\(I_{bCa}\)) currents. In addition to these, the GPB model includes \(Ca^{2+}\)-activated \(Cl^-\) (\(I_{CaCl}\) or \(I_{to2}\)), plateau \(K^+\) (\(I_{Kp}\)), and background \(Cl^-\) (\(I_{bCl}\)) currents, as well as fast and slow components of \(I_{to}\), and the OVVR model includes a background \(K^+\) current (\(I_{KK}\)). Another difference in transmembrane currents is the inclusion of both \(Na^+\) and \(K^+\) transport through L-type \(Ca^{2+}\) channels in the OVVR model, whereas the GPB model accounts for \(Na^+\) but not \(K^+\) transport.

Along with differences in transmembrane currents, the two models incorporate different local subspaces, each of which includes ion concentrations and state variables. The GPB model tracks separate \(Na^+\) and \(Ca^{2+}\) concentrations in the junctional cleft (submembrane space near the T-tubules), subsarcolemma (SL) (the submembrane space not near the T-tubules), and cytosol along with the concentration of \(Ca^{2+}\) in the sarcoplasmic reticulum (SR) and a single intracellular \(K^+\) concentration. The OVVR model includes separate cytosol and junctional cleft concentrations of \(Na^+\), \(K^+\), and \(Ca^{2+}\), along with junctional and network SR \(Ca^{2+}\) concentrations.

The different concentrations allow ion channels to sense different ion concentrations depending on their location and thus are related to the spatial distribution of ion channels within the cell. For most ion channels, the GPB model placed 89% of the channels in the SL and the remaining 11% in the junctional cleft, which represents a uniform distribution based on locating 11% of the membrane in the junctional cleft. Although the distribution of channels is uniform, different concentrations of \(Ca^{2+}\) and \(Na^+\) ions in the junctional cleft and SL regions lead to differences in the currents through the channels in those locations. Only \(I_{CaL}\) is distributed differently, with 10% of channels in the SL and 90% in the junctional cleft (in close proximity to the T-tubules and RyR \(Ca^{2+}\) release channels). Those currents that involve neither \(Ca^{2+}\) nor \(Na^+\) concentrations (\(I_{to}\), \(I_{Kr}\), \(I_{K1}\), \(I_{Kp}\), and \(I_{bCl}\)) are distributed uniformly and do not require any special consideration. For the OVVR model, uniform channel distribution is assumed.
except for $I_{CaL}$, which is located entirely in the junctional cleft, and $I_{NaCa}$, which is distributed as 20% in the junctional cleft and 80% elsewhere in the membrane, where cytosolic ion concentrations are sensed.

Several other features of the models are noteworthy. The GPB model includes extensive buffering of $Ca^{2+}$ and $Na^+$ to regulate ion homeostasis. The OVVR model includes phosphorylation by $Ca^{2+}$/calmodulin-dependent protein kinase II, which affects intracellular $Ca^{2+}$ cycling. In addition, both models include modifications for representing transmural differences in electrophysiological properties. The GPB model includes epicardial and endocardial formulations, which are obtained by varying the maximum conductance of $I_{to}$ alone. In contrast, the OVVR model reproduces epicardial, midmyocardial, and endocardial cells by modifying a large number of parameter values, including maximal conductances of most transmembrane currents and some parameters governing calcium fluxes, along with the inactivation time constants for $I_{to}$.

For comparison, we also present results using the Priebe-Beuckelmann (PB) [193], Iyer-Mazhari-Winslow (IMW) [99], Ten-Tusscher-Panfilov (TP) [233], and Bueno-Orovio-Cherry-Fenton (BCF) [18] human ventricular models. The PB, IMW, and TP models have 22, 67, and 19 state variables, respectively, and 10, 13, and 12 transmembrane currents, respectively. The BCF model uses a different formulation focused on reproducing mesoscale electrophysiological properties (such as action potential shape and rate-dependent behavior). It includes four state variables and tracks the sum of fast inward, slow inward, and slow outward transmembrane currents. The GPB, OVVR, PB, and TP models rely primarily on Hodgkin-Huxley representations of transmembrane currents, in contrast to the IMW model, which uses Markov formulations (leading to a significantly larger number of state variables). In addition, the IMW model utilizes data obtained from both recombinant human channels and isolated human ventricular epicardial myocytes, whereas the other models are based on isolated human ventricular myocyte data. To represent transmural heterogeneity, the TP and BCF models include formulations for epicardial, endocardial, and midmyocardial cells (through changing the maximum conductances of $I_{to}$ and $I_{Ks}$ for the TP model), whereas the PB and IMW models include only epicardial formulations.
Figure 4.1: Rate dependence of action potentials, primary transmembrane currents, and intracellular calcium concentration. Action potentials, currents, and calcium transient in a single cell for the GPB (columns 1 and 3) and OVVR (columns 2 and 4) models for cycle lengths of 1000 ms (solid black), 750 ms (dashed green), 500 ms (dashed red), and 300 ms (dashed blue). Insets show peak current values for the same cycle lengths following the same color scheme. The GPB model generally shows more rate dependence; however, the OVVR model shows greater rate dependence for $I_{K1}$ and $[Ca^{2+}]_i$. Both models show significant rate dependence for $I_{Ks}$, although the effect of rate is opposite for the two models, and for the $I_{CaL}$.
4.3 Results

4.3.1 Action potentials, transmembrane currents, and calcium transients

We compared the action potentials, main transmembrane currents ($I_{CaL}$, $I_{NaCa}$, $I_{K1}$, $I_{Kr}$, $I_{Ks}$, and $I_{to}$), and calcium transients in single cells of the GPB and OVVR models for a range of different CLs for the epicardial formulations. As shown in Fig. 4.1 A-B, the action potentials of the two models have similar shapes, although action potentials obtained using the OVVR model have higher plateaus and shorter durations and exhibit less rate dependence than those of the GPB model.

The main transmembrane currents of the two models generally show differences in magnitude and in the degree of rate dependence. Neither model displays much rate dependence of $I_{CaL}$ (see Fig. 4.1 C-D), but the peak current at long cycle lengths is nearly twice as large for the GPB model (24.3 pA/pF) as for the OVVR model (22.4 pA/pF). $I_{NaCa}$ exhibits stronger rate dependence for the GPB model and limited but biphasic rate dependence for the OVVR model, as shown in Fig. 4.1 E-F. The peak inward current is twice as large for the GPB model as for the OVVR model at longer CLs (1000 ms) and is similar for the two models at short CLs (300 ms) with a value of 20.53 pA/pF, but the GPB model has a more pronounced outward component early in the action potential than the OVVR model.

$I_{K1}$ is similar in the two models; however, the peak current is about 50% larger for the GPB model than for the OVVR model, as shown in Fig. 4.1 G-H. In addition, $I_{K1}$ in the GPB model displays almost no rate dependence, whereas for the OVVR model the peak value of the current decreases slightly with decreasing CL. As shown in Fig. 4.1 I-J, $I_{Kr}$ exhibits very slight rate dependence in both models, but in opposite directions, and its peak value for the OVVR model is six times larger than for the GPB model, indicating that it plays a more significant role during repolarization for the OVVR model. $I_{Ks}$ also is larger for the OVVR model than for the GPB model by more than a factor of ten (see Fig. 4.1 K-L). Both models show rate dependence of $I_{Ks}$, but in opposite ways: as CL decreases,
the peak value of $I_{Ks}$ decreases for the GPB model but increases for the OVVR model. For $I_{Io}$, the OVVR model shows limited rate dependence, in contrast to the GPB model where the peak value decreases considerably with decreasing CL, as shown in Fig. 4.1 M-N. The peak current is two times larger for the GPB model than for the OVVR model at slow pacing rates, but both models have the same peak value at fast rates.

Fig. 4.1 O-P shows the calcium transients (intracellular calcium concentration $[Ca^{2+}]_i$) for both models. The peak value is about twice as large for the OVVR model as for the GPB model during slow rates and more than four times as large during fast rates. In both models, the $[Ca^{2+}]_i$ peak value increases as the CL increases from 1000 ms to 300 ms, so that the $[Ca^{2+}]_i$ peak-frequency relationship is always positive. In addition, the calcium transient rises and falls more slowly for the GPB model than for the OVVR model.

4.3.2 Transmural variations in action potentials

Both the GPB and OVVR models include endocardial cell formulations, and the OVVR also includes a midmyocardial cell formulation, as shown in Fig. 4.2. Action potentials obtained using the endocardial formulations do not have a promi-
nent notch because of decreased Ito density and are longer than epicardial action potentials. For the midmyocardial cell type, the OVVR model exhibits a prominent dome with the height of the plateau higher than the peak of the upstroke for both single cell and tissue. The APD of the midmyocardial cell for the OVVR model at a CL of 1000 ms is 348.6 ms, which is longer than that of the epicardial cell by 119.7 ms and that of the endocardial cell by 90.2 ms. The OVVR model APDs for both epicardial and endocardial cells are shorter than those of the corresponding cell types in the GPB model, and the difference in GPB epicardial and endocardial APDs is also smaller (11.8 ms), as shown in Fig. 4.2. Additional details are given in Table 4.1.
Figure 4.3: Action potentials for the epicardial formulations of six human ventricular models. Action potentials in single cells (left column) and in 1D tissue (right column). Data are taken from the middle of the cable (cell 50) with a 100 cells cable after pacing for 30 s at a CL of 1 s. Because of electrotonic coupling effects, all of the model APs lose amplitude in tissue compared to single cells, with the PB model decreasing the most (23.7%) followed by the GPB model (17.6%), the TP model (12.9%), the OVVR model (12.4%), the IMW model (10.5%), and the BCF model (4.0%).
4.3.3 Comparisons with other models

For comparison, we also analyzed the properties of action potentials of the PB, IMW, TP, and BCF models and compared them with those of the GPB and OVVR models in single cells and in 1D cables. Figure 4.3 (left column) shows action potentials obtained after pacing for 30 s at a CL of 1000 ms, and Table 4.1 includes action potential characteristics obtained from the epicardial cell type of all four models at the same CL. In single cells, all of the models have similar spike-and-dome action potential morphologies for epicardial cells; however, the prominence of the action potential notch and the plateau potential as well as the resting membrane potential (RMP) vary among the models. The PB model has the largest upstroke peak and AP amplitude, whereas the GPB model has the smallest peak and AP amplitude. The RMP is lowest for the IMW model (-90.7 mV) and highest for the GPB model (-81.4 mV). In terms of action potential morphology, the PB model has a clear two-phase repolarization, in contrast to the other models where the transition is smoother, and the plateau phase for the TP model is longer than for the other models, for which repolarization begins sooner. APDs vary significantly among the models, ranging between 228.9 ms for the OVVR model and 393.2 ms for the PB model for epicardial cells.

In tissue, the action potential upstrokes are decreased by electrotonic effects (see Fig. 4.3, right column). For the OVVR model, the membrane potential continues to increase after the upstroke, so that the plateau height is greater than the upstroke depolarization, and there is no clear distinction between the upstroke and the plateau. For the GPB, PB, IMW, and TP models, a distinct upstroke spike still is observed, but with a peak lower than the plateau value. Only the BCF model has a maximum upstroke potential higher than the plateau in tissue. The maximum upstroke velocities vary considerably among the models, ranging from 81.6 V/s for the OVVR model to 302.9 V/s for the GPB model. Despite the morphological changes near the action potential upstrokes, APD does not change much between 0D and 1D; the APD in tissue increases by 0.8 and 1.4 ms for the OVVR and BCF models, respectively, and decreases by 1.1, 1.3, 7.1 and 0.9 ms for the GPB, PB, IMW, and TP models, respectively. The maximum upstroke velocity, however, decreases significantly from single cells to tissue: for
the GPB model, the decrease is 23% (from 394 to 303 V/s), but for the OVVR model, the decrease is 62% (from 217 to 82 V/s for epicardial cells). The PB, TP, and BCF models also show decreases of 32%, 28%, and 12%, whereas the IMW model shows no decrease in this quantity.

Figure 4.4: Rate dependence in a 1D cable for the GPB and OVVR models. (A,D) Action potentials at cycle lengths of 1000, 600, 500, 400, and 300 ms. Compared to isolated cell APs, the upstroke amplitude is decreased because of electrotonic effects. (B,E) Steady-state and S1-S2 APD restitution curves. Steady-state restitution curves (solid lines) were obtained after pacing for 30 s and S1-S2 restitution curves (dashed lines) were obtained after 30 s of pacing for five different S1 cycle lengths. Both models show memory in APD. (C,F) Steady-state and S1-S2 CV restitution curves. The GPB model shows no apparent memory in CV, whereas the OVVR shows limited CV memory.
4.3.4 Rate dependence of APD and CV and short-term memory

Action potentials for both the GPB and OVVR models exhibit significant rate adaptation, as shown in Fig. 4.1 A-B for single cells and Fig. 4.4 A and D for 1D cables. The steady-state restitution curves reflect this adaptation to rate, with the APD in 1D varying by 70.6 ms and 37.5 ms for the GPB and OVVR models, respectively, over CLs below 1000 ms, as shown in Fig. 4.4 B and E (solid lines). The slopes of the steady-state restitution curves in tissue for both models are <1 over all DIs, with a maximum slope of 0.3 for the GPB model and 0.2 for the OVVR model. Similar behavior is seen for single cells (not shown).

Short-term memory, which reflects the influence of pacing history, is an important property demonstrated by both the GPB and OVVR models. The effects of short-term memory can be observed through differences in S1-S2 APD and CV restitution curves as the S1 CL is varied. Figure 4.4 B and E (dashed lines) show S1-S2 APD restitution curves for a range of S1 CLs superimposed with the steady-state restitution curve for the GPB and OVVR models. Both models show memory; we quantify the memory using the memory amplitude, which we define as the difference between the maximum and minimum APDs over the range of S1 CLs at the longest DI of 1000 ms [29]. The memory amplitude for the epicardial cell type is considerably larger for the GPB model (54.2 ms) than for the OVVR model (22.8 ms) in a 1D cable. In terms of restitution curve shapes and slopes, S1-S2 curves for the GPB model are nearly flat, but generally become biphasic at shorter DIs (< 200 ms). In contrast, S1-S2 restitution curves decrease monotonically for the OVVR model, a phenomenon not observed for the GPB model.

Figure 4.5 A shows steady-state APD restitution curves from all six models. All the curves decrease monotonically. However, the IMW model shows a marked decrease for long DIs and abrupt slope changes arising from lack of convergence to a steady state, which renders the model strongly sensitive to pacing protocol. For CLs below 1000 ms, APDs vary the most for the TP model (with a 119.8 ms or 39.5% decrease) and the least for the OVVR model (with a 37.5 ms or 16.4% decrease). The GPB APD range is in between, at 70.6 ms, as shown in Fig. 5A.
As shown in Fig. 4.4 C and F (solid lines), wave propagation is considerably faster in the GPB model than in the OVVR model over all DIs; in fact, the minimum steady-state CV obtained for the GPB model in a 1D cable is larger than the maximum CV for the OVVR model. Over the range of DIs, the CV decreases by 27.9 cm/s (39.1% of the maximum CV) for the GPB model and by 9.1 cm/s (24.1% of the maximum CV) for the OVVR model. Although all S1-S2 CV restitution curves decrease monotonically for both the GPB and OVVR models (see Fig. 4C and F; dashed lines), the GPB model exhibits almost no memory in CV; at long DIs, the CV changes by less than 1.0 cm/s as the S1 CL decreases from 1000 to 320 ms. The OVVR model shows a modest degree of memory in CV of 3.1 cm/s as the S1 CL decreases from 1000 to 165 ms.

Figure 4.5: Steady-state APD and CV restitution curves for all six models in 1D epicardial cables. (A) APD restitution curves. (B) CV restitution curves. Curves were obtained after pacing for 30 s and show significant differences among the models.

Across all six models, the BCF model has the largest maximum CV and the OVVR model has the smallest, as shown in Fig. 4.5 B. The CVs of the GPB and BCF models fall within a realistic range [109; 167; 230] with a maximum of
71.4-74.6 cm/s, and the CVs of the PB, IMW, and TP models are only slightly slower, ranging from 62.2 to 65.3 cm/s. However, the CV of the OVVR model is nonphysiologically slow with a maximum of 37.8 cm/s. As discussed below, this can be remedied by substituting the TP model formulation for $I_{Na}$. The PB model displays the least variation in CV as the DI is varied, with a steady-state CV range of 7.6 cm/s, followed by the IMW and OVVR models, with ranges of 9.0 cm/s and 9.1 cm/s, respectively. The TP and GPB models show the widest steady-state CV ranges of 32.6 cm/s and 27.9 cm/s, respectively. The steady-state CV range for the BCF model is in between, with a value of 15.3 cm/s.

Figure 4.6: Alternans in the OVVR model. Action potential traces (left) and bifurcation diagrams (right) for (A) epicardial single cell, (B) epicardial cable, (C) endocardial single cell, and (D) endocardial cable. Cycle lengths in the action potential traces are (A) 165, (B) 320, (C) 200, and (D) 310 ms.

### 4.3.5 Alternans

Alternans was never observed for the GPB model, however, it occurs for a small number of CLs in 0D and 1D for the OVVR model in both the epicardial and
endocardial cell types (but not in midmyocardial cells). Fig. 4.6 A shows that in a
single epicardial cell, alternans occurs only for a CL of 165 ms, with a magnitude
(difference in the APDs of two consecutive beats) of 0.9 ms. In tissue, the OVVR
epicardial model shows alternans for a single CL of 320 ms with a magnitude of
25.2 ms, as shown in Fig. 4.6 B. Alternans for a single endocardial cell occurs for
CLs between 200 and 280 ms, with a maximum magnitude of 12.0 ms, as shown
in Fig. 4.6 C, but in tissue, alternans occurs only for a single CL of 310 ms with a
magnitude of 70.8 ms (see Fig. 4.6 D). Although alternans occurs in both single
cells and 1D cables, the CLs exhibiting alternans were lower in 0D than in 1D
for both cell types.
Figure 4.7: Reentrant spiral wave dynamics in 2D for the GPB and OVVR models. (A) The epicardial cell type of the GPB model features wave fronts that often stall and reform, and the dominant period is 308 ms. (B) The endocardial cell type of the GPB model shows similar stalling and recombining without breakup and a dominant period of 321 ms. (C-E) Spiral wave dynamics for (C) epicardial, (D) endocardial, and (E) midmyocardial cell types in the OVVR model. The epicardial model exhibits a quasi-breakup where a new spiral wave tip is created before the previous one has dissipated. It has two dominant periods of 337 ms and 481 ms. The endocardial model shows similar dynamics to the epicardial formulation with a dominant period of 405 ms. The midmyocardial model features an unstable hypocycloidal trajectory with a dominant period of 430 ms. Frames in all cases correspond to 5.45, 5.50, 5.55, and 5.60 s, and tissue sizes are 14.4 cm × 14.4 cm except for the OVVR epicardial cell type, where the size is 18.0 cm × 18.0 cm. Dominant periods were obtained using the full 10 s of simulation time.
4.3.6 Spiral wave dynamics

The dynamics and stability of reentrant spiral waves in two-dimensional homogeneous and isotropic tissue also differ between the GPB and OVVR models, as shown in Fig. 4.7. Spiral waves in the GPB model feature a precessing linear tip trajectory about 4 cm long for both the epicardial and endocardial formulations (see Fig. 4.7 A-B), with the epicardial spiral wave precessing more quickly. In the OVVR model, predominantly linear trajectories are observed for the epicardial and endocardial formulations with the maximum distances traversed about 10 and 4 cm, respectively, as shown in Fig. 4.7 C-D. However, in these cases, each time the tip turns, it does so rapidly, causing it to encounter refractory tissue and die out. A new tip then forms along the spiral arm where propagation remains possible. The midmyocardial formulation shows different dynamics, with an unstable hypocycloidal trajectory featuring petals approximately 0.6 cm in length, as shown in Fig. 4.7 E.

By recording the times between action potential upstrokes at all sites in the tissue, histograms of periods were recorded and dominant APDs and periods calculated for each case. The dominant periods for the GPB model were 308 ms and 321 ms for the epicardial and endocardial formulations, respectively. The dominant periods for the OVVR model generally were longer, with the endocardial and midmyocardial formulations showing periods of 405 ms and 430 ms, respectively. For the OVVR epicardial cell types, two prominent dominant periods of 337 ms and 481 ms were observed, with the broad spectrum of periods reflecting the especially highly meandering nature of the spiral wave for this case (note the much longer lengths in the tip trajectory compared to the other formulations).
Figure 4.8: Spiral waves for all six models using epicardial formulations. Tissue sizes are 14.4 cm × 14.4 cm for the GPB model, 18.0 cm × 18.0 cm for the OVVR model, and 23.0 cm × 23.0 cm for the PB, IMW, TP, and BCF models. The spatial resolution is 0.015 cm in all cases and the time step is 0.02 ms except for the IMW model, where it is 0.01 ms. The IMW model used initial values corresponding to pacing a single cell at 3 Hz. Color bar is in mV.

Figure 4.8 shows snapshots of spiral waves for all six models. Note that the other models exhibit a variety of dynamics, including quasi-breakup (PB model), sustained breakup (IMW model), and stable spiral waves (TP and BCF models). For the PB, TP, and BCF models, the dominant periods were 318, 233, and 286 ms, respectively. The IMW model displayed three dominant periods of 121, 178, and 283 ms and a much broader spectrum of periods overall, between about 120 and 300 ms, due to its high degree of meandering and sustained breakup.
4.4 Discussion

4.4.1 Action potential rate adaptation and APD restitution

It is important to compare the model properties with available observations, although experimental data on rate adaptation and restitution of APD in normal human tissue are somewhat limited due to the difficulty in obtaining nondiseased human cardiac tissue. Therefore, most studies are performed during other cardiac surgical procedures. Koller et al. [124] reported maximum APD restitution curve slopes of $0.97 \pm 0.16$ (steady-state protocol) and $0.83 \pm 0.15$ (S1-S2 protocol, $S1 = 500$ ms) for right ventricular endocardium. Similarly, Nash et al. [171] found a median value of 0.91 for the maximum S1-S2 restitution curve slope in human epicardium; only 27% of all electrode sites recorded slopes less than 0.5. Pak et al. [183] found even higher maximum slopes using an S1-S2 protocol in normal human tissue: $1.9 \pm 0.8$ at the right ventricular outflow tract and $1.7 \pm 1.1$ at the right ventricular apex, with similar values obtained for a steady-state protocol. In contrast, the maximum restitution curve slopes in the models in tissue as measured by the steady-state protocol were considerably lower: the GPB model achieved a maximum slope of 0.3 for both cell types, whereas with the OVVR model maximum slopes were 0.1 for the epicardial cell type and 0.2 for both the endocardial and midmyocardial cell types. Thus, neither model achieves a maximum restitution curve slope in tissue comparable to experimentally measured values.

Bueno-Orovio et al. [19] observed APDs varying between about 165 and 205 ms for endocardial cells using the S1-S2 protocol ($S1 = 500$ ms). In comparison, Franz et al. [63] found a larger variation in APD, between about 190-200 ms and 245-270 ms, and they also observed biphasic S1-S2 restitution curves. In terms of the models, the GPB model has nearly flat S1-S2 APD restitution curves for nearly all S1 cycle lengths. However, the OVVR model more closely matches the experimental values, with APD varying between 197 and 215 ms. Changes to the $I_{Na}$ formulation, as discussed below, may reduce the OVVR model minimum APD further in this case and thus achieve better agreement with the data of Bueno-
Orovio et al. The OVVR model showed no indication of biphasic restitution curves (see Fig. 4.4 E), whereas the GPB model showed an increase in APD at shorter DIs for longer S1 cycle lengths (see Fig. 4.4 B). However, the biphasic restitution curves observed by Franz et al. showed an increase in APD at short, but not the shortest, DIs, and a significant decrease in APDs for the smallest DIs, in contrast with findings for the GPB model.

Figure 4.9: Action potentials for the OVVR model using the TP formulation of $I_{Na}$. Traces show action potentials for (A) epicardial, (B) endocardial, and (C) midmyocardial cell types of the OVVR model using the TP model formulation of $I_{Na}$ (green solid) compared to the original OVVR model (blue dashed). Insets show upstrokes, where the action potential shapes change most.

4.4.2 Transmural heterogeneity

The GPB model includes epicardial and endocardial formulations, and the OVVR includes both of these as well as a midmyocardial formulation. The different cell types of the models in tissue exhibit some action potential properties similar to experimental observations, but there are also a number of differences. The amplitudes of epicardial action potentials (100.4 and 107.8 mV for the GPB and OVVR models, respectively) are smaller than experimental observations of 123 mV [165] and 131 mV [131]; most likely this results from the decreased upstroke amplitude of the model APs in tissue compared to single cells (see Fig. 4.3). The values of $dV/dt_{max}$ for the epicardial formulations of the GPB and OVVR models are 302.9 and 81.6 V/s, which are significantly different from observations of 228±11 V/s [49] and 196±20 V/s [185]. The human epicardial APD at a CL of
1000 ms has been measured at 271±13 ms [131], which is nearly the same as for
the GPB epicardial model (275.0 ms), but longer than that of the OVVR model
(229.7 ms).

Human endocardial AP amplitudes have been measured at 119 mV [165] and
123 mV [131]; in tissue, the GPB model is still below these values with an AP
amplitude of 100.7 ms, but the OVVR model amplitude of 114.4 ms is close to
the experimental values. As for the epicardial models, the maximum upstroke
velocities of the endocardial models are still larger (GPB model, 303.3 V/s) and
smaller (OVVR model, 83.9 V/s) compared to experimental values (234±28 V/s
[49] and 231±30 V/s [185]). However, the endocardial APDs for both models
(288.0 ms for the GPB model and 258.6 ms for the OVVR model) are within
the range of what some experimental studies have found for endocardial APD
values (263±33 ms [131] and 270±7 ms [124]), although longer than reported in
other studies (196.7±20.1 ms and 207.8±21.5 ms for right and left ventricular
endocardium, respectively [19]).

Perhaps because of continued controversy surrounding the existence and func-
tion of midmyocardial cells [102; 173; 265], only the OVVR model includes a mid-
myocardial formulation. The model AP amplitude of 105.2 ms is lower than the
experimentally observed value of 128 mV [131], and its upstroke velocity remains
quite low at 81.9 V/s compared to the experimentally observed value of 326±16
V/s [49].

Overall, both the GPB and OVVR models in tissue exhibit action potential
amplitudes smaller than experimental observations. Also, the GPB model over-
estimates and the OVVR model underestimates the maximum upstroke velocity.
In addition, the APDs in the GPB model are close to experimental values for
both epicardial and endocardial cells, whereas the in OVVR model, endocardial
but not epicardial, APDs are close to experimental measurements.
Figure 4.10: Rate adaptation and spiral wave properties for the OVVR model with the TP $I_{Na}$ formulation. (A-B) Steady-state APD restitution curves in isolated cells (A) and a one-dimensional cable (right) for epicardial (green), endocardial (red), and midmyocardial (blue) cells. Original model restitution curves are shown as dots (A) or dashed lines (B). The different $I_{Na}$ formulation decreases the minimum DI that can be reached in tissue. (C) Steady-state CV restitution curves for the epicardial (green), midmyocardial (blue) and endocardial (black) cells in a one-dimensional cable. Original model CV restitution curves are shown as dashed lines. The modification increases the maximum CV by almost a factor of two. (D-F) Spiral wave snapshots, tip trajectories, and dominant periods for the epicardial, endocardial, and midmyocardial formulations of the modified model. Frames in all cases correspond to 1.85, 1.90, 1.95, and 2.00 s, and tissue sizes are 18.0 cm $\times$ 18.0 cm. Dominant periods were obtained using the full 2 s of simulation time.
4.4.3 Conduction velocity

Maximum conduction velocity values for the GPB model as well as for the earlier models are between 60 and 75 cm/s. This range agrees well with the range of 65-87 cm/s obtained in human heart studies [167; 230]. The minimum conduction velocity obtained has been found experimentally using an S1-S2 protocol to be 25% lower than the maximum [271], which is comparable to the OVVR model, which has a decrease of 24.1%. The GPB, however, shows a larger decrease of 39.1% using the S1-S2 protocol with an S1 CL of 1000 ms. Thus, the GPB model may show extra rate adaptation.

However, the main discrepancy where CV is concerned is in the maximum CV of the OVVR model, which, at about 38 cm/s, is about half of what has been observed experimentally. The low velocity is related to the sodium channel formulation of the OVVR model. This could include temperature-related adjustments to the data from Sakakibara et al. [211] which is used as the basis for many $I_{Na}$ formulations along with the novel incorporation of $Ca^{2+}$/calmodulin-dependent protein kinase II effects. One simple remedy is to substitute the $I_{Na}$ formulation of the TP model, which nearly doubles the maximum CV. Figure 4.9 shows the effect of this substitution on the epicardial, endocardial, and midmyocardial action potential shapes. In all cases, the revised sodium current increases action potential amplitude in isolated cells by 10-15 mV, but otherwise there is little effect on action potential shape; APD is decreased slightly by 2.2, 6.6, and 1.4 mV for epicardial, endocardial, and midmyocardial cells. Figure 4.10 demonstrates the rate adaptation and spiral wave properties of the modified model. The primary effects in tissue of the $I_{Na}$ substitution are an increase in maximum conduction velocity to nearly twice its original value, a decrease in minimum CL by 65-115 ms (and thus the minimum APD by 20-30 ms), a decrease in dominant APD and spiral wave period, and changes to spiral wave dynamics. Spiral wave stability is not affected. Thus, the $I_{Na}$ substitution provides a realistic CV for the OVVR model while leaving many other model properties unchanged.
4.4.4 Alternans

Although alternans is known to occur in normal human hearts from both clinical [124] and ECG studies [204], the GPB model does not exhibit alternans at any CL. Alternans occurs in the OVVR model in tissue for a CL of 320 ms in epicardial cells a CL of 310 ms in endocardial cells; the magnitudes of alternans for those cell types were 25.2 and 70.8 ms, respectively. Koller et al. [124] found the alternans of onset occurred at a much lower CL of 267 ms, with a maximum alternans magnitude of 11 ms. Thus, although alternans occurs for the OVVR model but not the GPB model, alternans in the OVVR model is present earlier and achieves a significantly greater magnitude than what has been observed clinically.

4.4.5 Reentrant wave dynamics

All of the GPB and OVVR model variations exhibit stable or quasi-stable dynamics, with no sustained breakup of spiral waves occurring. Well-defined periods occur in all cases except for the OVVR epicardial formulation, which has two peaks associated with the spiral wave rotation and the broadly meandering trajectory of the spiral wave. Converting these dominant periods to dominant frequencies facilitates comparison with experiments. The dominant frequencies of the GPB model, which are 3.25 and 3.12 Hz for epicardial and endocardial cells types, respectively, both lie within the range of clinically observed dominant frequencies of VT, 2.9-4.2 Hz [124] (VF frequencies are higher, up to about 7.5 Hz [34; 167; 168]). For the OVVR model, the dominant frequencies measured of 2.08, 2.47, and 2.33 Hz for epicardial, endocardial, and midmyocardial preparations, respectively, are lower than those observed clinically for VT, except for the second epicardial frequency, which at 2.97 Hz is just inside the clinical range. Thus, the GPB model corresponds well to VT, whereas the OVVR model frequencies are somewhat lower than the values typically observed for VT clinically. However, the substitution of the TP model formulation of INa changes the observed dominant frequencies of the OVVR model to 4.74, 4.35, and 2.94 Hz for the epicardial, endocardial, and midmyocardial formulations. The modification thus brings the dominant frequency for midmyocardial cells within the clinical range, with the frequencies for epicardial and endocardial cells just above that range.
Although induced reentrant waves do not produce breakup in two dimensions, it is possible that additional breakup mechanisms specific to three-dimensional tissue [58] could produce fibrillatory-like states. Further study is needed to determine how tissue thickness and anatomy affect the stability of reentry for these models.

4.5 Conclusions

We have analyzed quantitatively the dynamics of two recently published models of human ventricular cells, the GPB model and the OVVR model, in isolated cells and in one- and two-dimensional tissue constructs and have compared the observed properties with those of other ventricular models and with available experimental and clinical data. We have shown that each model has strengths and limitations that suggest how it can be best utilized for cardiac tissue studies. The GPB model produces APDs and a maximum CV value closer to experimentally observed values along with clinically relevant dominant frequencies corresponding to VT. The OVVR model shows greater fidelity of APD variation with S1-S2 restitution curves and produces alternans, although with a magnitude greater than observed experimentally. Using the TP model formulation for \( I_{Na} \) restores the maximum CV of the OVVR model, decreases minimum DI, and increases dominant spiral wave periods. Both models exhibit action potential amplitudes and maximum restitution curve slope values below what has been reported experimentally, do not agree well with observations of maximum upstroke velocity in tissue, and show APD restitution curve maximum slopes below typical experimental values.

Although the models studied in many cases generate different predictions, we emphasize that model disagreement may arise for many possible reasons. The models may exhibit normally observed biological variability or may reflect spatial heterogeneity other than transmural heterogeneity, such as apico-basal [171], left-right [19; 171], or other regional [171; 183] gradients. Differences also may arise from study subject differences such as age and gender. In addition, it is important to note although models generally are designed to reproduce normal cells, it is difficult to access healthy human tissue experimentally. The other models used
for comparison also have limitations, although, like the GPB and OVVR models, many of them match experimental data for some properties well [18]. Thus, reproducing observed dynamical properties of the human ventricles remains a significant modeling challenge.
Table 4.1: Action potential characteristics for the GPB, OVVR, PB, IMW, TP, and BCF models. Characteristics include resting membrane potential ($RMP$), amplitude, minimum phase 1 voltage ($V_{notch}$), plateau voltages ($V_{plateau}$), maximum upstroke velocity ($dV/dt_{max}$), action potential duration ($APD$) at a CL of 1000 ms, APD memory amplitude ($MA_{APD}$), minimum cycle length ($CL_{min}$), minimum diastolic interval ($DI_{min}$), maximum steady-state restitution curve slope, and alternans onset CL. Epicardial formulations are used for the TP and BCF models.
<table>
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<th>GPB</th>
<th>GPB</th>
<th>OVVR</th>
<th>OVVR</th>
<th>OVVR</th>
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<th>IMW</th>
<th>TP</th>
<th>BCF</th>
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<td>Endo</td>
<td>Epi</td>
<td>Endo</td>
<td>Mid</td>
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<td></td>
<td></td>
<td></td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<td>17.7</td>
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<td>303.3</td>
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<td>83.9</td>
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<td>279.6</td>
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<td>APD (ms)</td>
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<td>229.7</td>
<td>258.6</td>
<td>347.8</td>
<td>391.9</td>
<td>317.4</td>
<td>303.4</td>
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<td>MA_{APD} (ms)</td>
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<td>56.9</td>
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<td>95.6</td>
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<td>0.7</td>
<td>0.8</td>
<td>1.1</td>
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<td>310</td>
<td>-</td>
<td>-</td>
<td>330</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Dominant period in 2D (ms)</td>
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<td>430</td>
<td>318</td>
<td>121,178,283</td>
<td>233</td>
<td>286</td>
</tr>
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</table>

Table 4.2: Action potential characteristics for the GPB, OVVR, PB, IMW, TP, and BCF models. Characteristics include resting membrane potential \((RMP)\), amplitude, minimum phase 1 voltage \((V_{notch})\), plateau voltages \((V_{plateau})\), maximum upstroke velocity \((dV/dt_{max})\), action potential duration \((APD)\) at a CL of 1000 ms, APD memory amplitude \((MA_{APD})\), minimum cycle length \((CL_{min})\), minimum diastolic interval \((DI_{min})\), maximum steady-state restitution curve slope, alternans onset CL, maximum conduction velocity \((CV_{max})\), and dominant period of reentry for 2D spiral waves. Epicardial formulations are used for the TP and BCF models.
Chapter 5

Quantitative Analysis of Electrophysiological Heart Failure Model

The purpose of this chapter is to present the electrophysiological activity of a transmural single myocyte, which was simulated using well-justified modifications of a recent mathematical model of the human ventricular AP [181] to replicate the experimentally reported human HF phenotypes. In addition, systematic and quantitative variability in ionic currents and exchangers was introduced utilizing experimental observations published in the literature. In order to reproduce action potential properties under heart failure electrophysiological conditions, as observed by experimentalists, it is essential to investigate all currents, pumps, concentrations, and exchangers activity, which impact the dynamics of an AP. In this chapter, we start by itemizing the identified hallmarks that were observed in a single HF myocyte. These hallmarks include: reduction of AP amplitude and upstroke velocity, diminishing the notch of an AP, prolongation of an APD, increasing the accumulated $[Na^+]$, concentration, and altering the $[Ca^{2+}]$, dynamics. Then, we explain in detail how each current/exchanger was remodeled based on experimental observations. This is one of the aims of this thesis: to simulate remodeling currents/pumps that have physiological meaning and in a comprehensive manner. We explain how each remodeled current/exchanger con-
tributes to AP properties and to which phase. After that, we present the analysis results of our HF model with fixed set of parameters. This developed HF model used to simulate electrical properties in a 0D single cell considering remodeling variations for each ion channel expression. Then, we simulate 1D cable and 2D tissue aiming to investigate the effects of remodeling currents and exchangers in a single myocyte on the properties of arrhythmias on tissue. Finally, we discuss the results and relate it with experimental observations.

5.1 Introduction

There are vast numbers of cellular cardiac electrophysiological models that have been created, which represent either normal or diseased cases. The objective of these models is to explain how the biological system works, replicate the experimental observations, predict quantitatively and simultaneously all properties that are complex to be measured experimentally, and suggest the direction of future experiments and drugs for certain diseases.

In many cases, animal models are used to investigate cardiac electrophysiological properties for both control and HF cases. However, mathematical models and computer simulations also are important tools for studying arrhythmias. To study the mechanisms of VA in humans arising from HF, the mathematical model should be based on recent human data and reproduce important arrhythmogenic phenomena, such as the AP, $[Ca^{2+}]_i$, and alternans. Therefore, we developed a human ventricular cell model under HF conditions that is based on a recently published undiseased human ventricular cell model, namely Thomas O’Hara, László Virág, András Varró, and Yoram Rudy (OVVR) model [181]. This physiologically-based mathematical model of a normal human ventricular cell was chosen because it is formulated to reproduce the normal human ventricular AP with a broad range of essential physiological properties. This original undiseased OVVR model was evaluated through the steady-state (S-S) rate-dependence and restitution curves of an action potential in a single myocyte based on data from more than one hundred normal human hearts. Furthermore, the model can reproduce alternans. In addition, it presents new formulations for unavailable measurements of $I_{Ca,L}$, potassium currents, and $I_{NaCa}$. However, the model was not formulated to in-
vestigate disease-specific situations such as HF, which is our aim in the present thesis. In addition, the OVVR model was designed to simulate heterogeneous transmural cell types, i.e. epicardial, midmyocardial, and endocardial cell types. Unlike comparable models that represent either two cell types, epicardial and endocardial, such as the Grandi, Pasqualini, and Bers (GPB) model [73], or other models which simulate one cell type, i.e. epicardial, such as Iyer, Mazhari, and Winslow (IMW) model [99].

5.2 Remodeling of heterogeneous transmural AP HF conditions

This section will explain in detail the quantitative changes of ion channels, transporters, and pump activities with respect to the original OVVR model to represent the HF model in a single myocyte. The refined parameters are chosen based on the published observations from the previous experimental studies on transmural cell types in failing hearts considering the interval of remodeling for each current/exchanger. We will start by enumerating the characteristics that the HF cell type possesses, which are different from a normal cell type. These identified hallmarks of a single myocyte can be summarized as follows:

- Prolongation of an APD in failing myocytes compared to control myocytes.
- Slight nonsignificant increase in the RMP in failing myocytes.
- Heightened plateau phase of an AP in failing myocytes.
- Decrease in the AP amplitude in failing myocytes.
- Decrease in the maximum upstroke velocity of an AP in failing myocytes.
- Diminishment in the notch during phase 1 of early repolarization of an AP in failing myocytes.
- Increased minimum cycle length in failing myocytes.
- Increased minimum diastolic interval (refractory period) in failing myocytes.
• Decline of the \([Ca^{2+}]_i\) decay time in failing myocytes.
• Reduction in the \([Ca^{2+}]_i\) systolic amplitude in failing myocytes.
• Shortening in the \([Ca^{2+}]_i\) time to peak in failing myocytes.
• Increase in the \([Ca^{2+}]_i\) diastolic steady-state in failing myocytes.
• Increase in the accumulated \([Na^+]_i\) concentration in failing myocytes.
• Raise in the alternans cycle length onset in failing myocytes.
• Expansion in the range of alternans in failing myocytes.
• Steep steady-state APD restitution curve in failing myocytes.
• Dispersion of repolarization in the failing myocytes.

To accomplish the desired remodeling of an AP, \([Ca^{2+}]_i\), \([Na^+]_i\), and all other related properties that should match observed AP properties of ventricular human cell type under HF conditions, we modulate the maximum conductances and permeabilities of the undiseased human ventricular cell model, the OVVR model. This modulation is based mainly on the experimental measurements of human HF cells. In addition, to make our developed HF model more realistic in simulating ventricular myocytes under HF conditions, we simulate all three ventricular cell types, i.e. epicardial, midmyocardial, and endocardial cells, with different parameter settings.

We simulated our developed heart failure OVVR model under two different sets of parameters:

• Fixed set of parameters: In this type of simulation, we setup each remodeled current conductance under heart failure conditions with a single value which represents the percentage of each remodeled current. Table 5.1 summarizes the remodeled current conductances with fixed set of parameters.

• Variable set of parameters: To make the HF model more robust and be able to cover all variabilities encountered during HF, we represent the remodeled data currents and exchangers as mean ± standard deviation (\(\mu \pm SD\)), as indicated in Table 5.2.
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<th>Current</th>
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<th>Independent Effect</th>
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<td></td>
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<tr>
<td>$I_{Na}$</td>
<td>↓(%57)</td>
<td>↓(%57)</td>
</tr>
<tr>
<td>$I_{NaL}$</td>
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<td>↓(%42)</td>
</tr>
<tr>
<td>SERCA</td>
<td>↓(%25)</td>
<td>↓(%55)</td>
</tr>
</tbody>
</table>

Table 5.1: Summary of the remodeling current of the Heart Failure model. ↑: increase; ↓: decrease; epi: epicardium; endo: endocardium; mid: midmyocardial.
Table 5.2: Summary of the remodeled currents and exchangers of the HF-OVVR model in a single myocyte expressed as mean±standard deviation (µ±SD). Some of the data used in remodeling ionic currents are animal data.
In this work, the $I_{\text{ion}}$ of the aforementioned equation 3.1 can be represented by the following equation:

$$I_{\text{ion}} = I_{Na} + I_{NaL} + I_{CaL} + I_{CaK} + I_{K1} + I_{Kr} + I_{Ks} +$$

$$I_{to} + I_{NaCa} + I_{NaK} + I_{NaK} + I_{CaK} + I_{Kb} + I_{pCa}$$  

(5.1)

For the main ionic currents and pumps, we will explain each one of them and its function separately. In addition, we will highlight the degree and phase that each current/pump participates in reproducing HF AP properties. The remodeled currents are presented first followed by remodeled exchangers and pumps:

- **Fast Sodium Current ($I_{Na}$):** This current is activated during the depolarization phase of an AP, which is responsible for upstrokes during the normal impulses in a single myocyte. Most experimental studies on HF-affected myocytes show that the peak $I_{Na}$ is decreased in a range from $\downarrow39.3\pm6.5\%$ to $\downarrow91.1\pm9.3\%$ [65; 220; 246], except for one study [211], which indicates that the peak $I_{Na}$ is unchanged from normal levels. We calculated the mean ($\mu$) and standard deviation ($SD$) of observed remodeling of $I_{Na}$ in cardiomyocytes isolated with these recent experimental studies [65; 220; 246]. In our simulations, we use ($\mu\pm2SD$) to express the range of variations. Fig. 5.3 (A) shows the simulated reduction of the $I_{Na}$. Figure 5.1 shows the simulated reduction of $I_{Na}$ current (upper panel) along with the observed experimental results (lower panel). Figure 5.2 exhibits the effect of reducing $I_{Na}$ current on the amplitude of the simulated AP during the depolarization phase.

- **Late Sodium Current ($I_{NaL}$):** The participation of this current is during the plateau and repolarization phases, not during the depolarization phase of an AP due to its slow dynamics. Most experiments on HF human myocytes [151; 152; 244; 246] show that the $I_{NaL}$ density is increased within a range from $\uparrow30.0\pm0\%$ to $\uparrow238.5\pm1.3\%$. However, one study [150] showed similar $I_{NaL}$ densities in failing and normal hearts, although the small sample size did not allow a statistically significant comparison. Therefore, we
Figure 5.1: (A) Simulation results of the peak $I_{Na}$ current under normal conditions. (B) Simulation results of the peak $I_{Na}$ current under HF conditions expressed within a range of mean+2SD and mean-2SD at CL=1000 ms. (C) Peak $I_{Na}$ current recorded from myocytes of normal human hearts that have been recorded in control solution. (D) Peak $I_{Na}$ current recorded from myocytes of failing human hearts that have been recorded in control solution. Reproduced from [246]
Figure 5.2: Simulation results of the OVVR model. (A) Action potential under normal conditions. (B) The corresponding effect of reducing the $I_{Na}$ current on AP properties under HF conditions expressed within a range of mean $\pm$ 2SD.
computed the average of these experimental observations in human HF myocytes from [151; 152; 244; 246] considering the variation between these studies. Figure 5.4 shows the simulated increase of $I_{NaL}$ current (upper panel) at CL=1000 ms along with the observed experimental data (lower panel). Figure 5.5 exhibits the effects of increasing $I_{NaL}$ current on the plateau and repolarization phases of the simulated AP.

- **L-type Calcium Current ($I_{CaL}$):** This current plays an essential role in shaping the AP morphology, especially in the long plateau phase. Also, it initiates the excitation-contraction coupling. The majority of previous HF observations report that there is no significant difference between $I_{CaL}$ in failing and non-failing myocytes [9; 12; 14; 26; 114; 133; 158; 198; 213; 215; 235]. However, one study [231] observed a decrease in the dihydropyridine (DHP) binding sites within a range from ↓35% to 48% and mRNA by ↓47%. We decided to use the same $I_{CaL}$ density as in non-failing myocytes as reported by most of these experiments for all cell types. Figure 5.6 shows the simulated $I_{CaL}$ current (upper panel) along with the observed $I_{CaL}$ current (lower panel) under normal and HF conditions.

- **Transient Outward Current ($I_{to}$):** This current impacts the notch portion during the rapid phase 1 repolarization of an AP. It is agreed across most experimental observations on human ventricular species that $I_{to}$ is de-
Figure 5.4: (A) Simulation results of the OVVR model peak $I_{NaL}$ current under normal conditions. (B) Simulation results of the OVVR model peak $I_{NaL}$ current under HF conditions expressed within a range mean+2SD and mean-2SD at CL 1000 ms. (C) A representative traces from normal and failing myocytes obtained from human hearts that have been recorded in control solution. Reproduced from [246]
Figure 5.5: Simulation results of the OVVR model (A) Action potential under normal conditions. (B) The corresponding effect of increasing $I_{NaL}$ current on AP properties under HF conditions expressed within a range mean+2SD and mean-2SD at CL 1000 ms.
Figure 5.6: (A) Simulation results of the OVVR model peak $I_{CaL}$ current under normal (green) conditions. (B) Simulation results of the OVVR model peak $I_{CaL}$ current under HF (red) conditions. (C) Original recordings of the $I_{CaL}$ myocytes, that are expressed as current densities (pA/pF), which isolated from non-failing and (D) failing ventricular hearts. Reproduced from [158]
creased with a range from $\downarrow 26.4 \pm 1.3\%$ to $\downarrow 73.2 \pm 5.8\%$ under HF conditions [13; 91; 114; 133; 164; 165; 235; 261; 274]. However, these studies claim that there is no significant change in the kinetics of $I_{lo}$ in failing myocytes when compared with non-failing myocytes. Therefore, we chose to incorporate a downregulation of $I_{lo}$ under HF conditions heterogeneously. This means that different outward potassium conductance settings ($G_{to}$ values) are used to model the transmural heterogeneity of cardiac ventricular cells based on the previous experimental observations [91; 133; 165; 274] for epicardial cells, [13; 91; 114; 164; 235] for midmyocardial cells, and [91; 165; 261; 274] for endocardial cells. As a consequence, $I_{lo}$ is reduced by $\downarrow 40.4 \pm 8.7\%$, $\downarrow 37.6 \pm 3.3\%$, and $\downarrow 50.8 \pm 2.0\%$ for epicardial, midmyocardial, and endocardial cell types, respectively. Figure 5.7 shows the simulated decrease of the $I_{lo}$ current (upper panel) along with compared experimental observations (lower panel), for the midmyocardial cell type. Figure 5.8 exhibits the effects of decreasing the $I_{lo}$ current on the notch as well as the plateau amplitude of the simulated AP at CL=1000 ms.

- **Inward Rectifier Current ($I_{K1}$):** $I_{K1}$ plays a significant role in stabilizing the resting membrane potential (RMP) and in shaping the last portion of the repolarization phase of an AP [280]. Observations from numerous studies have shown that $I_{K1}$ is significantly downregulated within a range from $\downarrow 40 \pm 0\%$ to $\downarrow 64 \pm 0\%$ [2; 13; 101; 114; 125; 133; 231; 235]. Hence, we adopted a reduction of the peak $I_{K1}$ by reducing its conductance ($G_{K1}$) heterogeneously, after calculating the mean and standard deviation, by $\downarrow 55.3 \pm 13.9\%$, $\downarrow 52.7 \pm 14.8\%$, and $\downarrow 55.0 \pm 16.1\%$ for epicardial, midmyocardial, and endocardial cell types, respectively. The transmural remodeling is based mainly on the experimental observations from [125; 133; 231; 235] for epicardial, [13; 125; 231; 235] for midmyocardial, and [125; 231; 235] for endocardial cells. Figure 5.9 shows the simulated decrease of the $I_{K1}$ current (upper panel) along with the observed experimental data (lower panel), for the epicardial cell type. Figure 5.10 exhibits the effects of decreasing the $I_{K1}$ current on the terminal repolarization phase of the simulated HF AP.
Figure 5.7: (A) Simulation results of the OVVR model peak \( I_{to} \) current under normal conditions of the epicardial cell type. (B) Simulation results of the OVVR model peak \( I_{to} \) current under HF conditions of the epicardial cell type that are expressed within a range mean+2SD and mean-2SD at CL=1000 ms. (C) The \( I_{to} \) current recorded from human ventricular myocytes isolated from the midmyocardial wall of the left ventricle. (D) The \( I_{to} \) current recorded from human ventricular myocytes isolated from the midmyocardial wall of the left ventricle. Reproduced from [235]
Figure 5.8: Simulation results of the OVVR model (A) Action potential under normal conditions. (B) The corresponding effect of reducing $I_{to}$ current on AP properties under HF conditions at CL=1000 ms.
Figure 5.9: (A) Simulation results of the OVVR model peak $I_{K1}$ current under normal conditions of the epicardial cell type. (B) Simulation results of the OVVR model peak $I_{K1}$ current under HF conditions of the epicardial cell type that are expressed within a range mean+2SD and mean-2SD at CL=1000 ms. (C) The $I_{K1}$ current recorded at 0.5Hz from human ventricular myocytes isolated from the epicardial surface tissue, which isolated from relatively normal histology cells. (D) The $I_{K1}$ current recorded at 0.5Hz from human ventricular myocytes isolated from the epicardial surface tissue, which isolated from failing cells. Reproduced from [133].
Figure 5.10: Simulation results of the OVVR model. (A) Action potential under normal conditions. (B) The corresponding effect of reducing the \( I_{K1} \) current on AP properties under HF conditions at CL=1000 ms.
• **Rapid Delayed Rectifier Potassium Current** ($I_{Kr}$): $I_{Kr}$ plays an important role in the repolarization phase of an AP (see Fig. 5.12). This current has been studied extensively with controversial observations. Many experiments observed a reduction within a range from ↓27.3±1.7% to ↓51±0% [2; 91; 203; 238], but some studies [114; 115; 133] indicated that $I_{Kr}$ is unchanged. This controversial observation is due in part to the cell type investigated. We speculate that the $I_{Kr}$ current has a prominent effect on characterizing an AP and contributing to induced-HF including the increased susceptibility of alternans onset and initiating an EADs phenomenon based on the great effect of this current that has been reported in the original OVVR model [181]. Therefore, we decided to incorporate remodeling of this current based on the cell type, due to the differences in the shape and duration of APs between these cells, by ↓45.9±9.5% for epicardial cells [91], unchanged for midmyocardial cells [114; 115; 133], and ↓27.3±1.7% for endocardial cells [91]. The simulated $I_{Kr}$ current traces are shown in Fig. 5.3 (B). Figure 5.11 shows the simulated decrease of the $I_{Kr}$ current under normal and HF conditions (upper panel), along with the observed experimental current (middle panel), for the epicardial cell type. The unchanged observations of the midmyocardial cell type between normal and HF conditions is shown in the lower panel. Figure 5.12 exhibits the great effects of decreasing $I_{Kr}$ current on both the plateau and repolarization phases of the simulated HF AP.

• **Slow Delayed Rectifier Potassium Current** ($I_{Ks}$): $I_{Ks}$ is a slow activating current that affects the last portion of repolarization of an AP. Most of the former studies show an agreement on the downregulation of $I_{Ks}$ within a range from ↓49.5±1.6% to ↓61.7±1.4% [2; 132; 133]. Only one study [258] exhibits that the KCNE1 mRNA increases by ↑25%. Another noticeable result from experiments, shows that the reduction of the $I_{Ks}$ current density in all three layers becomes more homogeneous during HF, as opposite to non-failing myocytes in these layers. We decided to follow the majority of the previous experimental observations through reducing the peak current density of $I_{Ks}$ heterogeneously by ↓59.4±2.1% [132; 133], ↓49.5±1.6% [132],
Figure 5.11: (A) Simulation results of the OVVR model peak $I_{Kr}$ current under normal conditions of the epicardial cell type. (B) Simulation results of the OVVR model peak $I_{Kr}$ current under HF conditions of the epicardial cell type that are represented within a range mean+2SD and mean-2SD at CL=1000 ms (upper panel). (C-D) Representative tracings of the $I_{Kr}$ current recorded from rabbit ventricular myocytes, which isolated from control and failing cells [238] (middle panel). (E-F) The $I_{Kr}$ current recorded at 0.1Hz from rabbit LV midway free wall [239] (lower panel).
Figure 5.12: Simulation results of the OVVR model. (A) Action potential under normal conditions. (B) The corresponding affect of reducing the $I_{Kr}$ current on AP properties under HF conditions at CL=1000 ms.
and $\downarrow57.7\pm2.2\%$ [132] for epicardial, midmyocardial, and endocardial cell types, respectively. Figure 5.13 shows the simulated decrease of the $I_{Ks}$ current (upper panel), along with the compared experimental observations (lower panel), for the epicardial cell type. Figure 5.14 exhibits the effects of decreasing $I_{Ks}$ current on the second half of the repolarization phase of the simulated AP.

- **Sodium-Calcium Exchanger Current ($I_{NaCa}$):** $I_{NaCa}$ supports regulating the intracellular calcium concentration. Many experimental observations on the myocardium of HF patients found that the measured activity of the $Na^+/Ca^{2+}$ exchanger is modified in a wide range from $\uparrow80.0\pm0\%$ to $\uparrow200.0\pm0\%$ compared to non-failing myocytes [61; 81; 199; 228; 229]. Therefore, a homogeneous upregulation of $I_{NaCa}$ by $\uparrow131.4\pm62.8\%$ for all different cell types is incorporated into the undiseased OVVR model, which includes both the membrane $I_{NaCa}$ and subspace $I_{NaCa_{ss}}$. Fig. 5.3 (C) exhibits the simulation results of the modified $I_{NaCa}$. Figure 5.15 shows the simulated regulation of the $I_{NaCa}$ current for an epicardial cell type. Figure 5.16 exhibits the effects of regulating $I_{NaCa}$ current on almost all phases of the simulated AP starting from the spike and dome, the plateau amplitude, and the repolarization phase where it effects the APD. This is because the $I_{NaCa}$ current involves both the $Na^+$ and $Ca^{2+}$ concentrations that contributes to all stages of an AP.

- **Sodium-Potassium Exchanger Current ($I_{NaK}$):** $I_{NaK}$ maintains the resting membrane potential (RMP) and ionic homeostasis inside the cell. The majority of experimental studies report that $Na^+/K^+$ pump activity is downregulated within a range from $\downarrow36\pm0\%$ to $\downarrow56\pm0\%$ [113; 121; 145; 216; 219]. One study [106], observed a non-significant decrease of $\downarrow10\%$. We decreased the peak of $I_{NaK}$ homogeneously by $\downarrow40.2\pm15.5\%$ in our HF-OVVR cellular model. Figure 5.17 shows the simulated reduction of the $I_{NaK}$ current for an epicardial single myocyte. Figure 5.18 exhibits the small effects of reducing $I_{NaK}$ current on the repolarization phase of the simulated HF AP.
Figure 5.13: (A) Simulation results of the OVVR model peak $I_{Ks}$ current under normal conditions of the epicardial cell type. (B) Simulation results of the OVVR model peak $I_{Ks}$ current under HF conditions of the epicardial cell type that are represented within a range mean+2SD and mean-2SD at CL=1000 ms. (C) The voltage dependent $I_{Ks}$ recordings at 0.1Hz in relatively normal histology cells isolated from the epicardial surface tissue. (D) The voltage dependent $I_{Ks}$ recordings at 0.1Hz in abnormal histology cells isolated from the epicardial surface tissue [133].
Figure 5.14: Simulation results of the OVR model. (A) Action potential under normal conditions. (B) The corresponding effect of reducing the $I_{Ks}$ current on AP properties under HF conditions at CL=1000 ms.
Figure 5.15: Simulation results of the QVVR model of the epicardial cell type (A) Peak $I_{NaCa}$ current under normal conditions. (B) Peak $I_{NaCa}$ current under HF conditions that are represented within a range mean$-2SD$ and mean$+2SD$ at CL=1000 ms.
Figure 5.16: Simulation results of the OWIR model. (A) Action potential under normal conditions. (B) The corresponding effect of increasing the $I_{NaCa}$ current on AP properties under HF conditions at CL=1000 ms.
Figure 5.17: Simulation results of the OVV model of the epicardial cell type. (A) Peak $I_{Na,K}$ current under normal conditions. (B) Peak $I_{Na,K}$ current under HF conditions that are represented within a range mean $\pm$ 2SD and mean $\pm$ 2SD at CL = 1000 ms.
Figure 5.18: Simulation results of the OVVR model (A) Action potential under normal conditions. (B) The corresponding effect of reducing the $I_{NaK}$ current on AP properties under HF conditions at CL=1000 ms.
• Sarcoplasmic Reticulum $Ca^{2+}$ (SERCA) pump: This pump transports calcium ions from the cytosol into the SR. Most of the experimental observations claim that an alteration of $[Ca^{2+}]_i$ in failing human and animal myocytes is based on the dynamics of the SR $Ca^{2+}$ pump, which is decreased in a range from ↓15.4±0% to ↓50.0±0% [7; 46; 78; 80; 81; 107; 144; 157; 187; 192; 268]. $[Ca^{2+}]_i$ under HF conditions is characterized by a reduction of calcium levels during the systolic phase, an elevation of calcium levels during the diastolic phase, and prolongation of calcium levels during the relaxation phase. We decided to incorporate a remodeling of SERCA in our HF-OVVR model through decreasing the SERCA activity heterogeneously by ↓41.3±12.5% [78; 80; 81; 144; 157; 192; 268], ↓42.3±11.3% [78; 80; 81; 157; 187; 192; 268], and ↓41.1±10.1% [78; 80; 81; 107; 144; 157; 192; 268] for epicardial, midmyocardial, and endocardial cell types, respectively. Figure 5.19 shows the simulated normal $[Ca^{2+}]_i$ dynamics (upper panel), along with validated experimental observation for the epicardial cell type (lower panel). Figure 5.20 depicts the simulated HF $[Ca^{2+}]_i$ dynamics (upper panel), along with validated experimental observation for the epicardial cell type (lower panel). Figure 5.21 shows the simulation results of the OVVR model peak $I_{CaL}$ current after remodeling SERCA under HF conditions. Figure 5.22 exhibits the small effects of reducing SERCA dynamics on the plateau and early repolarization phases of the simulated HF AP.

5.3 Single cell results with the general set of HF-OVVR model parameters

5.3.1 Heart failure simulation of an action potential in a single cell

Both action potentials of control and failing myocytes were simulated and compared for all kinds of cells. Figure 5.23, shows the simulated normal and HF APs (upper panel), along with experimental observations (lower
Figure 5.19: (A) Simulation results of the OVVR model \([Ca^{2+}]_i\) dynamics under normal conditions of the epicardial cell type at CL=1000 ms. (B) Cytosolic \(Ca^{2+}\) transients in a myocyte from a control heart in physiologic solution, Reproduced from [12].
Figure 5.20: (A) Simulation results of the OVVR model $[Ca^{2+}]_i$ dynamics under HF conditions of the epicardial cell type that are represented within a range mean+2SD and mean-2SD at CL=1000 ms. (B) Cytosolic $Ca^{2+}$ transients in a myocyte from a failing heart. Reproduced from [259].
Figure 5.21: (A) Simulation results of the OVVR model peak \(I_{Ca,L}\) current under normal conditions. (B) Simulation results of the OVVR model peak \(I_{Ca,L}\) current under SERCA HF conditions that are represented within a range of mean\(\pm\)2SD and mean\(\pm\)SD at CL=1000 ms.
Figure 5.22: Simulation results of the OVVR model (A) Action potential under normal conditions. (B) The corresponding effect of reducing the SERCA on AP properties under HF conditions that are expressed within a range mean±2SD and mean±2SD at CL=1000 ms.
panel) that are reproduced from [133] for epicardial cell types. Figure 5.24, exhibits the simulated normal and HF APs (upper panel), along with experimental observations (lower panel) for midmyocardial cell types. Figure 5.25, depicts the simulated normal and HF APs (upper panel), along with experimental observations (lower panel) for endocardial cell types. To obtain a steady-state for all of the following: AP, currents, as well as intracellular \([Ca^{2+}]_i\) concentration, for both undiseased and HF models; the simulation was run for 60 s, and the last AP was elicited with its currents and concentrations at a pacing frequency of 1Hz (CL=1000 ms). Table 5.3, depicts the quantitative biomarkers difference between normal and HF properties of the OVVR model in a single myocyte, along with Table 5.4 that shows quantitative comparison of these biomarkers with experimental observations under HF conditions. The values of HF are represented as a range to cover many variations of observed action potentials as can be seen in Figures 5.26 and 5.27. 5.6, 5.7.

As you can see from Figures 5.23, 5.24, and 5.25 for epicardial, midmyocardial, and endocardial cell type, respectively, the AP at 90% repolarization of failing myocytes is prolonged within a range 339.1 - 606.9, 441.7 - 869.7, and 404.5 - 609.3, respectively, over non-failing myocytes due to sustained plateau (like epi-), or much slower repolarization (like mid- and endo-) dynamics of an AP. These results are in agreement with experimental observations from [12; 133; 193]. The same pattern is observed for \(APD_{50}\). The AP amplitude is decreased for all three cell types. The upstroke velocity is significantly reduced within a range 113.8 - 114.6, 114.6 - 116.2, and 115.2 - 117.8 in failing epi-, mid-, and endo- myocytes, respectively, compared with corresponding non-failing myocytes. These observations matched the previous findings where previous studies report that the upstroke velocity reduces to its half value under HF conditions compared to control conditions. Additionally, the resting membrane potentials are barely increased in all cell types in the developed HF model, which are in agreement with experimental observations of HF cells [126; 132; 159; 238; 248].

The prolongation of an APD induces the \(I_{CaL}\) peak current to increase and
Figure 5.23: (A) Simulation results of an AP dynamics OVVR model of the epicardial cell type at CL=1000 ms under normal and HF conditions. (B) Experimental observations of an AP dynamics in an epicardial myocyte extracted from relatively normal histology (RNH) and abnormal histology (AH). Reproduced from [133].
Figure 5.24: Simulation results of an AP dynamics OVVR model of the midmyocardial cell type at CL=1000 ms under (A) normal conditions. (B) HF conditions. Experimental observations of an AP dynamics in a midmyocardial myocyte extracted from (C) normal tissue. (D) HF tissue.
Figure 5.25: Simulation results of an AP dynamics OVVR model of the endocardial cell type at CL=1000 ms under (A) normal conditions. (B) HF conditions. Experimental observations of an AP dynamics in an endocardial myocyte extracted from (C) normal tissue. (D) HF tissue.
Figure 5.26: Experimental observation of an AP in a single myocyte that was extracted from patients with HF [12].

contributes to the $I_{NaCa}$ to remove $Ca^{+2}$ during the repolarization phase. The cause of this alteration is that the rate of the SR buffer is decreased, which causes the intracellular $[Ca^{+2}]_i$ concentration to slowly decay and at the same time it reduces the $Ca^{+2}$ stored in the SR buffer. This leads to reduced $Ca^{+2}$ release from the SR buffer, which induces more influx of $Ca^{+2}$ during the plateau phase that causes increasing the height of the plateau phase. Two factors contributed to this additional $Ca^{+2}$ influx, the increased of $I_{CaL}$ peak current and the slow decay of intracellular $[Ca^{+2}]_i$ concentration. This means that the sodium-calcium exchanger increased its contribution for $Ca^{+2}$ removal.

For $Ca^{2+}$ dynamics, the $[Ca]_i$, systolic amplitude in the developed HF model matches the experimental observations [12; 44; 47; 85; 189; 190; 270], where it decreases to almost half values compared to non-failing myocytes. One of the prominent proarrhythmia biomarkers is the repolarization time from $APD_{50}$ to $APD_{90}$, which is known as triangulation, because as the time difference between $APD_{50}$ and $APD_{90}$ prolongs, the action potential takes a more triangular shape. It is an important proarrhythmia biomarker because it measures the slow rate of repolarization of an AP, which is one phenomenon observed in the failing myocytes. Triangulation is one of the
Figure 5.27: Experimental observation of (A) non-failing and (B-D) failing myocytes [193].
main factors that induces proarrhythmia whether the APD is lengthened (PVT) or shortened (MVT) [92]. Also, it has been shown that triangulation increases the incidence of EADs [142; 260]. As observed in our modified HF OVVR model that the range of triangulation values are increased in all kinds of cells, but with different values, by 69.8 - 128.0 ms, 89.8 - 120.6 ms, and 86.1 - 132.7 ms for epi-, mid-, and endocardium, respectively, when compared with the original undiseased OVVR model. The increased triangulation is in agreement with experimental observations of HF cells [12; 193].

Even with our consideration of the variability that was observed during HF, there are some experiments that observed an increase APD that was less than our results, where the measured difference of APD at 80% of repolarization at, 94 ms, 40 ms, and 12 ms, for subepicardial, midmyocardial, and subendocardial, respectively. These measurements were taken from non-failing and failing human ventricle myocytes with stimulation duration of 2000 ms. However, [12] observed an increase in APD, measured at 90% of repolarization, by 389 ms in myocytes isolated from hearts with end stage heart failure caused by dilated cardiomyopathy (DCM) or ischemic cardiomyopathy (ICM). This is in agreement with our results.

5.3.2 Rate dependence of APD and major currents

We compared the action potentials, main transmembrane currents ($I_{CaL}$, $I_{NaCa}$, $I_{K1}$, $I_{Kr}$, $I_{Ks}$, and $I_{to}$), and calcium and sodium transients in single cells of the normal and HF OVVR models for a range of different CLs for the epicardial formulations. As shown in Figure 5.28 A-B, the action potentials of the two models have different shapes where the HF APs do not have spikes during early repolarization phase, due to the reduction of $I_{Na}$ current. Also, the repolarization dynamics more slowly on HF cells where the shape of an action potential appears like a triangle. Although action potentials obtained using the normal OVVR model have higher amplitude during the depolarization phase, the HF OVVR model possesses higher
### Table 5.3: Normal and Heart Failure properties of the OVVR model in a single cell.

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<th>Heart Failure</th>
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<td>(APD_{50}) (ms)</td>
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<td>Triangulation (ms)</td>
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<td>(DI_{min}) (ms)</td>
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<td>$APD_{90}$ (ms)</td>
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<td>$APD_{50}$ (ms)</td>
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<td>Triangulation (mV)</td>
<td>[12; 193] NQ</td>
<td>56.25</td>
</tr>
<tr>
<td>$RMP$ (mV)</td>
<td>1.0[^132]</td>
<td>0.38</td>
</tr>
<tr>
<td>$dV/dt$ (V/s)</td>
<td>-</td>
<td>↓47.7%</td>
</tr>
<tr>
<td>$[Ca^{2+}]_i$ systolic amplitude</td>
<td>[44; 189; 190]</td>
<td>↓45.75%</td>
</tr>
<tr>
<td>$[Ca^{2+}]_i$ time to peak (ms)</td>
<td>-</td>
<td>59.7</td>
</tr>
<tr>
<td>$[Ca^{2+}]_i$ diastolic steady state</td>
<td>-</td>
<td>↑1.48%</td>
</tr>
<tr>
<td>$[Ca^{2+}]_i$ diastolic steady state (µM)</td>
<td>-</td>
<td>78.38</td>
</tr>
</tbody>
</table>

Table 5.4: Comparison Between Experimental Observations and modified OVVR Model of Heart Failure (OVVR-HF) properties in a single cell. NQ: Not Quantified
plateaus, longer durations and exhibits more rate dependence than those of the normal OVVR model.

The main transmembrane currents of the two models generally show differences in magnitude and in the degree of rate dependence. Neither model displays much rate dependence of $I_{CaL}$ current (see Figure 5.28 C-D), but the peak current at all cycle lengths is more than twice as large for the HF OVVR model (-4.9 pA/pF) as for the normal OVVR model (-2.0 pA/pF) at CL=1000 ms. $I_{NaCa}$ exhibits stronger rate dependence for both models with a larger degree for the HF OVVR model, as shown in Figure 5.28 E-F. The peak inward current is twice as large for the HF OVVR model as for the normal OVVR model for all ranges of CLs.

$I_{K1}$ has similar patterns in the two models, however, the peak current is about 100% larger for the normal model than for the HF OVVR model, as shown in Figure 5.28 G-H. In addition, $I_{K1}$ in the HF OVVR model displays almost no rate dependence, whereas for the normal OVVR model the peak value decreases slightly with decreasing CL. As shown in Figure 5.28 I-J, $I_{Kr}$ exhibits very slight rate dependence in both models, but its peak value for the normal OVVR model is two times larger than for the HF OVVR model, indicating that it plays a more significant role during repolarization for the normal OVVR model. $I_{Ks}$ is also a little bit larger for the normal OVVR model than for the HF OVVR model (see Figure 5.28 K-L). The HF OVVR model shows almost no rate dependence of $I_{Ks}$ with slight decreasing amplitude, but in the opposite way: as CL decreases, the peak value of $I_{Ks}$ increases for the normal OVVR model. For the $I_{Lo}$ current, both models show limited rate dependence, as shown in Figure 5.28 M-N. The peak current is five times larger for the normal OVVR model than for the HF OVVR model at slow pacing rates, and increases at fast rates six times.

Figure 5.28 O-P, shows the calcium transients (intracellular calcium concentration $[Ca^{2+}]_i$) for both models. The peak value is about twice as large for the normal OVVR model as for the HF OVVR model during slow and fast rates. In both models, the $[Ca^{2+}]_i$ peak value increases as the CL decreases.
<table>
<thead>
<tr>
<th>Metric</th>
<th>Cell Status</th>
<th>Repo.</th>
<th>epicardium</th>
<th>midmyocardium</th>
<th>endocardium</th>
</tr>
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<tr>
<td></td>
<td>Normal</td>
<td>50%</td>
<td>65.8 ms (35.1%)</td>
<td>84.8 ms (30.1%)</td>
<td>71.3 ms (34.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90%</td>
<td>65.5 ms (28.6%)</td>
<td>79.3 ms (23.0%)</td>
<td>74.1 ms (28.3%)</td>
</tr>
<tr>
<td></td>
<td>HF</td>
<td>50%</td>
<td>126.3 ms (36.1%)</td>
<td>117.6 ms (32.0%)</td>
<td>118.3 ms (31.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90%</td>
<td>127.4 ms (28.8%)</td>
<td>97.4 ms (19.8%)</td>
<td>112.5 ms (22.7%)</td>
</tr>
</tbody>
</table>

Table 5.5: Summary of the steady state $APD_{50}$ and $APD_{90}$ rate dependency observed in normal and HF single cell; Repo.: Repolarization threshold.

from 1000 ms to 300 ms, so that the $[Ca^{2+}]$, peak-frequency relationship is always positive. In addition, the calcium transient rises and falls more slowly for the HF OVVR model than for the normal OVVR model.

5.3.3 Restitution curves and short-term memory

Action potentials for both the original and HF OVVR models exhibit significant rate adaptation, as shown in Figure 5.30 for single cells. The steady-state restitution curves reflect this adaptation to rate, with the APD in a single myocyte varying by about 65.5 ms and 127.3 ms for the normal and HF OVVR models, respectively, over CLs below 1000 ms, as shown in Figure 5.31 A and D (solid lines). For all cell types detail, see Table 5.5. The slopes of the steady-state restitution curves in single cells for both models are $<1$ over all DIs, with a maximum slope of 0.54 for the endocardial cell type of the normal OVVR model and 0.62 for the midmyocardial cell type of the HF OVVR model. Also, as it expects that all APDs measured either at 90% or 50% are longer for the HF OVVR model than the normal OVVR model as depicted in Figure 5.31.

Figure 5.31 shows steady-state APD restitution curves at 90% and 50% of repolarization from both normal and HF OVVR models. All curves decrease monotonically with different degrees. For CLs below 1000 ms, APDs vary the most for the epicardial cell types of the HF OVVR model (with a 126.3 ms or 36.1% decrease) at 50% of repolarization and the least for the midmyocardial cell types of the HF OVVR model (with a 97.4 ms or 19.8%
Figure 5.28: Rate dependence of action potentials, primary transmembrane currents, and intracellular calcium concentration in a single cell for the normal OVVR (columns 1 and 3) and HF OVVR (columns 2 and 4) models for cycle lengths of 1000 ms (solid black), 800 ms (dashed green), 600 ms (dashed red), and 400 ms (dashed blue). The HF OVVR model generally shows more rate dependence; however, the normal OVVR model shows greater rate dependence for $I_{Ks}$ and $[Ca^{2+}]_i$. 
Figure 5.29: Rate dependence of the primary transmembrane currents, and intracellular sodium concentration in a single cell for the normal OVVR (columns 1 and 3) and HF OVVR (columns 2 and 4) models for cycle lengths of 1000 ms (solid black), 800 ms (dashed green), 600 ms (dashed red), and 400 ms (dashed blue). The HF OVVR model generally shows more rate dependence; however, the normal OVVR model shows greater rate dependence for $I_{NaK}$.
Figure 5.30: Steady-state APD 90% and 50% restitution curves for OVVR model in a single cell. (A-D) epicardial. (B-E) endocardial. (C-F) midmyocardial. The curves are colored as normal (green) and HF (red). Curves were obtained after pacing for 60 s and show significant differences among the status condition of cell type.
Figure 5.31: Steady-state APD 90% restitution curves for normal and HF OVVR models in a single cell. (A) epicardial, (B) endocardial, (C) midmyocardial. Steady-state APD 50% restitution curves for normal and HF OVVR models in a single cell. (D) epicardial, (E) endocardial, (F) midmyocardial. Curves were obtained after pacing for 60 s and show significant differences among the status condition of cell type.
decrease) at 90% of repolarization. It is obvious that the APD range of HF cells is wider than the normal OVVR model which reflects the phenomenon known as dispersion of repolarization. The normal OVVR APD range is in between for all cell types, as shown in Figure 5.30 and Figure 5.31.

Short-term memory, which reflects the influence of pacing history, is an important property demonstrated by both the normal and HF OVVR models, but with different degrees. The effects of short-term memory can be observed through differences in the S1-S2 APD restitution curve as the S1 CL is varied. Figure 5.30 (dashed lines) shows S1-S2 APD restitution curves for a range of S1 CLs superimposed with the steady-state restitution curve for the normal OVVR model (upper panel), but not for the HF OVVR model (lower panel). Both models show memory; we quantify the memory using the memory amplitude, which is defined as the difference between the maximum and minimum APDs over the range of S1 CLs at the longest DI of 1000 ms [29]. The memory amplitude for the epicardial cell type is considerably lower for the normal OVVR model (18.1 ms) than for the HF OVVR model (35.1 ms) in a 0D single cell, as well as for other cell types (see Figure 5.30). In terms of restitution curve shapes and slopes, S1-S2 curves for both the normal and HF OVVR models decreases monotonically and with more steep decreasing at shorter DIs (≤ 200 ms).

To examine the changes in APD after a sudden sustained change in CL, the cell was first paced at a constant CL=1000 ms until the APD reaches a steady-state, for 8 min. Then, the CL was abruptly decreased to CL=600 ms and maintained for 8 min with this new CL until the APD reaches a steady-state. Finally, the CL was restored to the original CL=1000 ms and held for this CL until the APD reached a steady-state, for 8 min.

Figure 5.33 exhibits the time course (24 min.) of APD adaptation for an abrupt decreasing and increasing CL for both the normal and HF OVVR models. For abruptly decreasing CL, three cell types, namely normal endocardial, and HF epicardial and midmyocardial, possess two phases of adaptations; the first phase is fast and has blunted decrease and increase of an APD, where the second phase is characterized by slow decay until
Figure 5.32: Steady-state and S1-S2 APD 90% restitution curves for the OVVR model in a single: (A) normal epicardial cell. (B) normal endocardial cell. (C) normal midmyocardial cell. (D) HF epicardial cell. (E) HF endocardial cell. (F) HF midmyocardial cell. Curves were obtained after pacing for 60 s and show significant differences among the status condition of cell type.
it reaches a steady state APD. The APD adaptation for the other three
types of cells, namely normal epicardial and midmyocardial and HF endo-
cardial, are decreasing monotonically with greater degree after an abrupt
CL change. For abruptly increasing CL, all of the cell types exhibit spike
and dome, but with different degrees, resembling the shape of an action po-
tential, except the normal endocardial cell type which shows monotonically
increasing APD until it reaches a steady state.

5.3.4 Alternans

Alternans occurs for a small number of CLs in 0D for the normal OVVR
model in both the epicardial and endocardial cell types, but not in midmy-
ocardial cells. For the HF OVVR model alternans appears only in epicardial
cell types. Figure 5.34 A-B, shows that in a non-failing single epicardial cell,
alternans occurs only for a CL of 165 ms, with a magnitude (difference in
the APDs of two consecutive beats) of 1.48 ms, as depicted in Figure 5.35 A.
In a failing single epicardial cell, an alternans occurs at higher CLs accom-
panied by an extended alternans range, which develops to between 320 and
460 ms, as shown in Figure 5.34 C-D, and increased alternans magnitude
to become 8.0 ms, as depicted in Figure 5.35 A. Alternans for a non-failing
single endocardial cell occurs for CLs between 200 and 280 ms, as shown in
Figure 5.34 E-F, with a maximum magnitude of 11.76 ms, as depicted in
Figure 5.35 B. However, for HF an alternans does not occur.

5.4 Single cell results with more human-specific
set of HF-OVVR model parameters

5.4.1 HF Simulation of an AP in transmural cells:

Figure 5.36 depicts the transmural simulated APs of the normal OVVR
model (dotted green lines) and HF-OVVR model (solid black lines) for epi-
cardial (A), midmyocardial (B), and endocardial (C) cell types at CL 1000
Figure 5.33: Time course of APD adaptation after two consecutive step decreases and increases in CL for normal (upper panel) and HF (lower panel) heterogeneous cell type. In both abruptly changing CL are followed by an immediate rapid phase followed by a slow phase in all cell types, except in normal epicardial cell type and HF endocardial cell type. (A) Normal epi. (B) Normal endo. (C) Normal mid. (D) HF epi. (E) HF endo. (F) HF mid.
Figure 5.34: Alternans in a single cell from the OVVR model. (A) AP traces of normal epicardial, (B) Bifurcation diagram of normal epicardial, (C) AP traces of HF epicardial, (D) Bifurcation diagram of HF epicardial, (E) AP traces of normal endocardial, and (F) Bifurcation diagram of normal endocardial.
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Normal</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>epi</td>
<td>endo</td>
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<tr>
<td>$APD_{90}$ (ms)</td>
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<td>262.35</td>
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<td>$APD_{50}$ (ms)</td>
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<td>204.36</td>
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<td>57.99</td>
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<td>-87.87</td>
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<td>Amplitude (mV)</td>
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<td>127.47</td>
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<td>-</td>
</tr>
<tr>
<td>$V_{\text{plateau}}$ (mV)</td>
<td>31.41</td>
<td>37.25</td>
</tr>
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<td>$dV/dt$ (V/s)</td>
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<td>220.7</td>
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<td>0.5351</td>
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<td>-</td>
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<td>401.5</td>
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<td>$[Na^+]_i$ peak (ms)</td>
<td>-</td>
<td>-</td>
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Table 5.6: Normal and Heart Failure properties of the OVVR model in a single cell.
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<th>epi exp.</th>
<th>model</th>
<th>mid exp.</th>
<th>model</th>
<th>endo exp.</th>
<th>model</th>
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<td>APD&lt;sub&gt;90&lt;/sub&gt; (ms)</td>
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<td>211.76</td>
<td>145.00&lt;sup&gt;[203]&lt;/sup&gt;</td>
<td>150.00&lt;sup&gt;[132]&lt;/sup&gt;</td>
<td>146.88</td>
<td>295.00&lt;sup&gt;[132]&lt;/sup&gt;</td>
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<td></td>
<td>155.51</td>
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<td>233.13</td>
<td>150.00&lt;sup&gt;[132]&lt;/sup&gt;</td>
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<td>56.25</td>
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<td>71.59</td>
<td>130</td>
<td></td>
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<td>0.4&lt;sup&gt;[132]&lt;/sup&gt;</td>
<td>0.82</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>V&lt;sub&gt;plateau&lt;/sub&gt; (mV)</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>dV/dt (V/s)</td>
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<td>-</td>
<td>↓48.9%</td>
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<td>-</td>
<td>-</td>
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<td>-</td>
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<td>D1&lt;sub&gt;min&lt;/sub&gt; (ms)</td>
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<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
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<td>Max. slope</td>
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<td>-</td>
<td>-</td>
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<tr>
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<td>-</td>
<td>-</td>
<td>-</td>
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<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sub&gt;i&lt;/sub&gt; decay (ms)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sub&gt;i&lt;/sub&gt; systolic amplitude</td>
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<td>59.7</td>
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<td>-</td>
<td>241.0</td>
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<td>↑1.48%</td>
<td>-</td>
<td>↑35.59%</td>
<td>-</td>
<td>↑13.79%</td>
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<td>-</td>
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Table 5.7: Comparison Between Experimental Observations and modified OVVR Model of Heart Failure properties in a single cell. NQ: Not Quantified
<table>
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<th>Biomarker</th>
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<th>Heart Failure</th>
</tr>
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<tr>
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<td>midmyo</td>
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<td>345.0</td>
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<td>281.3</td>
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<td><strong>Triangulation</strong> (ms)</td>
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<tr>
<td><strong>RMP</strong> (mV)</td>
<td>-87.8</td>
<td>-87.6</td>
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<td><strong>Amplitude</strong> (mV)</td>
<td>123.2</td>
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<td><strong>V&lt;sub&gt;notch&lt;/sub&gt;</strong> (mV)</td>
<td>27.8</td>
<td>28.6</td>
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<td><strong>V&lt;sub&gt;plateau&lt;/sub&gt;</strong> (mV)</td>
<td>31.4</td>
<td>41.5</td>
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<td><strong>(dV/dt)&lt;sub&gt;max&lt;/sub&gt;</strong> (V/s)</td>
<td>217.1</td>
<td>213.2</td>
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<td>21.9</td>
<td>24.0</td>
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<td><strong>Alternans magnitude</strong> (ms)&lt;sup&gt;+&lt;/sup&gt;</td>
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<td>-</td>
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<td>-</td>
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<td>697.4</td>
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<td><strong>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sub&gt;i&lt;/sub&gt; time to peak</strong> (ms)</td>
<td>41.5</td>
<td>32.3</td>
</tr>
<tr>
<td><strong>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sub&gt;i&lt;/sub&gt; diastolic steady state</strong> (µM)</td>
<td>77.1</td>
<td>92.8</td>
</tr>
<tr>
<td><strong>[Na&lt;sup&gt;+&lt;/sup&gt;]&lt;sub&gt;i&lt;/sub&gt; peak</strong> (ms)</td>
<td>7.7</td>
<td>8.2</td>
</tr>
</tbody>
</table>

Table 5.8: Comparison between extracted electrophysiological biomarkers from the simulations of the OVVR model under normal and heart failure conditions for transmural cell types. The pacing CL=1000 ms. + Downsweep pacing protocol was used starting from CL=1000 ms. * For EADs, the pacing protocol begins at CL=2000 ms.
Figure 5.35: (A) Alternans magnitude of the non-failing (green bar) and failing (red bars) epicardial cell type. (B) Alternans magnitude of the non-failing (green bars) endocardial cell type.

ms. As shown in the left panel of Fig. 5.36, the HF settings of the OVVR model diminish the spike-and-dome morphology of an epicardial AP and the plateau is increased. In addition, $APD_{90}$ is increased due to the slow repolarization dynamics. Similar behavior is observed in the failing midmyocardial cell type (see Fig. 5.36 middle panel), where $APD_{90}$ is increased. Some HF population cases exhibit a two-phase repolarization, which also has been observed experimentally [12]. For the failing endocardial cell type, Fig. 5.36 left panel, the maximum amplitude is unchanged, but the AP gets delayed due to the reduction of $I_{Na}$ for all of the HF population. Table 5.8 summarizes all the extracted biomarkers of the OVVR model under undiseased and HF conditions for heterogeneous cell types.

5.4.2 Rate dependence of APD and major currents:

An important role in excitation is the adaptation of an AP to changes in pacing cycle length. As illustrated in Fig. 5.37 A-B, the APs of the HF-
Figure 5.36: Representative variation of the simulated OVVR action potentials under normal (dotted green) and different HF (solid black) conditions for (A) epicardial, (B) midmyocardial, and (C) endocardial cell types. (*) The four black solid lines represent different variations in parameter values of $\mu-2SD$, $\mu-SD$, $\mu$, and $\mu+SD$ for all ionic currents at a CL of 1000 ms.

OVVR model exhibit stronger rate dependence than APs of the OVVR model. For $I_{CaL}$, the HF-OVVR also exhibits stronger rate dependence than the OVVR model. However, the maximum amplitude in the HF-OVVR is two times larger than in the OVVR model for all CLs (see Fig. 5.37 C-D). Due to the reduction of SERCA, the systolic calcium amplitude is reduced and contributes to the slow diastolic decay of calcium, which induces more calcium influx during the AP plateau phase. Similar rate adaptation is observed for $I_{NaCa}$, where the HF-OVVR model possesses stronger rate adaptation than the OVVR model, as shown in Fig. 5.37 E-F. Regarding $I_{K1}$, both models exhibit limited rate dependence, as depicted in Fig. 5.37 G-H, but the OVVR model possesses maximum values larger than the HF-OVVR model by $\sim$100%. For $I_{Kr}$, both models show limited rate dependence, with the HF-OVVR model peak current values smaller than the OVVR model by $\sim$50% for all CLs (see Fig. 5.37 I-J). For $I_{Ks}$, the OVVR model exhibits larger rate dependence than the HF-OVVR model. As shown in Fig. 5.37 K-L, the maximum value is increased as the CL is decreased for the OVVR model, but it is slightly decreased for the HF-OVVR model before it is increased at shorter CLs. In contrast, the HF-OVVR model has stronger rate dependence for $I_{NaL}$ than the OVVR
Figure 5.37: Rate dependence of action potentials, primary transmembrane currents, and intracellular calcium concentration in a single myocyte for the normal OVVR (columns 1 and 3) and HF-OVVR (columns 2 and 4) models for cycle lengths of 1000 ms (solid black), 800 ms (dashed green), 600 ms (dashed red), 400 ms (dashed blue), and 350 ms (dashed purple). The HF-OVVR model generally shows more rate dependence; however, the normal OVVR model shows greater rate dependence for $I_{K_s}$ and $[Ca^{2+}]_i$. The inset bar diagrams indicates the peak values for each specific curve.

model at shorter CLs (see Fig. 5.37 M-N). Both models exhibit large rate dependence of the calcium transient for all CLs, as shown in Fig. 5.37 O-P. However, the OVVR model has a peak calcium value four times larger than that of the HF-OVVR model.

5.4.3 Restitution curves and short-term memory (STM):

Figure 5.38 (dashed lines) shows S1-S2 APD restitution curves for a range of S1 CLs for the HF-OVVR model. These S1-S2 curves are superimposed with S-S APD restitution curves. All HF-OVVR restitution curves decrease.
monotonically with CL. Also, all transmural cell types exhibit short-term memory with the midmyocardial cell possessing the largest STM=23.6 ms, and the epicardial cell having the shortest, STM=14.7 ms. The endocardial cell falls in between with STM=20.9 ms. Fig. 5.39 exhibits the time course (24 min) of APD adaptation to an abrupt decrease and increase of CL for both the normal OVVR and HF-OVVR models. When accommodating to a decrease in CL, the HF-OVVR model for the epicardial cell type has two phases of accommodation. In the first phase the APD has a rapid decrease and increase in the AP duration followed by slow decay until it reaches a steady state. However, for the normal epicardial cell type of the OVVR model, the APD is consistently decreasing. Similar behavior was observed for accommodation to an increase in CL (see Fig. 5.39).

5.4.4 Alternans (ALTs):

Alternans occurs for all three types of cells of the HF-OVVR model, but with a different alternans window and magnitude. For epicardial cells, Fig. 5.40 A-B, the alternans onset occurs at a CL of 400 ms and lasts to a CL of 350 ms with a maximum alternans amplitude of ∼30.0 ms. As shown in Fig. 5.40 C-D, which represents the midmyocardial cell, the alternans
Figure 5.39: Time course of APD accommodation after an abrupt change in cycle length for the (A) normal OVVR and (B) HF-OVVR model. The epicardial cell type was used.

window is 420 - 600 ms with ∼36.0 ms maximum $APD_{90}$ difference. The endocardial cell type, as depicted in Fig. 5.40 E-F, has the lowest alternans amplitude (∼22.0 ms) along with the lowest alternans onset CL of 380 ms. The alternans window falls between 270 and 380 ms.

5.4.5 Early afterdepolarizations (EADs):

Usually, ventricular arrhythmias (VA) and sudden cardiac death (SCD) are associated with HF [108], and EADs are thought to play a major role in the initiation of arrhythmias. As depicted in Fig. 5.41, the HF-OVVR model favors the occurrence of EADs because of the prolongation of $APD_{90}$, shown here for a cycle length of 1000 ms. This $APD_{90}$ prolongation is caused by both $I_{CaL}$ and $I_{NaL}$, which lengthen the plateau phase and allow the late calcium current to reactivate. When preventing $I_{CaL}$ recovery or blocking $I_{NaL}$ in the HF-OVVR model, EADs were suppressed.

5.4.6 Comparison with previous HF models:

In this subsection, we compare HF biomarkers of the HF-OVVR model with previous HF simulation studies:
Figure 5.40: Alternans in a single epicardial (first row), midmyocardial (second row), and endocardial (third row) cell from the HF-OVVR model. (A-C-E) AP traces. (B-D-F) Bifurcation.
Figure 5.41: Mechanisms for early afterdepolarizations (EADs) of the HF-OVVR model for the epicardial cell type. (A) AP traces. (B) $I_{CaL}$. (C) $I_{NaL}$. (D) $I_{NaCa}$ under normal (solid green lines), HF (solid red lines), and blocked $I_{NaL}$ (dotted blue lines) with CL=$1000$ ms.
- AP duration at 90%: \( APD_{90} \) in [193], 548.8 ms, increased by 46.7%; in [273], 273.0 ms, increased by 22.9%, 369.0 ms, increased by 44.1%, and 338.0 ms, increased by 50.2% for epicardial, midmyocardial, and endocardial cell types, respectively; in [237], \( \sim 470.0 \) ms, increased by 24.0%; in [266], 500.0 ms, increased by 66.7%; in [272], 600.0 ms, increased by 106.9%; in [222], increased by \( \sim 30.0\% \); in [160], increased by 562.5 ms; in [143], increased by \( \sim 45.0\% \); in [72], increased by \( \sim 400.0 \) ms for epicardial and endocardial cell types in one of their HF model; and in [161], 350.0 ms, increased by \( \sim 18.0\% \). Two studies [195; 254] measured different repolarization thresholds; [254] calculated \( APD_{80} \) and had a population median increased by 19.6%, while [195] computed \( APD_{75} \) and found 215.0 ms increased by \( \sim 30.0\% \). In our HF-OVVR model, the variability of parameters covers these APD prolongations, where \( APD_{90} \) increased within a range from 306.9 to 590.7 ms (33.6% - 157.2%), 392.8 to 628.8 ms (13.9% - 82.3%), and 352.2 to 512.2 ms (34.3% - 95.3%) for epicardial, midmyocardial, and endocardial cell types, respectively.

- AP duration at 50%: Two studies [193; 237] quantified \( APD_{50} \), where in [193] quantified \( APD_{50} \) with a measured value 374.5 ms, increased by 20.7%; in [237] increased by 18.0% from normal level. For the HF-OVVR model, the \( APD_{50} \) ranges were increased by 249.0 - 436.9 ms (32.7% - 132.9%), 318.3 - 466.4 ms (13.2% - 65.8%), and 277.7 - 373.1 ms (33.8% - 79.7%), for epicardial, midmyocardial, and endocardial cell types, respectively.

- AP triangulation: For triangulation, a sole study [237] quantified it and found an increase of 43.0%. In our HF-OVVR model, the ranges are increased by 57.9 - 153.8 ms (37.5% - 265.3%), 74.5 - 162.4 ms (16.9% - 154.9%), and 74.5 - 139.1 ms (19.8% - 154.3%), for epicardial, midmyocardial, and endocardial cell types, respectively. In addition, [254] measured the median population and found an increase ranging between 7.0 and 10.0%.
Calcium transient dynamics: The peak value of $[Ca^{2+}]_i$ was 334.0 nmol/L as reported by [193] with a reduction of 45.6% from the normal level. A study [272] found that the amplitude was 580.0 µM with a decrease of 22.7% from the normal peak. Another study [237] measured that the amplitude was reduced by 41.0% from the normal model. Another study [222] found a reduction in the calcium peak levels under HF without quantifying it. Yet another study [195] found a decrease less than 40.0%. In our HF-OVVR model, the peak value of $[Ca^{2+}]_i$ falls within a range increased by 193.3 - 627.8 µM, 255.7 - 793.6 µM, and 267.5 - 352.3 µM, for epicardial, midmyocardial, and endocardial cell types, respectively. One study [272] measured the time to peak $[Ca^{2+}]_i$ as 420.0 ms, increased by 460.0%, while our ranges increased by 44.7 - 175.5 ms, 47.6 - 181.7 ms, and 64.9 - 168.5 ms, for epicardial, midmyocardial, and endocardial cell types, respectively. The diastolic steady-state was reported by [193] with a value of 136.0 nmol/L increased by 13.3%; our HF-OVVR model obtains values of 82.1 - 89.3 µM, 94.1 - 96.8 µM, and 94.8 - 99.1 µM, for epicardial, midmyocardial, and endocardial cell types, respectively. The time to reach steady-state for $[Ca^{2+}]_i$ is 630.0 ms, increased by 39.7%, as reported by [237]. One study [254] measured the median calcium transient peak value, duration, and triangulation for the whole population and found a reduction of 44.4%, increase of 51.7%, and reduction of 11.6%, respectively. Another study [143] found that $[Ca^{2+}]_{SR}$ under HF conditions is reduced by 15.0% in store because the restoring rate is slower.

Sodium dynamics: For $[Na^+]_i$ accumulation, [237] observed an increase in levels compared with a normal model. Also, [161] found that the intracellular sodium concentration level was 11.45 mM, increased by $\sim$28.7%. In our HF-OVVR model, the peak $[Na^+]_i$ values are increased by 2.6-15.6%, 6.1-15.9%, and 5.3-18.7% for epicardial, midmyocardial, and endocardial cells, respectively.

Induction of EADs: For EADs, only one HF simulation study [237] reported that EADs can be induced. As shown in Fig. 5.41, our HF-
Figure 5.42: Rate dependence in a 1D cable for the undiseased OVVR model. (A) Action potentials at cycle lengths of 1000, 600, 500, 400, and 300 ms. Compared to isolated cell APs, the upstroke amplitude is decreased because of electrotonic effects. (B) Steady-state and S1-S2 APD restitution curves. Steady-state restitution curves (solid lines) were obtained after pacing for 30 s and S1-S2 restitution curves (dashed lines) were obtained after 30 s of pacing for five different S1 cycle lengths. OVVR model shows memory in APD. (C) Steady-state and S1-S2 CV restitution curves. The OVVR shows limited CV memory.

OVVR can induce EADs. Table 5.8 indicates the EADs CLs range and \(APD_{90}\) in the EADs regime for all cell types.

### 5.5 1-Dimensional cable results

While we worked on the OVVR model under both normal and HF conditions, we discovered that the CV of the original undiseased model was too low and worse when we implement our HF settings. As you can see from Fig. 5.42, the conduction velocity is nonphysiologically slow. The effect of this slow CV makes the OVVR original model reach 2:1 faster than it should, see Fig. 5.43.

After investigation, we found that the problem was caused by the formulation of a fast sodium current \(I_{Na}\). We solved this dilemma by replacing the original \(I_{Na}\) with a more accurate \(I_{Na}\) current from the Ten, Noble, Noble,
Figure 5.43: Steady-state and S1-S2 APD 90% restitution curves for OVVR model in a 1D strand for: (A) normal epicardial cell. (B) normal endocardial cell. (C) normal midmyocardial cell. (D) HF epicardial cell. (E) HF endocardial cell. (F) HF midmyocardial cell. Curves were obtained after pacing for 60 s and show significant differences among the status condition of cell type.
and Panfilov (TNNP) model. The effect of this adaptation can be seen in Fig. 5.44.

5.5.1 Heart failure simulation of an AP in a 1D cable of OVVR-TP

We analyzed the properties of action potentials of the OVVR-TP in a 1D strand under normal and HF conditions. In 1D tissue, the action potential upstrokes are decreased by electrotonic effects in both cases. For epicardial cell types, Fig. 5.45 shows the simulation results of action potential dynamics of the updated model under HF conditions at CL=1000 ms (left panel) and comparable experimental observations (right panel). For midmyocardial cell types, Fig. 5.46 shows the simulation results of action potential dynamics of the updated model under HF conditions at CL=1000 ms (left panel) and comparable experimental observations (right panel).

Fig. 5.47 shows the simulation results of endocardial action potential dynamics of the updated model under HF (upper panel) and normal (lower panel) conditions at CL=1000 ms. Fig. 5.48 exhibits comparable experimental observations of failing (upper panel) and non-failing myocytes (lower panel).

One of our aims was to introduce uncertainties to the model through adapting variations to the currents and exchangers parameters to reproduce the maximum variations of an AP that were observed in experiments, see Fig. 5.49.

5.5.2 Rate dependence of APD and Major Currents:

We compared the action potentials, main transmembrane currents ($I_{NaL}$, $I_{NaCa}$, $I_{K1}$, $I_{Kr}$, $I_{Ks}$, and $I_{CaL}$), and calcium transients in a 1D strand of the normal and HF OVVR-TP models for a range of different CLs for the epicardial formulations. As shown in Figure 5.50 A-B, the action potentials of the two models have different shapes, where the HF APs do not have
Figure 5.44: Action potentials for the OVVR model using the TP formulation of $I_{Na}$. Traces show action potentials for (A) epicardial, (B) endocardial, and (C) midmyocardial cell types of the OVVR model using the TP model formulation of $I_{Na}$ (green solid lines) compared to the original OVVR model (blue dashed lines). Insets show upstrokes, where the action potential shapes change most.
spikes during the early repolarization phase. Also, the repolarization dynamics are slower on HF tissue. The HF OVVR-TP model possesses higher plateaus, longer durations and exhibits significantly more rate dependence than those of the normal OVVR-TP model.

The main transmembrane currents of the two models generally show differences in magnitude and in the degree of rate dependence. Both models display rate dependence of $I_{NaL}$ current (see Figure 5.50 C-D). However, the peak current at larger cycle lengths is more than three times as large for the HF OVVR-TP model (-0.49 pA/pF) as for the normal OVVR-TP model (-0.13 pA/pF) at CL=1000 ms. $I_{NaCa}$ exhibits stronger rate dependence for both models with a larger degree for the normal OVVR-TP model, as shown in Figure 5.50 E-F. The peak inward current is twice as large for the HF OVVR-TP model as for the normal OVVR-TP model for all CLs range.

$I_{K1}$ has similar patterns in the two models, however, the peak current is about 100% larger for the normal model than for the HF OVVR-TP model, as shown in Figure 5.50 G-H. In addition, $I_{K1}$ in the HF OVVR model displays almost no rate dependence, whereas for the normal OVVR model the peak value decreases slightly with decreasing CL. As shown in Figure

Figure 5.45: (A) Simulation results of an AP dynamics OVVR model of the epicardial cell type at 1000 ms under HF conditions. (B) representative optical recordings of AP and CaT from location within subepicardium. Reproduced from [139]
Figure 5.46: (A) Simulation results of an AP dynamics OVVR model of the mid-myocardial cell type at 1000 ms under HF conditions. (B) representative optical recordings of AP and CaT from location within midmyocardium. Reproduced from [139]

5.50 I-J, $I_{Kr}$ exhibits very slight rate dependence in both models, but its peak value for the normal OVVR-TP model is more than two times larger than for the HF OVVR-TP model, indicating that it plays a more significant role during repolarization for the normal OVVR-TP model. $I_{Ks}$ is a little bit larger for the normal OVVR-TP model than for the HF OVVR-TP model (see Figure 5.50 K-L). HF OVVR-TP model shows rate dependence of $I_{Ks}$ with slight decreasing amplitude, but in the opposite way: as CL decreases, the peak value of $I_{Ks}$ increases for the normal OVVR-TP model. For the $I_{CaL}$ current, both models show limited rate dependence, as shown in Figure 5.50 M-N. The peak current is about 50% larger for the HF OVVR-TP model than for the normal OVVR-TP model at slow pacing rates.

Figure 5.50 O-P, shows the calcium transients (intracellular calcium concentration $[Ca^{2+}]_i$) for both models. The peak value is more than twice as large for the normal OVVR-TP model as for the HF OVVR-TP model during slow rates, and increases to more than five times as large at fast rates. In both models, the $[Ca^{2+}]_i$ peak value increases as the CL decreases from 1000 ms to 200 ms, so that the $[Ca^{2+}]_i$ peak-frequency relationship
Figure 5.47: Simulation results of an AP dynamics OVVR model of the endocardial cell type at 1000 ms under HF and normal conditions.

Figure 5.48: Simultaneous recordings of AP and CaT at one site at subendocardium from a failing human heart (F, top) and a nonfailing human heart (NF, bottom). Reproduced from [138]

is always positive. In addition, the calcium transient rises and falls more slowly for the HF OVVR-TP model than for the normal OVVR-TP model.

5.6 2-Dimensional sheet results

Fig. 5.55 illustrate the procedure of inducing spiral wave. We begin with generating a wave by stimulating one side of the tissue known as S1 stimulation. This wave propagates from the stimulated side of the tissue to the other side. The, we stimulate another part of the tissue known as S2 stimulation. In this case, the wave could not propagate in one direction.
Figure 5.49: Representative AP recordings from individual failing (n=5, blue traces) and nonfailing (n=5, red traces) human hearts at the pacing CL=2000ms. On the left, the AP recordings with the maximum APD in the field of view (FOV). In the middle, the AP recordings with the mean APD in the FOV. On the right, the AP recordings with the minimum APD in the FOV. All traces are recorded from the RV endocardium. Reproduced from [138].
Figure 5.50: Rate dependence of action potentials, primary transmembrane currents, and intracellular calcium concentration in a 1D cable for the normal OVVR (columns 1 and 3) and HF OVVR (columns 2 and 4) models for cycle lengths of 1000 ms (solid black), 800 ms (dashed green), 600 ms (dashed red), 400 ms (dashed blue), and 200 ms (dashed purple). The HF-OVVR model generally shows more rate dependence; however, the normal OVVR model shows greater rate dependence for $\left[Ca^{2+}\right]_i$. 
Figure 5.51: Steady-state APD 90% restitution curves for normal and HF OVVR model in 1D cable for (A) epicardial, (B) midmyocardial, (C) endocardial cell type.
Figure 5.52: Steady-state and S1-S2 APD 90% restitution curves for the OVVR model in a 1D cable: (A) normal epicardial cell. (B) normal midmyocardial cell. (C) normal endocardial cell. (D) HF epicardial cell. (E) HF midmyocardial cell. (F) HF endocardial cell. Curves were obtained after pacing for 60 s and show significant differences among the status condition of cell type.
Figure 5.53: Steady-state and S1-S2 CV 90% restitution curves for the OVVR model in a 1D cable: (A) normal epicardial cell. (B) normal midmyocardial cell. (C) normal endocardial cell. (D) HF epicardial cell. (E) HF midmyocardial cell. (F) HF endocardial cell. Curves were obtained after pacing for 60 s and show significant differences among the status condition of cell type.
Figure 5.54: Steady-state restitution curves in heterogenous single cell, epi (blue), endo (red), and mid (green). (A) Simulation results of non-failing myocytes of the OVVR model. (B) Simulation results of failing myocytes of the HF-OVVR model. (C) Experimental observations in isolated nonfailing human heart. (C) Experimental observations in isolated failing human heart. Reproduced from Glukhov et al. [70] with slow pacing (CL=2000 ms).
Figure 5.55: Illustration of inducing spiral wave. (A) A wave generated by an S1 stimulation that propagates from the left side of the tissue to the right side. (B).
Figure 5.56: spiral wave properties for the normal OVVR model with the TP $I_{Na}$ formulation. Spiral wave snapshots, tip trajectories, and dominant APD and period for the epicardial (upper panel), endocardial (middle panel), and midmyocardial (lower panel) formulations of the modified model. Frames in all cases correspond to 1.85, 1.90, 1.95, and 2.00 s, and tissue sizes are 18.0 by 18.0 cm. Dominant periods were obtained using the full 2 s of simulation time.
Figure 5.57: Spiral wave properties for the HF-OVVR model with the TP $I_{Na}$ formulation. Spiral wave snapshots, tip trajectories, and dominant APD and period for the epicardial (upper panel), endocardial (middle panel), and midmyocardial (lower panel) formulations of the modified model. Frames in all cases correspond to 1.85, 1.90, 1.95, and 2.00 s, and tissue sizes are 18.0 by 18.0 cm. Dominant periods were obtained using the full 2 s of simulation time.
because the cells of the tissue are still in the refractory period. This causes
the wave to curl and propagate in the other direction and constitute a spiral
wave. As shown in Figs. 5.56 and 5.57 that there are differences regarding
the tip trajectory, dominant APD, and dominant period. For the epicardial
cell type, the tip trajectory has a cycloidal shape for failing cells while it
does not has a clear shape for normal myocytes. The dominant APD for
failing myocytes are 488.0ms, while it is 178.0ms for normal myocytes. The
dominant period peaks for failing myocytes are 537.0ms and 574.0ms, while
for normal myocytes are 211.0ms.

For the midmyocardial cell type, the tip trajectory has a cycloidal shape
with increasing the diameter each period for failing cells while it has stable
cycloidal shape for normal myocytes. The dominant APD peaks for failing
myocytes are 344.0ms, 355.0ms, and 376.0ms while it is 295.0ms for normal
myocytes. The dominant period peaks for failing myocytes are 375.0ms,
401.0ms, and 438.0ms while for normal myocytes are 340.0ms

For the endocardial cell type, the tip trajectory has a stable cycloidal shape
for failing cells while it does not has a clear shape for normal myocytes.
The dominant APD peaks for failing myocytes are 307.0ms, 320.0ms, and
338.0ms while it is 205.0ms for normal myocytes. The dominant period
peaks for failing myocytes are 352.0ms, 364.0ms, and 397.0ms while for
normal myocytes are 230.0ms

5.7 Discussion

In this chapter, we present a human heart failure model (HF-OVVR) de-
\[APD_{90}\]

- derived from experimental observations on remodeling of ion channels mainly
from human data and for comparison use the undiseased ventricular cell
model (OVVR) [181]. Our new HF-OVVR model can reproduce many of
the AP properties of failing human myocytes. We have compared the prop-
eties of the HF-OVVR model with available experimental observations and
found good agreement. We have found that \(APD_{90}\) is prolonged by 77.2 -
361.0 ms, 47.8 - 283.8 ms, and 89.9 - 249.9 ms for epicardial, midmyocardial,
and endocardial cells in our model, which agrees with experimental observations of $\sim181\pm28$ ms prolongation for the HF case [133]. In addition, we found that $APD_{50}$ is prolonged by 61.4 - 249.3 ms, 37.0 - 185.1 ms, and 70.1 - 165.5 ms during HF for epicardial, midmyocardial, and endocardial cells, which are close to experimental findings of $\sim156\pm22$ ms at a CL of 2000 ms [133].

We defined AP triangulation as the difference between $APD_{90}$ and $APD_{50}$ and found that our simulated AP triangulation was comparable with experimental studies [12; 12]. Also, experiments showed a non-significant increase in the resting membrane potential ranging between 0.2 and 1.0 ms [126], which is in agreement with the 0.0 - 1.3 ms, 0.1 - 1.8 ms, and 0.1 - 1.4 ms increases in resting membrane potential for epicardial, midmyocardial, and endocardial cells in our HF-OVVR model.

In addition, the dynamics of simulated $[Ca^{2+}]_i$ match experimental findings, including decreased systolic amplitude (SA) range 10.0 - 72.3%, 23.0 - 75.2%, and 12.3 - 33.4% for epicardial, midmyocardial, and endocardial cells in our HF-OVVR model compared to a reduction of 41% in experiments [12], [259]. Also, previous experiments observed a slight increase in diastolic $[Ca^{2+}]_i$ [12], which matches our simulation results, which increased by 6.5 - 15.8%, 1.4 - 4.3%, and 8.5 - 13.4% for epicardial, midmyocardial, and endocardial cells. The difference between the systolic amplitude of $[Ca^{2+}]_i$ in HF and normal cells has been observed to be $379\pm140$ nM [193], which is in the range of the difference observed for our HF-OVVR model of 69.6 - 504.1 nM and 237.4 - 775.3 nM for epicardial and midmyocardial cells. The difference of the upstroke time or time to peak (TT) for the $Ca^{2+}$ transient is $20\pm11$ ms for a CL of 3000 ms [77], whereas in our HF-OVVR model it is 3.2 - 134.0 ms, 15.3 - 149.4 ms, and 9.5 - 113.1 ms for epicardial, midmyocardial, and endocardial cells, respectively. $[Na^{+}]_i$ is increased in HF-OVVR cells for all stimulation rates when compared with the normal cell, which matches previous findings [41].

Our approach includes some limitations. Recent work on mRNA [254] has shown that alternans in human HF cells begins at a CL of 350 ms, whereas
alternans in our case is higher by 50 ms, 250 ms, and 30 ms for epicardial, midmyocardial, and endocardial cells, respectively. However, alternans onset CLs are in the range of the observed values reported in other studies [264] of ≤500 ms for epicardial and endocardial cells, respectively. In addition, in our simulation results, we observed that the maximum range of APD S-S restitution curve slopes are 0.26 - 0.60, 0.23 - 0.70, and 0.28 - 0.86 for epicardial, midmyocardial, and endocardial cells. For epicardial and midmyocardial cells, the maximum range of APD S1-S2 restitution curve slopes are less than the slope value of 0.86±0.12 measured in the LV free wall of the failing human heart [70] for epicardial and midmyocardial cells, but it matches the measured endocardial cells.

In addition, to build the HF-OVVR model that was used in this thesis, the experimental data came from various sources of previously published studies. The data for each study has various HF causes, and we do not have access to the raw data of these studies. Therefore, in our HF-OVVR simulations, we calculated the mean of the means of these studies and the standard deviation as the square root of the squared sum of the variances of these studies. This would not represent uncertainty arising from different HF causes; instead, it is averaging the variability within each of these studies across different HF causes.

In comparing our model with previous HF simulation models [193; 272], we found that many of those models did not reproduce as many of the properties of HF that are observed in a single human HF-remodeled myocyte, such as increased accumulated $[Na^+]_i$, alternans, and EADs. These models were designed to reproduce the two prominent properties: prolonged $APD_{90}$ and altered $[Ca^{2+}]_i$ dynamics. Also, these studies used more limited data and did not show most of the HF-remodeled properties in a quantitative manner. Most of the previous models [193; 272], did not consider remodeling $I_{Na}$ in reproducing the reduction in the upstroke velocity of HF cells. Also, these models either did not remodel the $I_{NaL}$ [193] or increased it more than has been observed [272]. Moreover, previous simulation studies did not incorporate remodeling of $I_{to}$ and $I_{Kr}$. Previous simulation studies [193; 272]...
did not change these currents. Regarding APD rate dependence, only one study [273] compared with control at a fast rate.

The aim of 2D simulations is to explore the behavior of spiral wave dynamics on the developed HF cellular model in a 2D sheet and how the spiral wave dynamics differ from the undiseased cellular model. It is already known that reentrant waves underlie life threatening arrhythmias, but the detailed mechanisms are still unclear. Therefore, understanding the response of the 2D cardiac sheet to an electrical stimulation is important for appropriate treatment and alleviation of cardiac arrhythmias. We quantify the dominant APD and rotation period for all cells that constitute the tissue sheet. Also, we extract the tip trajectory of each cell type under both conditions. This extraction will help disclose the area that the core reentrant waves move on. This can be applied to find the cardiac area that needs to be defibrillated.
Chapter 6

An Arrhythmia Application: Inducing Early Afterdepolarizations (EADs) for the HF OVVR Model

The purpose of this chapter is to present an arrhythmia application of the developed human heart failure model (HF-OVVR), which is an early afterdepolarization (EAD). The organization of the chapter will be as follows: it begins with a brief introduction, which includes cellular level remodeled ionic currents and reviews some experimental studies. Then, it discusses the general heart failure model that was used to induce an EAD for each cell type and is explained. After that, it discusses how we measured the formation of EAD in the human-specific heart failure myocytes across population-level variability in ion channel expression. Then, a comparison between simulated and experimentally observed EADs is discussed along with the discrepancies among cell types of the simulated results. Finally, a conclusion is presented.
6.1 Introduction

Ventricular arrhythmias and sudden cardiac death (SCD) are often associated with cardiac hypertrophy and failure [15; 108], which can take many forms. In the clinic, some of these observations under certain conditions are long-QT syndrome [118; 137; 162; 269], cardiotoxicity [116; 134], Torsade de Pointes (TdP) [178; 252; 260], and many other forms [224; 250]. All of these syndromes associated with prolongation of an action potential and increased regional dispersion of repolarization [235], share the same underlying characteristic, known as early afterdepolarizations (EADs) [39; 197; 201], which are action potentials that get excited during the plateau, or repolarization phase.

From the cellular level point of view, to induce EADs, there are many mechanisms which incorporate several currents for each mechanism. It is difficult to know what is the percentage of each involved current is in inducing EADs for each mechanism.

Previous experimental studies prolong an action potential duration using pharmacological agents in many ways including, reducing the $I_{Kr}$ current [6; 23; 129], slowing down an inactivation of the $I_{Na}$ current [16; 98; 112; 223], or slowing down an inactivation of the $I_{CaL}$ current [103; 104], with much attention to reactivating both the $I_{Na}$ and $I_{CaL}$ currents [105; 163; 175]. A recent study [197], shows that the L-type calcium, sodium, and potassium channels as well as the sodium-calcium exchanger and intracellular $Ca^{2+}$ cycling are associated with inducing EADs.

6.2 Inducing EAD through APD prolongation

One important afterdepolarization proarrhythmia that may cause heart failure is early afterdepolarization (EAD). To reiterate, we developed two heart failure models where for both models the underlying model is human. The
HF remodeling is either general without considering species type, or more human-specific where it is mainly based on humans, except when there is a scarcity of data on humans, we used available animal species data. Therefore, this section is focusing on these two developed models. The first one is examining how the general heart failure set of remodeled ionic parameters can induce EAD. The second one discusses the inducibility of EAD with varying each remodeled ionic current under heart failure conditions for the more human-specific HF model.

### 6.2.1 General heart failure set of remodeled ionic conductances

Since EADs are often associated with arrhythmias such as heart failure [132; 179], long-QT, and TdP, it is important to reproduce EADs in a single myocyte from our developed HF OVVR model. Developing a fixed set of remodeled ionic conductances, which contribute to inducing an EAD for each cell type, will help in studying the dynamics of the EAD in tissue and predicting the consequences of inducing an EAD when the tissue cells are under heart failure conditions.
As a preliminary investigation, we started with the remodeled ionic currents of our developed general heart failure model. As we explained in previous chapters, our developed HF OVVR model is heuristically based on observations from former experimental studies. We based on that and further refined the ionic conductances for each cell type to investigate its influence on action potential prolongation for setting the stage to induce an EAD until one or more spikes are experienced at CL=4000 ms (see Table 6.1). For the epicardial cell type, we decreased $I_{Kr}$ to 70% when it exhibits an alternans EAD, which means that one AP exhibits an EAD while the other does not. For the midmyocardial cell type, decreasing $I_{Kr}$ by only 20% causes EADs to formulate. For the endocardial cell type, its behavior is closer to the epicardial cell, where 65% reduction of $I_{Kr}$ induces EADs. Figure 6.1 shows induced EADs for all cell types with one spike.

### 6.2.2 Towards more human-specific set of remodeled ionic conductances

Although animal HF models mimic human HF models in some aspects, models that were built based on remodeled animal species differ from human models. There are big differences between remodeled failing human myocytes and animal species myocytes. For example, the remodeled fast sodium current density under heart failure conditions in canines is ↓(39.3%±6.5), while in humans it is ↓(57.1%±1.6) [246]. For the late sodium current, the percentage of change under HF conditions in canines and humans are ↑(113.6%±10.0) and ↑(238.5%±1.3), respectively [246]. Also, the changes in the calcium independent transient outward potassium current under heart failure conditions differ between canines ↓(73.2%±5.8) [274] and humans ↓(32.1%±6.4) [133] and ↓(26.4%±1.3) [165] for epicardial cell type, for example. The inward potassium current in human heart failure for the epicardial cell type is ↓(56.3%±2.2) [133] which is larger than the observed remodeled current in canine species (↓(40.9%±0.8) [132] and ↓(50%±0) [2]). For the midmyocardial cell type, the inverse behavior was observed compared to one study, where the remodeled $I_{K1}$ for humans is ↓(43.4%±2.5) [13] and
Figure 6.1: Early afterdepolarizations (EADs) of the modified HF-OVVR model for all cell types (A) Epicardial (B) Midmyocardial (C) Endocardial.
for canine is ↓(64.0%±0) [2] and overlaps in another study ↓(40.7%±0.6) [132]. For $I_{Ks}$ current, the observed remodeled tail current density under HF conditions for the epicardial cell type in humans (↓(61.7%±1.4) [133]) is higher than the canine species (↓(57.1%±1.6) [132]). In addition, the remodeled $Na^+/Ca^{2+}$ exchanger for rat species (↓50% [229]) is less than the observed in humans (↓80% and ↓90% [229]). Moreover, the remodeled $Na^+/K^+$ pump differs between human (36%) and animal species (hamster 33% and rat 20%) for endocardial cell type [121]. Also, the remodeled SERCA2a in endocardial cells are different where for canine it is ↓(65%±7) and for human it is ↓(30%±5) [107].

Here, we focus on measuring the formation of EAD in heart failure myocytes across population-level variability in ion channel expression. For each cell type, we vary each ionic current conductance within a range between $\mu - 3SD$ and $\mu + 3SD$ with down sweep protocol starting with CL=10,000 ms. Tables 6.2, 6.3, and 6.4 depict the settings of ionic conductance variations for epicardial, midmyocardial, and endocardial cell types, respectively, for all considered remodeling ionic parameters.

We considered remodeling ten ionic conductances for each cell type, namely $G_{Na}$, $G_{NaL}$, $G_{to}$, $G_{Ks}$, $G_{Kr}$, $G_{NaCa}$, $P_{Ca}$, $P_{NaK}$, and SERCA pump activity. From these ten parameters, we found only three parameters ($G_{NaL}$, $G_{Kr}$, and $G_{NaCa}$) have substantial effect on the action potential duration, which is the essential factor for inducing early afterdepolarization arrhythmia.

Fig. 6.2 A, shows the steady-state curves for varying the late sodium current of the epicardial cell type. The range of $APD_{90}$ is between 611.9 ms and 624.6 ms. For the midmyocardial cell type, the variation of $I_{NaL}$ current causes $APD_{90}$ to increase within a range of 671.7 ms - 688.7 ms (see Fig. 6.2 B). As shown in Fig. 6.2 C, the range of $APD_{90}$ is between 628.4 ms and 649.9 ms which is caused by the variation of the slow sodium current for the endocardial cell type.

For the rapid delayed rectifier potassium current variation, the epicardial cell type exhibits the greatest $APD_{90}$ variation with a range of 454.8 ms.
and 1,873.0 ms as shown in Fig. 6.3 A. Also, it is the only varied current that can induce EAD. For the midmyocardial cell type, we did not vary its $I_{Kr}$ conductance because most of the previous experimental studies did not observe remodeling of this current. Fig. 6.3 B exhibits the range of varying the $G_{Kr}$ parameter, which falls within a range of 607.9 ms - 675.1 ms.

For the sodium-calcium exchanger variation, as shown in Fig. 6.4 A, the range of $APD_{90}$ is 454.5 ms - 734.6 ms for the epicardial cell type. For the midmyocardial cell type, varying the $I_{NaCa}$ current causes the $APD_{90}$ to range between 471.9 ms and 772.9 ms (see Fig. 6.4 B). Fig. 6.4 C depicts that the range of $APD_{90}$ falls between 458.0 ms and 734.2 ms, when changing the $G_{NaCa}$ parameter.

For the fast sodium current variation, the ranges for $APD_{90}$ of the epicardial, midmyocardial, and endocardial cell types are 617.1 ms - 619.8 ms, 677.9 ms - 682.4 ms, and 636.1 ms - 641.1 ms, respectively (see Fig. 6.5).

As shown in Fig. 6.6, the variation of the inward rectifier potassium current has a large effect on the duration of an action potential which ranges between 598.3 ms - 698.1 ms, 660.6 ms - 761.8 ms, and 619.0 ms - 672.1 ms for epicardial, midmyocardial, and endocardial cell types, respectively.

For the slow delayed rectifier potassium current variation, the epicardial cell type exhibits the greatest $APD_{90}$ variation with a range between 609.9 ms and 627.3 ms as shown in Fig. 6.7 A. Fig. 6.7 B exhibits a small range of variation, which falls between 674.5 ms - 686.2 ms. For the endocardial cell type, the duration of an action potential ranges between 632.5 ms - 643.9 ms, when varying the $G_{Ks}$ parameter (see Fig. 6.7 C).

Fig. 6.8 depicts that the variation of the outward potassium current has a very small effect on the $APD_{90}$. This effect ranges between 615.9 ms - 620.8 ms, 678.7 ms - 681.8 ms, and 639.0 ms - 639.4 ms for epicardial, midmyocardial, and endocardial cell types, respectively.

The sodium-potassium pump has a large effect on changing the action potential duration where it changes between 575.9 ms - 653.1 ms for the epicardial cell type (see Fig. 6.9 A). As shown in Fig. 6.9 B, the midmyocardial
cell type has a larger $APD_{90}$ variation (622.0 ms - 736.3 ms). For the endocardial cell type, the action potential duration ranges between 593.2 ms - 673.2 ms (see Fig. 6.9 C).

Also, $SERCA$ variation has greater effect on the $APD_{90}$, where the ranges fall between 537.0 ms - 742.0 ms, 594.1 ms - 748.3 ms, 560.6 ms - 687.2 ms for epicardial, midmyocardial, and endocardial cell types, respectively (see Fig. 6.10).
Table 6.2: Early afterdepolarizations (EADs) parameter settings variations for epicardial cell type.

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<tr>
<th>Current</th>
<th>(\mu - 3\sigma)</th>
<th>(\mu - 2\sigma)</th>
<th>(\mu - 1\sigma)</th>
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<th>(\mu + 2\sigma)</th>
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Table 6.3: Early afterdepolarizations (EADs) parameter settings variations for midmyocardial cell type.
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<td>6.82%</td>
<td>22.88%</td>
<td>38.94%</td>
<td>55.00%</td>
<td>71.06%</td>
<td>87.12%</td>
<td>103.18%</td>
<td>0.1908</td>
<td>55.00±16.06%</td>
</tr>
<tr>
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<td>0.11650248</td>
<td>0.08586</td>
<td>0.05521752</td>
<td>0.0245504</td>
<td>-0.00606744</td>
<td>0.0034</td>
<td>57.70±2.20%</td>
<td></td>
</tr>
<tr>
<td>$I_{Kr}$</td>
<td>22.20%</td>
<td>23.90%</td>
<td>25.60%</td>
<td>27.30%</td>
<td>29.00%</td>
<td>30.70%</td>
<td>32.40%</td>
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</tr>
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<td>0.033442</td>
<td>0.03266</td>
<td>0.031878</td>
<td>0.031096</td>
<td>0.0034</td>
<td>57.70±2.20%</td>
<td></td>
</tr>
<tr>
<td>$I_{Ks}$</td>
<td>51.10%</td>
<td>53.30%</td>
<td>55.60%</td>
<td>57.70%</td>
<td>59.90%</td>
<td>62.10%</td>
<td>64.30%</td>
<td>0.008</td>
<td>131.38±68.75%</td>
</tr>
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<td>0.001513</td>
<td>0.0014382</td>
<td>0.0013634</td>
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<td>0.0012138</td>
<td>0.0008</td>
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<tr>
<td>$I_{NaCa}$</td>
<td>-56.87%</td>
<td>5.88%</td>
<td>68.63%</td>
<td>131.38%</td>
<td>194.13%</td>
<td>256.88%</td>
<td>319.63%</td>
<td>30.0</td>
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</tr>
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<td>0.00134904</td>
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<td>0.00235304</td>
<td>0.0028504</td>
<td>0.0033504</td>
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<td>41.11±10.11%</td>
<td></td>
</tr>
<tr>
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<td>25.30%</td>
<td>40.80%</td>
<td>56.30%</td>
<td>71.80%</td>
<td>87.30%</td>
<td>0.004375</td>
<td>41.11±10.11%</td>
</tr>
<tr>
<td>31.71</td>
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<td>22.41</td>
<td>17.76</td>
<td>13.11</td>
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<td>3.81</td>
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</tr>
<tr>
<td>SERCA</td>
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<td>31.00%</td>
<td>41.11%</td>
<td>51.22%</td>
<td>61.33%</td>
<td>71.44%</td>
<td>0.004375</td>
<td>41.11±10.11%</td>
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<td>0.0016918125</td>
<td>0.0012495</td>
<td>0.004375</td>
<td>41.11±10.11%</td>
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</tr>
</tbody>
</table>

Table 6.4: Early afterdepolarizations (EADs) parameter settings variations for endocardial cell type.
Figure 6.2: Simulation results of varying $I_{NaL}$ of the modified HF-OVVR model for all cell types (A) Epicardial (B) Midmyocardial (C) Endocardial.
Figure 6.3: Simulation results of varying $I_{Kr}$ of the modified HF-OVVR model for (A) Epicardial and (B) Endocardial cell types.
Figure 6.4: Simulation results of varying $I_{NaCa}$ of the modified HF-OWVR model for all cell types (A) Epicardial (B) Midmyocardial (C) Endocardial.
Figure 6.5: Simulation results of varying $I_{Na}$ of the modified HF-OYVR model for all cell types (A) Epicardial (B) Midmyocardial (C) Endocardial.
Figure 6.6: Simulation results of varying $I_{K1}$ of the modified HF-OVVR model for all cell types (A) Epicardial (B) Midmyocardial (C) Endocardial.
Figure 6.7: Simulation results of varying \( I_{Ks} \) of the modified HF-OVVR model for all cell types (A) Epicardial (B) Midmyocardial (C) Endocardial.
Figure 6.8: Simulation results of varying $I_o$ of the modified HF-OVVR model for all cell types (A) Epicardial, (B) Midmyocardial, (C) Endocardial.
Figure 6.9: Simulation results of varying $I_{\text{NaK}}$ of the modified HF-OVVR model for all cell types (A) Epicardial (B) Midmyocardial (C) Endocardial.
Figure 6.10: Simulation results of varying SERCA of the modified HF-OVVR model for all cell types (A) Epicardial (B) Midmyocardial (C) Endocardial.
6.3 Discussion

The simulation results of our general heart failure model of an $APD_{90}$ are not as good compared with failing human experimental observations [76; 133]. However, our results are in good agreement with failing dog myocytes [132; 151; 243]. For example, our $APD_{90}$ simulation results are 1247.0 ms and 1248.0 ms for epicardial and endocardial cell types, respectively, while $APD_{90}$ experimental observations in failing human myocytes is $\sim 800$ ms [76]. But, our action potential durations match the $APD_{90}$ in cardiomyocytes from dogs with heart failure $\sim 1100.0 \pm 300.0$ ms (mean+SD) [243].

As shown in Fig. 6.11 with one initiation of EAD for the epicardial cell type the $APD_{90}$ is not in good agreement with the recorded action potentials in a left ventricular myocyte from failing human heart at cycle length 4,000 ms [76]. However, Fig. 6.12 exhibits that our action potential duration matched the $APD_{90}$ which was recorded from failed cardiomyocytes of 13 dogs [243]. In addition, our developed heart failure model can induce multiple EADs as depicted in Fig. 6.13 (A) and matches the experimental observations qualitatively, see Fig. 6.13 (B) [133].
For our second developed heart failure model towards more human-specific species, we varied the remodeled ionic conductances. The only remodeled current that causes EAD formulation is the $I_{Kr}$ current for the epicardial cell type. Remodeling the $I_{Kr}$ for midmyocardial and endocardial cell types can not induce EADs. Based on human experimental observations, the $I_{Kr}$ current does not remodel in our HF model. For the endocardial cell type, the range of variation is small, which does not allow the EAD to be induced. Remodeling $I_{Kr}$ for the epicardial cell type induces EADs with a different number of spikes under different cycle lengths. Because inducing EAD necessitates a slow pacing rate, we began our pacing with cycle length 10,000 ms. At this cycle length, a stable EAD was observed with $APD_{90}$ equalling 1,873.0 ms. An EAD formulation was continuously observed as we decreased the cycle length until the $CL=4,500$ ms.

Figure 6.12: (A) Simulated EADs of the modified-OVVR HF model for epicardial cell type with $CL=4000$ ms. (B) Action potentials recorded in cardiomyocytes from dogs with heart failure at $CL=4000$ ms [243].
When the cycle length reached 4,250 ms, 2:1 EAD alternate spikes were observed. This alternans EAD lasted for a single cycle length. When CL=4,000 ms, a new stable EAD was formulated, but with a single spike. This stable EAD formulation was observed until the CL=2,500 ms. Then, a 1:0 alternation of EAD was observed at cycle length 2,250 ms. This EAD alternation was observed continuously until an EAD formulation was diminished at CL=1,800 ms (see Fig. 6.14).

In terms of how the variation of each ionic current affects the $APD_{90}$, we found that the $I_{Kr}$ current variation has the most effect for epicardial cell types with a range of 1,418.2 ms. However, it has less effect for endocardial cell types with a range of 67.2 ms. This difference in response of inducing EAD is related to the variation range of remodeling $I_{Kr}$ for each cell type. As indicated in Table 6.2, the range of variation of the $I_{Kr}$ for the epicardial cell type is 17.4%-70.4%. However, for the endocardial cell type the remodeled $I_{Kr}$ variation range is 22.2%-32.4% (see Table 6.4).

The second greatest effect on $APD_{90}$ comes from the $I_{NaCa}$ current variation. The range of the action potential duration is 280.1 ms, 301.0 ms, and 276.2 ms for epicardial, midmyocardial, and endocardial cell types respectively.

For $SERCA$ variation, the $APD_{90}$ has a wide range, where it is 205.0 ms
for the epicardial, 154.2 ms for the midmyocardial, and 126.6 ms for the endocardial cell type. In addition, varying the $I_{NaK}$ current has a large effect on the $APD_{90}$ with the midmyocardial cell possessing the largest range (114.3 ms); the epicardial cell has the smallest range (77.2 ms), and the endocardial cell has an in-between with a range of 80.0 ms. The same behavior is observed where the range of $APD_{90}$ depends on the cell type when varying the $I_{K1}$ current. Both epicardial and midmyocardial cells have wider ranges (99.8 ms and 101.2 ms respectively) than the endocardial cell (53.1 ms).

Regarding the variation of the $I_{Ks}$ current, all three cell types have minimum effect with ranges of 17.4 ms, 11.7 ms, and 11.4 ms for epicardial, midmyocardial, and endocardial cell types, respectively. Also, the variation of the $I_{NaL}$ current has a similar effect with $APD_{90}$ ranges of 12.7 ms, 17.0 ms, and 21.5 ms for epicardial, midmyocardial, and endocardial cell types, respectively.

Both the $I_{Na}$ and $I_{to}$ currents have the least effect on the $APD_{90}$. The variation of the $I_{Na}$ current causes change of an $APD_{90}$ with ranges of 2.7 ms, 4.5 ms, and 5.0 ms for epicardial, midmyocardial, and endocardial cell types, respectively. Also, the variation of the $I_{to}$ has the same minimum effect on $APD_{90}$ with ranges of 4.9 ms, 3.1 ms, and 0.4 ms for epicardial, midmyocardial, and endocardial cell types, respectively.

For further investigation, we varied all ionic current conductances and investigated if we could observe EAD for each cell type under normal and heart failure conditions. Among ten ionic conductances, three of them, namely the $I_{NaL}$, $I_{Kr}$, and $I_{NaCa}$, show the ability to induce EAD, but with a different degree of remodeling. Table 6.5 summarizes the variations of ionic current conductances with observed EAD that has one spike. Table 6.6 shows the exact conductance values used in our simulations for each cell type under both conditions, i.e., normal and heart failure, for the onset of EADs.

As depicted in Fig. 6.15, the HF OVVR model favors the occurrence of EADs because of the prolongation of $APD_{90}$, shown here for a cycle length
of 1000 ms. This $APD_{90}$ prolongation is caused by both $I_{CaL}$ and $I_{NaL}$, which lengthen the plateau phase and allow the late calcium current to re-activate. When preventing $I_{CaL}$ recovery or blocking $I_{NaL}$ in the HF OVVR model, EADs were suppressed. These simulation results are in agreement with experimental observations of Undrovinas and his group when they showed that tetrodotoxin blocks late sodium current and causes shortened APs in isolated failing human ventricular myocytes and eliminates EADs [244].

6.4 Conclusion

We presented an arrhythmia application for our developed heart failure models, which is an early afterdepolarization (EAD). Since EAD is an important cause of ventricular arrhythmias in heart failure. Also, one of the hallmarks of failed myocytes is the prolongation of AP, which sets the stage to induce an EAD. Therefore, we measured the formulation of EAD for all cell types under heart failure conditions when varying the remodeled ionic currents, as observed experimentally. We found that the epicardial failing myocyte can induce EADs, when varying the rapid delayed rectifier potassium current between mean±3 standard deviations. In addition, we compared the initiation of EADs between the normal and failing myocytes. Based on our developed models we found that heart failure myocytes are more susceptible to induced EADs across population-level variability in ion channel expression.
Figure 6.14: Action potentials for epicardial cell type with different EAD spikes and CLs. (A) 2 spikes at CL=10,000 ms. (B) 2:1 spikes at CL=4,250 ms. (C) 1 spike at CL=4,000 ms. (D) 1:0 spike at CL=2,250 ms. (E) No spike at CL=1,800 ms.
<table>
<thead>
<tr>
<th>Cell Type</th>
<th>$I_{NaL}$</th>
<th>$I_{Kr}$</th>
<th>$I_{NCX}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>HF</td>
<td>Normal</td>
</tr>
<tr>
<td>Epicardial</td>
<td></td>
<td>↑100 times</td>
<td>↓(94%)</td>
</tr>
<tr>
<td>Midmyocardial</td>
<td>↑100 times</td>
<td>↑25 times</td>
<td>↓(65%)</td>
</tr>
<tr>
<td>Endocardial</td>
<td></td>
<td>↑125 times</td>
<td>↓(90%)</td>
</tr>
</tbody>
</table>

Table 6.5: Summary of the variations of ionic currents, which are under normal and HF conditions to observe EADs. (*) note: the remodeling variation percentage in each case representing the variation corresponds to the base specific condition, either normal or heart failure. For example: for midmyocardial cell, increasing $I_{NaL}$ 25 times under HF conditions, means from the basic HF settings NOT from the basic normal settings.
<table>
<thead>
<tr>
<th>Cell Type</th>
<th>$I_{NaL}$ Normal</th>
<th>$I_{NaL}$ HF</th>
<th>$I_{Kr}$ Normal</th>
<th>$I_{Kr}$ HF</th>
<th>$I_{NCX}$ Normal</th>
<th>$I_{NCX}$ HF</th>
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</thead>
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<td>Epicardial</td>
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<td>0.00276</td>
<td>0.0207</td>
<td>0.068</td>
<td>0.0048</td>
</tr>
<tr>
<td>Midmyocardial</td>
<td>0.75</td>
<td>0.1875</td>
<td>0.0161</td>
<td>0.0345</td>
<td>0.008</td>
<td>0.0024</td>
</tr>
<tr>
<td>Endocardial</td>
<td>-</td>
<td>0.9375</td>
<td>0.0046</td>
<td>0.0184</td>
<td>0.048</td>
<td>0.0056</td>
</tr>
</tbody>
</table>

Table 6.6: Summary of the parameter values that represent the variations of ionic currents, which are under normal and HF conditions to observe EADs.
Figure 6.15: Mechanisms for early afterdepolarizations (EADs) of the HF-OVVR model for the epicardial cell type. (A) AP traces. (B) $I_{CaL}$. (C) $I_{NaL}$. (D) $I_{NaCa}$ under normal (solid green lines), HF (solid red lines), and blocked $I_{NaL}$ (dotted blue lines) with CL=1000 ms.
Chapter 7

Conclusions and Future Work

7.1 Conclusions

Developing a robust cellular electrophysiological model under heart failure conditions involves incorporating remodeled ionic currents as observed in experiments, considering the uncertainty of the remodeled ionic currents, validating the developed model at the tissue level, and further applying this model into a specific application. In this thesis, the contributions are fourfold:

First due to a large number of ventricular cell models available, it becomes a challenge to select an appropriate mathematical model. Therefore, we analyzed quantitatively the dynamics of recently published models of human ventricular cells under normal condition in isolated cells to ease selecting an appropriate model. In addition, this analysis encompassed the tissue level by constructing a one-dimensional cable and a two-dimensional sheet because at higher spatial dimensions the passive current between cells can cause new properties to emerge and their characteristics differ from the characteristics of isolated cells [28; 33]. The extracted physiological properties from the simulation results were compared with those of previously developed ventricular models and with available experimental and clinical data. We had shown that
each model has strengths and limitations that suggest how it can be best utilized for cardiac tissue studies. For example, the GPB model produces APDs and a maximum CV value closer to experimentally observed values [167; 230] along with clinically relevant dominant frequencies corresponding to VT [124]. In addition, the OVVR model shows greater reliability of APD variation with S1-S2 restitution curves and produces alternans, although with a magnitude greater than observed experimentally. In order to avoid the unphysiological conduction velocity of the OVVR model, and to match the experimentally measured data, we used the TP model formulation for $I_{Na}$ current to restore the maximum CV of the OVVR model to a physiologically normal value. This decreases the minimum DI and increases the dominant spiral wave periods. However, there are 3 issues that the results from both models did not match experimental observations. These issues are: 1) Both models exhibited action potential amplitudes and maximum restitution curve slope values below what has been reported experimentally. 2) The maximum upstroke velocity in tissue did not agree well with experimental observations. 3) The APD restitution curve maximum slopes are below typical experimental values.

Although the models studied in many cases generate different predictions, we emphasize that model disagreement may arise for many possible reasons. The models may exhibit normally observed biological variability or may reflect spatial heterogeneity other than transmural heterogeneity, such as apico-basal [171], left-right [19; 171], or other regional [171; 183] gradients. Differences also may arise from study subject differences such as age and gender. In addition, it is important to note that although models generally are designed to reproduce normal cells, it is difficult to access healthy human tissue experimentally. The other models used for comparison also have limitations, although, like the GPB and OVVR models, many of them match experimental data for some properties well [18]. Thus, reproducing observed dynamical properties of the human ventricles remains a significant modeling challenge.
Second in many cases, animal cell models are used to investigate cardiac electrophysiological properties for heart failure cases. However, to study the mechanisms of ventricular arrhythmia in humans arising from HF, the mathematical model should be based on recent human data and reproduce important arrhythmogenic phenomena. Therefore, we developed a general heart failure model that was biologically inspired from experimental observations and based on the mathematical OVVR human ventricular cell model. Although, the original model used is based on human data, the remodeled ionic currents utilized in developing this general heart failure model relied upon human and animal species experimental observations without any differentiation between them. So, we analyzed the dynamics of the developed HF-induced model quantitatively in isolated cells, a one-dimensional cable and a two-dimensional sheet. We find that $APD_{90}$ is prolonged by 211.8 ms in our developed general HF model, which agrees with human-specific experimental observations of $\sim181\pm28$ ms prolongation for the HF case [133]. In addition, we find that $APD_{50}$ is prolonged by 155.5 ms during HF, similar to human-specific experimental findings of $\sim156\pm22$ ms at a CL of 2000 ms [133]. AP triangulation is the difference between $APD_{90}$ and $APD_{50}$. Our simulation results for AP triangulation were 56.3 ms, which falls within the range of experimental values $\sim25\pm35.6$ ms [133]. Experiments also showed a slight increase in resting membrane potential (RMP) ranging from 0.2 to 1.0 ms [126], which is in agreement with the 0.38 ms in our general HF model. Regarding the calcium dynamics, we found that our simulated $Ca^{2+}$ transient match experimental findings, including decreased systolic amplitude ($\downarrow46\%$ in our general HF model compared to $\downarrow41\%$ in experiments [12; 259]) and a slight increase in diastolic $[Ca^{2+}]_i$ [12]. Also, the difference between the systolic amplitude of $[Ca^{2+}]_i$ in HF and normal cells has been observed to be $379\pm140$ nM [12], which is in the range of the difference observed for our developed general HF model of 296 nM. Moreover, the difference of the upstroke time or time to peak for the $Ca^{2+}$ transient is $20\pm11$ ms for a CL of 3000 ms [77].
whereas in our general HF model it is 18.8 ms. We found that our results are in good accordance with experimental findings reported in the literature and might motivate further research on remodeling and simulation of heart failure at the whole organ level. The developed general HF-OVVR model established in this part of the thesis was mainly used to investigate the transmural electrophysiological heterogeneities of different ventricular cell types in failing hearts.

Third due to difference of remodeled ionic currents under heart failure conditions between human and animal species, we moved forward towards constructing a more specific human HF model based mainly on remodeled human heart failure experimental data. As a consequence, the baseline of the remodeled ionic currents differs between the general heart failure model and this new human-specific heart failure model. In addition, we enriched this new model with a new feature that was absent in the general heart failure model, which is the uncertainty of these remodeled ionic currents. The incorporated variability is also based mainly on the uncertainty observed in human remodeled ionic currents under heart failure conditions. To do so, we split the framework into two main components: First, the electrophysiological activity of a transmural single myocyte was simulated using well-justified modifications of a recent mathematical model of the human ventricular AP, the OVVR model, to replicate the experimentally reported human HF phenotypes. Second, systematic and quantitative variability in ionic currents and exchangers was introduced utilizing experimental observations published in the literature mostly from the human species. In this project, the contributions can be summarized as follows: 1- A simulation study of an AP waveform of different ventricular cell types was presented based on recent experimental studies of transmural electrophysiological heterogeneities in the HF-OVVR model and compared with the normal OVVR model. 2- We evaluated how major cellular ionic currents influence the AP repolarization phase and how the APD rate dependence changed in transmural cells. 3- We found that these results are in good accordance with experimental findings reported in
the literature and might motivate further research on remodeling and simulation of heart failure at both tissue and the whole organ levels.

Fourth we presented an arrhythmia application of our developed heart failure models, and this arrhythmia application is an Early afterdepolarization (EAD). The aim of this project begins with measuring the formation of an EAD in the general heart failure model for each cell type. Then, we assess the inducibility of an EAD across population-level variability in ion channel expression for epicardial, midmyocardial, and endocardial cell types for human-specific heart failure model. We performed simulations in a single cell on both HF-OVVR models. For the human-specific HF model, the simulations involved varying all ten remodeled ionic current parameters one at a time with fixing all other nine parameters. The assessment of inducing EADs based on three different quantitative measurements: 1- The onset of EAD cycle length (CL). 2- The range of CLs for which EADs can be induced. 3- The number of additional peaks (upstrokes) during the EAD phase in each cycle length. We found that the epicardial failing myocytes can induce EADs, when varying the rapid delayed rectifier potassium current between mean ± 3 standard deviations. In addition, we found that the heart failure myocytes are more susceptible to inducing EADs across population-level variability in ion channel expression than the normal myocytes.

7.2 Limitations

Our work has many limitations that should be considered:

First Associated tissue limitations

– Isotropic tissue assumption In our work, we assumed that the electrical conductivity is isotropic in all directions. For example, we constructed 2D sheets with equal tissue conductivities in the x-
and y-directions. Inclusion of anisotropy might alter the conduction pathway, conduction velocity, and upstroke velocity [36; 225]. This could be in the form of fiber directions, which has different representation at different dimensions. For instance, we could assume that the fiber direction aligned with the x-direction to represent fast electrical propagation and the y-direction represents the fiber transverse direction which has slower electrical propagation.

As reported by [245] that anisotropy has been increasingly recognized as a potential substrate for abnormal rhythms and reentry, both in normal as well as pathological conditions. This means that inclusion of anisotropy into our HF model will enhance the discontinuous propagation and increase the probability of unidirectional block which can lead to reentry.

– **Homogeneous tissue assumption** In this thesis, we constructed 1D and 2D tissues with homogeneous cell models. However, it is important to construct a transmural heterogeneous tissue and investigate how the heterogeneous APD can affect the related electrophysiological properties. For example, in a 2D sheet, it is believed that spiral waves are strongly associated with ventricular arrhythmias, such as tachycardia and fibrillation, and it is important to investigate their dynamics, such as their initiation, stabilization, maintenance, and diminishment. Inclusion of transmural heterogeneity could be a source of arrhythmogenic substrate and it could be applied for tissues under normal as well as heart failure conditions [2; 70; 140]. Even though electrotonic effects may smooth the transmural differences under normal conditions, it can be exposed under pathological conditions such as heart failure. In addition, from our simulation results, we experienced that our initiated spiral waves, in spite of their stability, have one rotor. This kind of observation is associated with tachycardia. However, tachycardia could be degenerated into fibrillation where it is associated with breakup spiral waves, which inclusion of transmural heterogeneous cells could setup a stage for it because wavebreak
occurs when wavefronts encounter patches of myocardium with heterogeneous excitability or refractoriness [84]. This could increase the dominant frequencies from our simulations to lie with the ventricular fibrillation frequencies.

- **Regular tissue discretization and resolution assumptions**

  In this work, we used uniform squared tissue with regular spatial discretization. However, the ventricular anatomy is usually irregular in shape. We strongly simplified the geometrical tissue shapes at the time where real anatomical geometries obtained always require irregular discretization to handle these arbitrary geometries. In addition, the spatial resolution itself can alter the dynamics of the cellular electrophysiological model in different ways. For instance, coarser spatial resolution can develop corners caused by curved wave fronts [33] and breakup spiral waves [58]. On the contrary, stable spiral waves with coarse spatial resolution can breakup using finer spatial resolution [18].

- **Tissue propagation model used**

  In this thesis, we used a monodomain approach to simulate the propagation of excited action potential in the tissue. This approach assumes that the extracellular domain is isopotential and only considers the intracellular domain. However, it is more accurate and physiologically realistic to consider the extracellular domain using a bidomain approach [205]. For example, this approach allows using more complicated boundary conditions setup [83].

**Second Associated data sources limitations**

- **Experimental disagreement**

  As we explained in the previous conclusion section, we found places where our work matched experimental observations. There are other places where our simulation results differ from experimental observations. For example, for the normal OVVR model, the dominant frequencies measured of 2.08, 2.47, and 2.33 Hz for epicardial, endocardial, and midmyocardial preparations, respectively, are lower than those observed
clinically for ventricular tachycardia, except for the second epicardial frequency, which at 2.97 Hz is just inside the clinical range. The simulation results of 2.08, 2.47, and 2.33 Hz do not match the ventricular fibrillation frequencies experimental observations of 7.5 Hz [58; 167; 168].

Recent work on mRNA [254] has shown that alternans in human HF cells begins at a CL of 350 ms, whereas alternans in our case is higher by 50 ms, 250 ms, and 30 ms for epicardial, midmyocardial, and endocardial cells. However, alternans onset CLs are in the range of the observed values reported in other studies [264] of \( \leq 500 \) ms for epicardial and endocardial cells. In addition, in our simulation results, we observed that the maximum range of APD S-S restitution curve slopes is 0.26-0.60, 0.23-0.70, and 0.28-0.86 for epicardial, midmyocardial, and endocardial cells. For epicardial and midmyocardial, the maximum range of APD S-S restitution curve slopes is less than the slope value of 0.86\( \pm 0.12 \) measured in the LV free wall of the failing human heart [70] for epicardial and midmyocardial cells, but it matches the measured endocardial cell.

- **Variability representation** In our work, we introduced the variability of the functional remodeled transmural cells under heart failure conditions. The experimental studies documented in the literature measured heart failure under different stages. However, in this thesis, we considered the remodeled ionic currents as mean and standard deviation. The calculated mean and standard deviation are based on various experimental studies without considering the stages of heart failure. In addition, we did not consider the heart failure etiology, species, and the sample size of every experiment when representing the variability of our developed model. Moreover, we did not take into account the variability of the original model. It is vital to study the variability of the undiseased model to get deep insights into the border zone, or overlap between both sets of parameters. This will help constraining each
parameter under every condition.

7.3 Future Work

In addition to the aforementioned contributions to the field of cellular models, this thesis opens new avenues for possible future directions of this field, as follows:

- **Enhancement of cellular heart failure model** In our developed HF model, we remodeled ionic currents and exchangers through changing their conductance explicitly. However, in reality each of these ionic currents represents the sum of currents of functional channels and their properties, which include the current amplitude, open probability, and availability. Any alteration of these properties will affect whole cell ionic currents. Therefore, it is important to consider the potential consequences of these properties under heart failure conditions. Especially, previous experimental studies observed agreement and alteration of these properties depending on the current type. One study, [213], shows that the single channel activity of L-type $Ca^{+2}$ channels is increased in failing myocardium compared to nonfailing myocardium. In addition, [244] studied single channel properties of the $I_{NaL}$ current in humans and compared its gating property in normal and failing hearts and found similar properties under both conditions.

- **Improvement of heart failure model in 1D cable** It is known that the remodeling development during heart failure creates many changes including molecular, cellular, structural, or functional alterations. During this development process many elements are involved such as fibroblasts. Our 1D simulation could be improved in two ways: 1) By including transmural cell types for building ventricular strands, instead of homogeneous cells. Including this factor will help elucidate how transmural cells affect the remodeled electrophysiological properties such as dispersion of repolarization, which is an important factor
to arrhythmia [1; 139] and has controversial experimental observations [70; 140]. 2) By including structural remodeling such as cellular uncoupling or proliferation of fibroblasts [100; 123; 279] because it is another contributor to arrhythmia [69; 91]. For this purpose, we could integrate a fibroblast model such as [147; 208] with our developed HF model.

– Electrophysiological and structural remodeling during heart failure in setting the stage for arrhythmias In this thesis, we focused on the electrophysiological side of remodeled ventricular myocytes. However, to have a more robust result and make better predictions, the structure of ventricular myocytes should be incorporated. If we integrate both the remodeled electrophysiology and structure of ventricular myocytes under heart failure conditions, we will get more realistic results when compared with experimental observations. For example, considering the remodeled fiber structure allows one to assess the relative effect of fibers on electrical propagation. The framework can be built upon the original ventricular cellular model and our developed heart failure model and incorporated with existing three-dimensional anatomical structures from normal and HF human hearts. Then, arrhythmia properties can be quantified with four possible combinations: 1) normal anatomy and normal electrophysiology, 2) HF anatomy and normal electrophysiology, 3) normal anatomy and HF electrophysiology, and 4) HF anatomy and HF electrophysiology.

– Electromechanical properties under heart failure conditions in human ventricular cells Since the heart is an electromechanical organ, it is important to incorporate mechanical properties such as kinematics, forces, and material properties of the heart in the analysis of remodeled ventricular myocytes. Therefore, integrating the cardiac electrophysiology and mechanical cellular models will provide clearer insights to diagnose failing myocytes. Also, performing this integration will be more realistic, but complicated cardiac functions can be simulated, which will help in predicting unseen properties under
pathological conditions, such as heart failure.

- **A drug application for the human heart failure model** Another new avenue could be using the developed heart failure model towards drug applications. For example, the inclusion of CaMK in the model will facilitate investigating how drug-induced alterations in ionic current and exchanger properties may modulate the electrophysiological properties in heart failure.

- **Artificial Neural Networks for parameter sensitivity analysis: applications to the understanding of heart failure mechanisms** During HF, electrophysiological properties in a single cell are altered. These alterations as observed by experimentalists include for example, ion channel remodeling, altered calcium homeostasis, and increased accumulated sodium concentration. Mathematical modeling of disease-specific electrical activity of human ventricular cell types is a powerful tool to complement experimental observations. However, given a ventricular cellular model with typically a large number of ionic parameters, it remains a great challenge to properly constrain the value of these parameters to simulate pathological conditions of interest, especially because distinctive sets of ionic parameters may reproduce similar action potential characteristics.

In this new avenue, artificial neural networks (ANNs) can be used in assessing the relative importance of various ionic parameters in their contribution to the alterations that occur in the action potential or calcium concentration during heart failure. The presented investigation could be done using our developed HF-OVVR model. By training an ANN on a large dataset of healthy versus HF electrophysiological conditions simulated by the OVVR model, one will learn the relationship between ionic parameters and action potential / calcium concentration characteristics. Using the learned ANN model, one can identify parameter sets that are most associated with electrophysiological remodeling in HF. In addition, this can provide quantitative predictions of these parameter values that correspond to experimentally observed
cellular alterations. Performing this study can provide new insights into the underlying mechanisms of HF, and potentially provide guidance in application areas such as pharmaceutical intervention.

– **Assessment of scroll wave dynamics** To this point, our developed heart failure model is not validated on three dimensional tissue. Even though we applied our HF model on 2D tissue and initiated spiral waves, it created stable and quasi-stable spiral waves. It could be the case in 3D where the scroll wave breaks up into multiple scroll waves, which is a mechanism associated with ventricular fibrillation.
## Appendix A

### Table A.1: Summary of changes in the fast sodium ($Na^+$) current density in human HF.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Percentage of change</th>
<th>Species investigated</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valdivia et al. [246]</td>
<td>↓(39.3%±6.5) &amp; ↓(57.1%±1.6)</td>
<td>canine &amp; human</td>
<td>-</td>
</tr>
<tr>
<td>Shang et al. [221]</td>
<td>↓(63%)</td>
<td>human</td>
<td>protein levels</td>
</tr>
<tr>
<td>Gao et al. [65]</td>
<td>↓(91.1%±9.3)</td>
<td>human</td>
<td>-</td>
</tr>
<tr>
<td>Sakakibara et al. [211]</td>
<td>unchanged</td>
<td>human</td>
<td>-</td>
</tr>
<tr>
<td>Reference</td>
<td>Percentage of change</td>
<td>Species investigated</td>
<td>Remarks</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Undrovinas et al. [244]</td>
<td>↑(-%)</td>
<td>human</td>
<td>Midmyocardium.</td>
</tr>
<tr>
<td>Valdivia et al. [246]</td>
<td>↑(113.6%±10) &amp; ↑(238.5%±1.3)</td>
<td>canine &amp; human</td>
<td>-</td>
</tr>
<tr>
<td>Maltsev et al. [152]</td>
<td>↑(30%)</td>
<td>human</td>
<td>HF slows late NaCh gating resulting an ↑(58%) in Na(^+) influx. Midmyocardium.</td>
</tr>
<tr>
<td>Maltsev et al. [151]</td>
<td>↑(30.6%±0.03) &amp; ↑(54%)</td>
<td>canine &amp; human</td>
<td>Midmyocardium.</td>
</tr>
<tr>
<td>Maltsev et al. [150]</td>
<td>unchanged</td>
<td>human</td>
<td>-</td>
</tr>
</tbody>
</table>

Table A.2: Summary of changes in the late sodium (Na\(^+\)) current density in human HF. ↑: increase; NaCh: Sodium channel; P, protein.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Percentage of change</th>
<th>Species investigated</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasmussen et al. [198]</td>
<td>-</td>
<td>human</td>
<td>unchanged DHP B sites &amp; ↓(50%) β-receptors</td>
</tr>
<tr>
<td>Beuckelmann et al. [14]</td>
<td>unchanged</td>
<td>human</td>
<td></td>
</tr>
<tr>
<td>Beuckelmann et al. [47]</td>
<td>unchanged</td>
<td>human</td>
<td></td>
</tr>
<tr>
<td>Beuckelmann et al. [12]</td>
<td>unchanged</td>
<td>human</td>
<td>in both DCM &amp; ICM</td>
</tr>
<tr>
<td>Mewes et al. [158]</td>
<td>unchanged</td>
<td>human</td>
<td></td>
</tr>
<tr>
<td>Tomaselli et al. [235]</td>
<td>unchanged</td>
<td>human</td>
<td></td>
</tr>
<tr>
<td>Ouadid et al. [9]</td>
<td>unchanged</td>
<td>human</td>
<td></td>
</tr>
<tr>
<td>Schröder et al. [213]</td>
<td>unchanged</td>
<td>human</td>
<td>↑ SCA activity, ↑(189.4%) peak average current in a single channel.</td>
</tr>
<tr>
<td>Kääb et al. [114]</td>
<td>-</td>
<td>human</td>
<td>unchanged mRNA</td>
</tr>
<tr>
<td>Schwinger et al. [215]</td>
<td>-</td>
<td>human</td>
<td>unchanged mRNA, P &amp; DHP</td>
</tr>
<tr>
<td>Chen et al. [26]</td>
<td>unchanged</td>
<td>human</td>
<td></td>
</tr>
<tr>
<td>Li et al. [133]</td>
<td>unchanged</td>
<td>human</td>
<td>epicardium.</td>
</tr>
<tr>
<td>Takahashi et al. [231]</td>
<td>↓(35%-48%) &amp; ↓(47%)</td>
<td>human</td>
<td>in DHP B sites &amp; mRNA</td>
</tr>
<tr>
<td>Piot et al. [188]</td>
<td>↑</td>
<td>human</td>
<td>with rapid stimulation</td>
</tr>
</tbody>
</table>

Table A.3: Summary of changes in the L-type Ca$^{2+}$ current density in human HF. ↓: decrease; DCM: dilated cardiomyopathy; ICM: ischemic cardiomyopathy; SCA: single channel activity; B, binding; P: protein; epi: epicardium; endo: endocardium; mid: mid-myocardial; DHP: dihydropyridine; CA: channel activity; $I_{CaT}$: transient Ca$^{2+}$ current.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Percentage of change</th>
<th>Species investigated</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beuckelmann et al. [13]</td>
<td>↓(36.3%±3.3)</td>
<td>human</td>
<td>midmyocardium.</td>
</tr>
<tr>
<td>Nääbauer et al. [164]</td>
<td>↓(36%)</td>
<td>human</td>
<td>midmyocardium.</td>
</tr>
<tr>
<td>Tomaselli et al. [235]</td>
<td>↓(35-40%)</td>
<td>human</td>
<td>midmyocardium.</td>
</tr>
<tr>
<td>Wettwer et al. [261]</td>
<td>unchanged &amp; ↓(47%)</td>
<td>human</td>
<td>subepi- &amp; subendo-</td>
</tr>
<tr>
<td>Nääbauer et al. [165]</td>
<td>↓(26.4%±1.3) &amp; unchanged</td>
<td>human</td>
<td>subepi- &amp; subendo-</td>
</tr>
<tr>
<td>Kääb et al. [114]</td>
<td>↓(48%)</td>
<td>human</td>
<td>↓(30%) in Kv4.3 mRNA. Midmyocardium.</td>
</tr>
<tr>
<td>Li et al. [133]</td>
<td>↓(32.1%±6.4%)</td>
<td>human</td>
<td>epi- cell.</td>
</tr>
<tr>
<td>Zicha et al. [274]</td>
<td>↓(73.2%±5.8) &amp; ↓(54.6%±2.0)</td>
<td>canine</td>
<td>epi- &amp; endo- ↓(36%) &amp; (56%) Kv4.3 protein expression epi- &amp; endo- human ↓(14%) &amp; (50%) in KChIP2 expression epi- &amp; endo- human</td>
</tr>
<tr>
<td>Holzem et al. [91]</td>
<td>↓(30%)</td>
<td>human</td>
<td>in Kv4.3 mRNA</td>
</tr>
<tr>
<td>Wettwer et al. [262]</td>
<td>unchanged</td>
<td>human</td>
<td>-</td>
</tr>
</tbody>
</table>

Table A.4: Summary of changes in the $Ca^{2+}$-independent transient outward potassium ($K^+$) current density in models of heart failure. ↓: decrease; P, protein; epi: epicardium; endo: endocardium; mid: mid-myocardial; $I_{K,slow}$: the slowly inactivating component of $I_K$.  

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<table>
<thead>
<tr>
<th>Reference</th>
<th>Percentage of change</th>
<th>Species investigated</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takahashi et al. [231]</td>
<td>↓(47%)</td>
<td>human</td>
<td>mRNA levels.</td>
</tr>
<tr>
<td>Beuckelmann et al. [13]</td>
<td>↓(43.4%±2.5)</td>
<td>human</td>
<td>Midmyocardium.</td>
</tr>
<tr>
<td>Tomaselli et al. [235]</td>
<td>↓(40%)</td>
<td>human</td>
<td>-</td>
</tr>
<tr>
<td>Koumi et al. [125]</td>
<td>↓</td>
<td>human</td>
<td>SCA in (56%) &amp; (77%) of patches are active in DCM &amp; ICM.</td>
</tr>
<tr>
<td>Kääb et al. [114]</td>
<td>↓</td>
<td>human</td>
<td>unchanged Kir2.1 mRNA. Midmyocardium.</td>
</tr>
<tr>
<td>Li et al. [132]</td>
<td>↓(40.9%±0.8), ↓(40.7%±0.6), ↓(41.1%±2.9)</td>
<td>canine</td>
<td>epi-, mid-, and endocardial cell type.</td>
</tr>
<tr>
<td>Li et al. [133]</td>
<td>↓(56.3%±2.2)</td>
<td>human</td>
<td>epi- cell.</td>
</tr>
<tr>
<td>Akar et al. [2]</td>
<td>↓(50%), ↓(47%) &amp; ↓(64%)</td>
<td>canine</td>
<td>epi-, endo-, &amp; mid- &amp; unchanged mRNA and P</td>
</tr>
<tr>
<td>Wang et al. [257]</td>
<td>-</td>
<td>human</td>
<td>unchanged IRK mRNA levels.</td>
</tr>
</tbody>
</table>

Table A.5: Summary of changes in the inward potassium ($K^+$) current density in human HF. ↓: decrease; DCM: dilated cardiomyopathy; ICM: ischemic cardiomyopathy; SCA: single channel activity; P, protein; epi: epicardium; endo: endocardium; mid: mid-myocardial; IRK: inward rectifier potassium current.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Percentage of change</th>
<th>Species investigated</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kääb et al. [115]</td>
<td>unchanged</td>
<td>canine</td>
<td>barley measure $I_K$ mid-myocardium.</td>
</tr>
<tr>
<td>Kääb et al. [114]</td>
<td>-</td>
<td>human</td>
<td>unchanged HERG gene</td>
</tr>
<tr>
<td>Li et al. [133]</td>
<td>unchanged</td>
<td>human</td>
<td>epicardium</td>
</tr>
<tr>
<td>Watanabe et al. [258]</td>
<td>-</td>
<td>human</td>
<td>endo- RV. Unchanged KCNH2 &amp; KCNQ1</td>
</tr>
<tr>
<td>Verkerk et al. [248]</td>
<td>unchanged</td>
<td>rabbit</td>
<td>in both DCM &amp; ICM</td>
</tr>
<tr>
<td>Akar et al. [2]</td>
<td>↓</td>
<td>canine</td>
<td>epi-, endo-, &amp; mid- &amp; unchanged mRNA and ↓(39%), ↓(46%), &amp; ↓(51%) cERG P in epi-, endo, &amp; mid-</td>
</tr>
<tr>
<td>Holzem et al. [50]</td>
<td>↓</td>
<td>human</td>
<td>↓(45.9%±9.5), ↓(27.3%±1.7) in Kv11.1 P &amp; ↑(40.4%±2.7), ↑(55.8%±2.5) in Kv11.1 hERG1b in epi- &amp; endo-</td>
</tr>
<tr>
<td>Beuckelmann et al. [13]</td>
<td>-</td>
<td>human</td>
<td>could not observe $I_K$ in normal hearts</td>
</tr>
</tbody>
</table>

Table A.6: Summary of changes in the rapid delayed rectifier potassium ($K^+$) current density in human HF. ↓: decrease; DCM: dilated cardiomyopathy; ICM: ischemic cardiomyopathy; SCA: single channel activity; P, protein; epi: epicardium; endo: endocardium; mid: mid-myocardial.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Percentage of change</th>
<th>Species investigated</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al. [132]</td>
<td>↓(57.1%±1.6),</td>
<td>canine</td>
<td>tail $I_{Ks}$ epi-, endo-, &amp; mid-</td>
</tr>
<tr>
<td></td>
<td>↓(57.7%±2.2),</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&amp; ↓(49.5%±1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al. [133]</td>
<td>↓(61.7%±1.4)</td>
<td>human</td>
<td>tail current density, epi- cell</td>
</tr>
<tr>
<td>Watanabe et al.</td>
<td>-</td>
<td>human</td>
<td>↑(25%) KCNE1 mRNA</td>
</tr>
<tr>
<td>[258]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beuckelmann et al.</td>
<td>-</td>
<td>human</td>
<td>could not observe $I_K$ in normal hearts</td>
</tr>
<tr>
<td>[13]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table A.7: Summary of changes in the outward slow delayed rectifier potassium ($K^+$) current density in human HF. ↓: decrease; P, protein; epi: epicardium; endo: endocardium; mid: midmyocardial.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Percentage of change</th>
<th>Species investigated</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studer et al. [228]</td>
<td>↑2.0-fold</td>
<td>human</td>
<td>↑55% in mRNA and ↑41% in CAD protein levels.</td>
</tr>
<tr>
<td>Reinecke et al. [199]</td>
<td>↑(86.9%±0.12)</td>
<td>human</td>
<td>↑(160%) immunoreactive Na(^+)/Ca(^{2+}) P</td>
</tr>
<tr>
<td>Flesch et al. [61]</td>
<td>↑Trend</td>
<td>human</td>
<td>↑(79%) &amp; ↑(58%) in DCM &amp; ICM mRNA and ↑(36%) &amp; ↑(20%) in DCM &amp; ICM P</td>
</tr>
<tr>
<td>Studer et al. [229]</td>
<td>↑(50%) &amp; ↑(80%) &amp; ↑(90%)</td>
<td>rat &amp; human</td>
<td>↑(36%) &amp; ↑(50%) in CAD &amp; DCM mRNA and ↑(170%) &amp; ↑(130%) in CAD &amp; DCM P &amp; ↑(250%) in rat P</td>
</tr>
<tr>
<td>Hasenfuss et al. [81]</td>
<td>↑2.0-fold</td>
<td>human</td>
<td>protein levels. ↑(80%) G1, unchanged G2, &amp; G3 P levels</td>
</tr>
<tr>
<td>Tomaselli et al. [235]</td>
<td>unchanged</td>
<td>human</td>
<td>-</td>
</tr>
<tr>
<td>Schwinger et al. [215]</td>
<td>unchanged</td>
<td>human</td>
<td>protein levels.</td>
</tr>
<tr>
<td>Diedrichs et al. [45]</td>
<td>unchanged</td>
<td>human</td>
<td>in DCM</td>
</tr>
</tbody>
</table>

Table A.8: Summary of changes in the sodium/calcium (Na\(^+\)/Ca\(^{2+}\)) exchanger in human HF. ↓: decrease; DCM: dilated cardiomyopathy; ICM: ischemic cardiomyopathy; CAD: coronary artery disease; NF: non-infarct; MI: myocardial infarction; P, protein; epi: epicardium; endo: endocardium; mid: mid-myocardial; G1: group I; G2: group II; G3: group III.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Percentage of change</th>
<th>Species investigated</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kjeldsen et al. [121]</td>
<td>↓(36%), ↓(33%) &amp; ↓(20%)</td>
<td>human, hamster &amp; rat</td>
<td>Na(^+)/K(^+)-ATPase concentration of ednorgaard et al. [113]</td>
</tr>
<tr>
<td>Na\⊘rgaard et al. [113]</td>
<td>↓(40.8%±15.5)</td>
<td>human</td>
<td>DCM endo-</td>
</tr>
<tr>
<td>Schwinger et al. [145]</td>
<td>↓</td>
<td>human</td>
<td>-</td>
</tr>
<tr>
<td>Schwinger et al. [22]</td>
<td>-</td>
<td>human</td>
<td>↓(38%) OUA</td>
</tr>
<tr>
<td>Shamraj et al. [219]</td>
<td>↓(42%)</td>
<td>human</td>
<td>↓(26%-56%) range of decrease.</td>
</tr>
<tr>
<td>Zahler et al. [253]</td>
<td>↓</td>
<td>canine, rat &amp; human</td>
<td>↓(27%) in α isoform mRNA of canine</td>
</tr>
<tr>
<td>Schwinger et al. [216]</td>
<td>↓(42%)</td>
<td>human</td>
<td>↓(39%) in both β1 &amp; OBS</td>
</tr>
<tr>
<td>Allen et al. [106]</td>
<td>tendency to decrease</td>
<td>human</td>
<td>non-significantly ↓(10%) in DCM &amp; ICM</td>
</tr>
</tbody>
</table>

Table A.9: Summary of changes in the sodium/potassium (Na\(^+\)/K\(^+\)) exchanger in human HF. ↓: decrease; DCM: dilated cardiomyopathy; ICM: ischemic cardiomyopathy; CAD: coronary artery disease; NF: non-infarct; MI: myocardial infarction; P, protein; epi: epicardium; endo: endocardium; mid: mid-myocardial; OBS: ouabain binding sites; OUA: glycoside ouabain.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Percentage of change</th>
<th>Species investigated</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercadier et al. [157]</td>
<td>↓(48%)</td>
<td>human</td>
<td>mRNA levels.</td>
</tr>
<tr>
<td>Hasenfuss et al. [79]</td>
<td>↓(50%)</td>
<td>human</td>
<td>$Ca^{2+}$ uptake function.</td>
</tr>
<tr>
<td>Hasenfuss et al. [81]</td>
<td>↓(41%), ↓(33%)</td>
<td>human</td>
<td>SERCA2a &amp; phospholamban protein levels.</td>
</tr>
<tr>
<td>Dipla et al. [46]</td>
<td>↓</td>
<td>human</td>
<td>SR $Ca^{2+}$ stores in midmyocardial tissue.</td>
</tr>
<tr>
<td>Hasenfuss et al. [80]</td>
<td>↓(48%)</td>
<td>human</td>
<td>SR $Ca^{2+}$-ATPase protein levels.</td>
</tr>
<tr>
<td>Prestle et al. [192]</td>
<td>↓(40%±5), ↓(25%±7), ↓(19.4%±16.2), &amp; ↓(33.6%±16.8)</td>
<td>human</td>
<td>SERCA2a protein &amp; mRNA levels in the endo-, endo-, mid-, &amp; endo- relative to protein levels in epi-.</td>
</tr>
<tr>
<td>Yamamoto et al. [268]</td>
<td>↓(55%)</td>
<td>human</td>
<td>The amount of $Ca^{2+}$ uptake.</td>
</tr>
<tr>
<td>Jiang et al. [107]</td>
<td>↓(65%±7), &amp; ↓(30%±5)</td>
<td>canine &amp; human</td>
<td>SERCA2a in endocardial.</td>
</tr>
<tr>
<td>Piacentino et al. [187]</td>
<td>↓(43.6%±2.7)</td>
<td>human</td>
<td>rate of SR in midmyocardium.</td>
</tr>
<tr>
<td>Lou et al. [139]</td>
<td>↓(15.4%), &amp; ↓(40%)</td>
<td>human</td>
<td>protein levels of SR $Ca^{2+}$-ATPase 2a in sub-epicardium &amp; sub-endocardium.</td>
</tr>
</tbody>
</table>
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