Modeling Human Atrial Electrodynamics and Arrhythmias through GPU Parallel Computing

From Cell to Tissue

Pol Canal Noguer

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Here I present the study of instabilities in human atrial cardiac tissue using a complex non-linear set of differential equations. More specifically, the topic I will focus on is atrial calcium alternans driven by SR Ca content fluctuations and SR refractoriness when extending the model from the cell level to tissue.

This thesis will be structured in four blocks, each of which will be separated in subsections. The first one will introduce the reasons why studying instabilities in cardiac tissue is a hot topic as well as a research motor that helps other disciplines like computer science advance faster. Then I will briefly talk about the state of art experimental setup (optical mapping) and not so briefly explain the bibliographic research about the biology behind this model for a better comprehension of the connection between the model and reality. To end with this second block I will summarize the GPU programming concept and compare CPU vs GPU to highlight the parallel programming benefits. The third block will summarize the main concepts of the model, providing the capability of understanding figures and results in the forth block. The forth block will focus on simulating the 2D model and analyzing its results in terms of instabilities and performance in order to understand why those instabilities appear when changing some parameter values in the equations. Finally, I will discuss the obtained results and conclude with limitations and future work.

The main concepts this thesis wants you to learn are calcium cycling, and more specifically what's the role of the Ryanodine Receptors in the SR, calcium and action potential sustained alternans and the mechanisms behind it and the differences between CPU and GPU and why is it important.
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Chapter 1

Introduction

Much has been studied about cardiophysiology recently: during the last 20 years it has been a hot research topic because of its impact for public health [3]. In effect, cardiovascular disease (CVD) accounts for a third of all deaths in the developed world, being the leading cause of death [4,5]. When the cardiac rhythmic electrical pulses that lead to proper blood pumping desynchronize, the heart starts malfunctioning and not supplying the oxygen needed to be alive. These phenomena are commonly associated with arrhythmias such as AF (Atrial Fibrillation), VF (Ventricular Fibrillation) and VT (Ventricular Tachycardia) [6]. VF/VT is the most relevant cause of sudden cardiac death (SCD), with an incidence estimated to be 4 to 5 million cases per year worldwide. On the other hand, AF is a sustained arrhythmia normally happening at an elder age that increases the risk of stroke, heart failure, dementia and death. In developed countries prevalence of AF was estimated to be 0.9% in 2013, and projected to more than double in the next two decades [7]. Moreover, in recent studies from 2015 it was estimated that 2.5% of the population worldwide has AF (in both developed and undeveloped nations).

An important motivation to model atria tissue derives from the relation between AF and cognitive dysfunction known as dementia, which was well described by T. Tsang et al. in the European Heart Journal in 2007 [8]: "Atrial fibrillation (AF) is a growing public health problem, which has reached epidemic proportions. Multiple studies have shown that AF is associated with stroke, congestive heart failure (CHF) and all-cause mortality. Recently, there has been increasing evidence that AF may contribute to the development of cognitive dysfunction. Notably, the cross-sectional study as part of the Rotterdam Study demonstrated that cognitive dysfunction was approximately twice as common in subjects with AF than in those without. Other cross-sectional studies have shown that AF was associated with cognitive dysfunction, independent of stroke and other cardiovascular risk factors. Added together, these studies suggest that patients with AF are at increased risk of cognitive dysfunction." The reason why this research field is an interesting widely spread topic is the global impact it has as explained before. Also the underlying mechanisms causing CVD are not completely understood, giving a
high relevance to the study of the nonlinear dynamics and models approaching reality of
this growing disease. I will focus on alternans, a sustained periodic instability that could
originate a conduction block at some point in the organ giving rise to spiral wave
dynamics, translated as AF if the system becomes chaotic. This phenomenon will be
explained in detail in the subsequent section.

Even if nowadays we count on a huge amount of experimental data available, from
detailed electrophysiological studies of myocytes to a more generalist perspective
through electrocardiogram (ECG) recordings, optical mapping cardiac tissue and
magnetic resonance imaging (MRI), mathematical modeling and simulating this system
turns out to be a complex problem: the heart works as an electromechanical pump of
blood and many disciplines come together to tackle the whole organ model in the most
strict and realistic sense. For a complete mathematical description one has to combine
electric wave propagation, muscle contraction and blood fluid dynamics at many
different time and space scales: from the cell behavior and extending it to the whole
organ, or even multiscale approaches to understand how processes in a small scale can
determine observable changes in a large one [9,10]. Thus, one can imagine how
complicated it would be to describe a whole heart in terms of a single cell's electromagnet,
contractile and fluid dynamics properties and as an extension of it to
every single myocyte; not only because of the nonlinear, turbulent and sometimes
chaotic regime of the system, which would be such a complex scenario itself, but also
because of the limits in terms of the mathematical and computational weight it would
carry with him.

With respect to the above mentioned problem and from a physicist point of view, the
tendency followed by many models to tackle macroscopic, continuum models at tissue
or organ level out of a discrete, heterogeneous, microscopic scale is the homogenization
averaged over this latter scale [11,12]. From that we get bidomain equations for
electrical propagation, which are commonly solved as a monodomain approximation
described by coupled reaction-diffusion equations. However, from a computational cost
perspective, big domains of integration in tissue or organ level carry with them a
massive computational cost when the number of ODEs of the model exceeds a small
number, giving poor approximations when optimizing the speed of the simulation. In
the matter at hand, I will be solving a 38 ODE model by using GPU programming,
otherwise calculations would take too long. We will see in subsequent sections that with
simple GPU programming one can save much computational time which is needed in
this situation. What GPU programming is and the differences between CPU and GPU
will be explained too.

One of the first well-known models to be studied concerning excitable media and ionic
models of cellular action potential was the so-called Hodgkin-Huxley model for a giant
squid axon nerve published in 1952, which has been then used by many others in their
models as a starting point. The main ideas of the model one has to keep in mind are the
following:
• The lipid bilayer is represented as a capacitance \( (C_m) \)
• Ionic channels on the membrane are represented as nonlinear ionic conductances \( (g_n, \text{ where } n \text{ is a specific ionic channel}) \) with their associated ionic gates.
• Gates on ionic channels are represented as linear conductances \( (g_L, \text{ same applies for } L) \)
• The electrochemical gradients that rule the ion flux are represented as batteries \( (E_n \& E_L) \) the values of which are given by the Nernst potential
• The ionic pumps are represented as current sources
• The derivative of the action potential (potential across the membrane) over time follows the equation:

\[
\dot{V}_m = -\frac{1}{C_m} \sum_i l_i
\]  

(1)

For this thesis we will consider the model presented in *Mathematical Model of an Adult Human Atrial Cell* published by Nygren et al., to which I will refer from now on as Nygren Model [1], with the adaptations and corrections by C. Lugo et al. [2].
Chapter 2

Biological Scope

2.1 Structure (cell and organ), basic functions and contraction

The structure of the heart and its main function are well-known. In this section we will present a brief reminder of cardiac physiology and the cardiac cycle. The heart is composed by four chambers: the top ones known as right atrium (RA) and left atrium (LA), and the bottom ones named as right ventricle (RV) and left ventricle (LV). Deoxygenated blood comes from the body to the right atrium from the superior and inferior vena cava and through the coronary sinus. Then blood is pumped from the right atrium to the right ventricle through the tricuspid valve and then pumped again through the pulmonary valve to the pulmonary artery. Blood exchanges carbon dioxide for oxygen in the lungs and then flows through the pulmonary vein to get to the left atrium. The left atrium pumps oxygenated blood into the left ventricle through the mitral valve and finally the ventricle pumps it to through the aorta for systemic circulation: provide the rest of the body with oxygen. So summarizing, the right heart is deoxygenated and the left heart is oxygenated. For a visual representation, see Figure 1.
Nevertheless, the physical description is not as simple as stated before. To have a complete description one should include the electrical propagation, the ionic diffusion, fluid dynamics and many others. In this project, I will focus on electrical propagation and ionic diffusion, more specifically calcium cycling. After explaining these two, I will compare a normal heart function with a diseased one and introduce the underlying known mechanisms causing a malfunction. Finally I will describe in depth the mechanism that will be simulated afterwards: alternans.

But first, the structure of a cardiomyocyte and the cardiac muscle contraction will be explained. Cardiac muscle cells or cardiomyocytes make up the cardiac muscle. They all share the same basic structure: actin and myosin filaments (thin and thick, respectively) intercalated to produce contraction covered by the sarcolemma (outer membrane), with a high concentration of mitochondria and sarcoplasmic reticulum (SR) [Figure 2]. The SR has a crucial role in this project so it will be explained in detail in the Calcium cycling section.

Fig. 1. The cardiac cycle, with systole meaning the contraction phase and diastole the relaxation one.
In a summarized version of the contraction mechanism, it can be explained as follows: when a large concentration of calcium is released inside the cell, Troponin (protein attached to Tropomyosin) lets Tropomyosin (protein attached to actin) stop from interacting with actin, which causes an interaction between actin and myosin. This produces contraction in the cell through the Cross-Bridge cycle [Figure 3] consuming energy from ATP, the reason why a high number of mitochondria is required.

To end with this subsection, there are two classifications for cardiomyocytes that must be known.
- The first one is the distinction between ventricle cardiomyocytes and atrial ones: ventricle cardiomyocytes contain t-tubules, invaginations of the sarcolemma that help transmitting the electrical wave simultaneously to all the domain of the cell, but atrial cells are thought not to have these t-tubule structures (although it is not clear). Atrial cardiomyocytes use saltatory conduction.

- The second classification refers to the capability of self-depolarizing, meaning that some of the cells are responsible for being able to spontaneously generate and send out electrical impulses to the rest of the organ. This type of cells are the so-called cardiac pacemaker cells, which can not only generate the electrical impulse but also receive and respond to brain activity as well as propagate waves from cell to cell like the rest of cardiomyocytes.

2.2 Electrical Propagation: the Action Potential (AP)

The action potential (AP) is change in the the membrane potential or the voltage across the membrane of an excitable cell, that rapidly rises and falls propagating this way the impulse to the neighboring cell. Action potentials occur in neurons, muscle cells (e.g. cardiomyocytes), endocrine cells and in some plant cells too. In this general scope (still not talking specifically about cardiomyocytes), action potentials are generated by specific types of voltage-gated ion channels (VGIC) encrusted in the plasma membrane or sarcolemma. VGIC are ensembles of proteins that open or close depending on the voltage across the sarcolemma, thus letting ions diffuse across the plasma membrane.

2.2.1 AP Shape: Phase Description

In order not to overextend a discussion about the underlying mechanism, a summarized version of it focusing on cardiomyocytes and the main features will be presented. The standard model for a cardiomyocyte AP is the ventricular AP. The whole process is divided in 5 phases, numbered from 0 to 4 [Figure 4]:

- Phase 4: this phase refers to the resting membrane potential, when cardiomyocytes are not being stimulated. Therefore, it is an horizontal line where the voltage remains constant. The normal resting potential for ventricular cardiomyocytes is about -85 to -95mV. In the atrial cells it is slightly higher, around -70 to -75mV. The value of this resting potential is determined by the sarcolemma's selective permeability to some ions, and dominated by K⁺ resting potential.
Phase 0: this is called the depolarization phase. When a cardiomyocyte's sodium current ($I_{Na}$) threshold is overcome due to a rise in voltage caused by electrical propagation from a neighbor myocyte, the sodium current gates open to let sodium in. The slope of this phase, in terms of the AP as a function of time, is the maximum one. That is, the membrane conductance to Na cation ($g_{Na}$) increases dramatically causing a large influx of Na$^+$ down to their electrochemical gradient. If for some reason the membrane potential is hyperpolarized (i.e. more negative AP), VGSC (voltage-gated sodium channels) will be inactive meaning that gates will be insensitive to opening. That leads to a cell or group of cells not being excitable, affecting conduction and being able to cause arrhythmias.

Phase 1: the myocyte undergoes phase 1 when the fast Na$^+$ channels inactivate. This causes a transient outward current ($I_{to}$) of K$^+$ ions that slightly repolarize the cell.

Phase 2: this is the so-called plateau phase. It consists of a flat constant AP value not equal to the resting potential value mentioned in phase 0. The responsible for that to happen is mainly Ca$^{2+}$. There is a sustained balance between an inward current of Ca$^{2+}$ ($I_{Ca,L}$) through L-type calcium channels (they play an important role, thus they will be explained in the next section) and an outward current of K$^+$ ions through the slow delayed rectifier K$^+$ channel ($I_{KS}$). During this phase, contraction initiates due to the large concentration of Ca$^{2+}$. Also, the sodium-calcium current ($I_{NaCa}$) and the sodium-potassium current ($I_{NaK}$) play a minor role during plateau phase beginning to restore ion concentrations.

Phase 3: the rapid repolarization phase. The L-type calcium channels close while the slow delayed rectifier K$^+$ channel remains open, causing a net outward positive current and leading to a repolarization of the sarcolemma. Additionally, more potassium leak channels open due to this repolarization: the rapid delayed rectifier K$^+$ channels ($I_{Kr}$) and the inwardly rectifying K$^+$ current ($I_{K1}$). Both delayed rectifier K$^+$ channels close as the AP approaches its resting value. However $I_{K1}$ remains conducting, as well as $I_{NaK}$ and $I_{NaCa}$ keep on exchanging ions, in order to help setting the resting AP and restore ionic concentration balances inside and outside the cell. As the intracellular calcium is pumped out, the cell stops from contracting and the myocyte relaxes.
There exists another aspect from AP to be considered: refractoriness. From the beginning of phase 0 until phase 3 when the membrane potential reaches -60mV, myocytes would be in an absolute refractory period, during which it is impossible to evoke another action potential. This is followed by a relative refractory period until the end of phase 3, during which a stronger than usual stimulus is required. These two refractory periods are caused by changes in the state of sodium and potassium channel molecules. After rapid depolarization of the cell due to rapid influx of sodium ions the membrane potential approaches 0mV and approaches sodium’s equilibrium potential. Sodium channels then enter an "inactivated" state, due to closing of the sodium inactivation gate, in which they cannot be opened regardless of the strength of the excitatory stimulus (this gives rise to the absolute refractory period). The relative refractory period is due to the leaking of potassium ions, which hyperpolarizes the membrane potential back to normal, thus resetting the sodium channels; opening the inactivation gate, but still leaving it in the closed conformation. Even after a sufficient number of sodium channels have transitioned back to their resting state, many potassium leak channels remain open, thus hyperpolarizing the cell to below normal AP, making it difficult but possible for depolarization to occur and an action potential to be initiated.

Furthermore, as it was mentioned in the second classification in the first part of this section, there also exist some cells that are capable of self-depolarizing. These cells, known as cardiac pacemaker cells, undergo a different process from that of the "regular"
cells, so that their AP shape over time is not the same [Figure 5]. For instance, automaticity takes place in phase 4 for a pacemaker cell: i.e. they are capable of spontaneously depolarize without any external source of excitation by opening their VGSC (voltage-gated sodium channels) right after the end of a previous action potential repolarization. Also, this particular type of cells are characterized by having an increased inward current of sodium through VGSC, an increased inward calcium current $I_{\text{Cat}}$ and a slowly decreasing potassium outward current, as well as a different threshold AP known as threshold pacemaker potential that is around -40mV. Accordingly, phase 0 depends on the activation of L-type calcium channels instead of the fast Na$^+$ current, the reason why the slope is more gradual. Phases 1 and 2 cannot be seen, during these phases there is a rapid outflow of K$^+$ and the L-type calcium channels close so that there is no plateau phase. Phase 3 is similar, but $I_{K1}$ plays no role.

2.2.2 Electrical Conduction System of the Heart

Electrical signals arising in the sinoatrial node's (SA node) pacemaker cells, located in the right atrium, stimulate the atria to contract and then travel to the atroventricular node (AV node), which is normally the only conduction pathway between the atria and the ventricles. After a delay, the stimulus diverges and is conducted through the left and right bundle of His to the respective Purkinje fibers for each side of the heart, as well as to the endocardium at the apex of the heart, then finally to the ventricular epicardium [Figure 6].
This subsection emphasizes the fact that conduction pathways of pacemaker cells evoke AP to their neighborhood from the top of the atria to the bottom of it, opposite to what ventricles do: ventricle's APs are evoked from the bottom to the top. This way, atrial contraction supplies the ventricles with blood and ventricle contraction pumps it to arteries.

2.2.3 Calcium Cycling

Calcium (Ca) plays an essential role in cardiophysiology, as well as in many other biological contexts. It is an intracellular second messenger involved in fertilization, contraction, electrical signaling, memory, gene transcription and cell death. We will discuss how Ca is important in electrophysiology via the mediation of AP shape, ion currents and exchangers, the regulation of other channels or exchangers, arrhythmogenic mechanisms, and the regulation of cell-cell communication. Before considering that, the sarcoplasmic reticulum (SR) and its function will be exposed.

The sarcoplasmic reticulum (SR) is a specialized type of smooth ER (endoplasmic reticulum) that regulates the calcium ion concentration of striated muscle cells like cardiomyocytes, it is mainly a Ca storage inside the cell. L-type VGCC (voltage-gated calcium channels), also known as Dihydropiridine Receptors (DHPR), are encrusted along the surface of the sarcolemma and have \( \alpha_1 \) subunits attached to them. These subunits are pore-like structures which allow diffusion of Ca from the extracellular medium to the intracellular one. When Ca diffuses from the extracellular to the intracellular medium (this phenomenon is known as calcium sparklet), Ca concentration around the VGCC will rise. However, this change in concentration will not cause contraction because it is too small, it needs to be amplified: this Ca rise will induce a Ca
release from the SR through the activation of Type II Ryanodine Receptors (RyR2), a massive protein attached to the surface of the SR. When activated, this protein will allow diffusion of Ca from the inside of the SR to the dyadic cleft, the space between the surface of the SR and the surface of the sarcolemma, leading to an amplified Ca concentration that will cause contraction. This last phenomenon is known as calcium spark, and the whole mechanism is the so-called calcium induced calcium release (CICR).

2.2.4 Arrhythmias: Alternans

During normal rhythm, the heart beats regularly, producing a single coordinated electrical wave. During arrhythmias such as ventricular tachycardia and ventricular fibrillation, this normal behavior is disrupted.

The underlying cause of many arrhythmias is the development of a reentrant circuit of electrical activity that repetitively stimulates the heart and produces contractions at a rapid rate, e.g. when a portion of the cardiac tissue does not stimulate (because of being damaged or because of refractoriness) it can generate a new focus of electrical activity that is undesired. During tachycardia, a single wave can rotate as a single spiral wave, producing fast beating rate and a fast contraction. During fibrillation, a single spiral wave can degenerate into multiple waves by twisting over itself and breaking [Figure 7]. Because contraction is stimulated by the pattern of electrical waves, arrhythmias can compromise the heart's ability to pump blood and sometimes may be lethal: tachycardia can be a sustained and chronic disease that increases your risk of fibrillation, but the latter cannot be sustained as it leads rapidly to heart stroke and death.

![Fig. 7. Arrhythmias: normal pulse propagation (top), tachycardia (middle) and fibrillation (bottom).](image-url)
There are many mechanisms that can be responsible for reentrant electrical activity, we will focus specifically on alternans.

Alternans is one of the most studied cardiac instabilities that are known to give rise to arrhythmias. It corresponds to a change in the duration of the action potential at the cell level, i.e. an alternating APD (action potential duration) from beat to beat. It can be better explained with an example: every beat has a cycle length in time, let's take 60 bpm (beats per minute) so a frequency of 1Hz. Each of these beats will have a total length of 1s, so the period of the oscillation is T=1s. This period T is split in two: APD (action potential duration) and DI (diastolic interval), which account for the time while the AP value is over a 90% of repolarization (APD) and the time while diastole occurs and the AP is below that 90%. APD will alternate every beat, which results in beats of weaker-stronger-weaker-stronger-etc contractions of the heart.

So basically, we have:

\[ T = APD_n + DI_n \]  

(2)

Additionally, the APD at a given beat depends on the DI of the previous one, meaning that there exists a relation called the AP restitution:

\[ APD_{n+1} = f(DI_n) \]  

(3)

Using these two equations and a cobweb diagram (Figure 8) one can study whether from a starting APD value the alternans will disappear over time or not, depending on the stability of the fixed point given by the intersection between the two equations. If the intersection between the two equations happens when the slope of the AP restitution curve is greater than one, it will diverge. If it's smaller than one, it will go to the fixed point with the system losing its alternans. The way to obtain this cobweb diagrams is the following: take the APD value of your n-step, place it on the APD restitution curve (black line) and draw a horizontal line \((APD_n = const)\) until you intersect the \(APD_n = T - DI_n\) function (blue line). Once you intersect it, draw a vertical line \((DI_n = const)\) until you intersect the APD restitution curve. This last one will give you \(APD_{n+1}\), and iterating the process one can extract the evolution of the system [3].

![Cobweb diagram](image)

Fig. 8. Cobweb diagram. Stable point, slope at the intersection <1 (left); unstable point, slope at the intersection >1 (right).
This way, one can see that the shorter the period is (blue line moving horizontally to the left), the steeper the slope gets so that a sustained alternans is more likely to happen, so that when the heart beats faster it is more likely to go through an alternans instability. According to what it has been said before, when pacing fast enough the system cannot be excited properly at every single beat due to refractoriness. However, this is a simple one dimensional map but the memory of the cells could reach previous steps such that $A_{n+1} = f(DI_n, DI_{n-1}, ...)$, giving rise to more complex dynamics and higher order maps.

There exists a classification for two different types of alternans: these APD alternans can be either in phase (concordant alternans) or out of phase in different parts of the tissue (discordant alternans). Discordant alternans can give rise to a conduction block, which can initiate reentry and fibrillation. For an example of discordant alternans, see Figure 9 [13].

![Fig. 9. Discordant alternans. The first time window shows a concordant alternans that has evolved into a discordant alternans in the second time window (AP is not the same throughout the tissue in the same beat).](image)

In our case, we will focus on intracellular calcium concentration alternans due to SR refractoriness and the cycle length on a tissue to study whether it is the key to APD alternans or other instabilities like tachycardia (i.e. check if spiral waves appear due to a change in SR refractoriness or the period).
Chapter 3

Numerical and Experimental Methods: GPU & Optical Mapping

The role computer simulations play in the scientific progress is crucial, and has been very well explained by Elizabeth M. Cherry et al. in the Cardiac Electrophysiology Review in 2001 [14]: "The most important use of computer simulation is in enabling “clean” experiments, in which exactly one parameter of interest is varied. This may be difficult or impossible to do in tissue experiments. Modeling provides other advantages when used to complement traditional experiments and clinical work. Computer simulations can guide experiments by providing hypotheses to test in vivo that have been verified already in silico. In addition, simulations can be used to investigate and to explain experimental and clinical observations. This continual feedback between simulation and experiment can reduce time and money spent on animal experiments and can generate valuable information about human arrhythmias while avoiding issues of patient safety". Additionally, I would add the value of not only reducing the economical costs of animal experiments but also the number of animal experiments themselves, making them more precise and reducing the ethical costs. The goal is to provide simulations through complex, accurate and fast models to the clinical practice with a user-friendly interface so that doctors can easily understand the program and change manually parameters on-the-fly for a patient-oriented treatment of cardiovascular disease. However, animal experiments must be performed in order to ensure that model predictions are correct as widely as possible. In the current project, a complex model of atria has been chosen to speed it up and compare experimental data with simulation results focusing on a very specific cause of arrhythmia: calcium alternans.

In the following, the concepts of GPU and CPU will be introduced. Then, I will compare GPU and CPU performance while highlighting the pros and cons depending on the scenario in which we use them. To end with this section, the two experimental
procedures that have been used to obtain data and ameliorate simulations will be introduced.

3.1 GPU vs CPU

The CPU (Central Processing Unit) has often been called the brain of the PC. But increasingly, that brain is being enhanced by another part of the PC: the GPU (Graphics Processing Unit).

A GPU is a specialized electronic circuit that was first designed to rapidly manipulate memory in order to accelerate the creation of images and display them. GPUs are used in all sorts of devices: embedded systems, mobile phones, personal computers, workstations and game consoles. In a personal computer, a GPU can be present on a video card, or it can be embedded on the motherboard or, in certain CPUs, on the CPU die. The term GPU was popularized by Nvidia in 1999, who marketed the GeForce 256 as "the world's first GPU". Rival ATI Technologies coined the term Visual Processing Unit or VPU with the release of the Radeon 9700 in 2002, but it did not spread as much as the term GPU.

On the other hand, a central processing unit (CPU) is the electronic circuitry within a computer that carries out the instructions of a computer program by performing the basic arithmetic, logical, control and input/output (I/O) operations specified by the instructions. The term has been used in the computer industry at least since the early 1960s.

From these definitions, one would immediately think that the GPU is used to display data in an efficient way (originally they were used for 3D game rendering) while CPU is used to obtain that data from compiling and executing simulations, but that would not be a complete answer. A simple way to understand the difference in simulation applications between a CPU and GPU is to compare how they process tasks and their architecture. A CPU consists of a few cores (up to eight for the moment) optimized for sequential serial processing while a GPU has a massively parallel architecture consisting of thousands of smaller cores designed for handling multiple tasks simultaneously. Currently, Nvidia's largest GPUs can have over 4000 cores.

This way, one can understand that for parallelizable codes (such as codes with many do loops) GPU programming has become a very powerful tool, being able to provide the ability to run codes in a time comparable to that for supercomputers. Apart from the fact that supercomputers (clusters of many CPUs) are more expensive (GPUs can cost up to thousands of dollars and supercomputers cost millions, so at least three orders of magnitude), they also need the codes to be adapted to their structure as well as book them for your purpose. These adaptations are computationally complicated and can take
a long time to be performed. However, with GPU programming one can tackle multiple tasks from home with a powerful graphics card just by adapting the code to GPU programming, which is a much easier task than understanding those for supercomputers. That's the main reason why there exist GPU based supercomputers like TITAN, an upgrade of JAGUAR supercomputer that became operational in 2012, which are capable of parallelizing processes in different GPUs. Figure 10 shows the evolution of GPU vs CPU performance over the past years as a function of the amount of data per second it can compute (in GB/s).

![Peak Memory Bandwidth](image)

Fig. 10. Evolution of GPU vs CPU performance over the past years as a function of the amount of data per second it can compute (in GB/s).

Nevertheless, GPU programming is not an all purpose computational mechanism: one can parallelize only the parts of the code which have simple operations due to the small computational power every core of the GPU has compared to that of each core of the CPU. Parallelizing parts of codes with a big enough computational weight could slow them down instead, but thanks to the way GPU works one can avoid those problems. Indeed, the GPU cannot work alone to compile and execute a program. The acceleration of codes work as it follows: the code is compiled and executed on the CPU, but certain parts of the code (like loops) will be sent to the GPU so that calculations are parallelized and made there [Figure 11]. In other words, GPU programming needs CPU programming. Also, when parallelizing many other facts have to be taken into account, such as not making any calculation for an array that depends on values contained in other slots of the same array. The reason for that is simple: determining the order of the calculations on a parallelization is both inaccurate and time consuming, as well as complicated.
During recent years, GPU-accelerated computing has grown into a mainstream movement supported by the latest operating systems from Apple (with OpenCL) and Microsoft (using DirectCompute). Also, there exist other languages like OpenACC or WebGL that work with free-software platforms like a simple html, i.e. a web browser.

3.2 Experimental Procedures

The data coming from experiments in cardiac tissue is obtained using the following preparation. The whole organ is taken and set inside a solution that keeps it fresh. After that, one has to cannulate the aorta to perfuse the heart with a previously made chemical solution called Tyrode that provides the heart with the ions it needs ($\text{Ca}^{2+}$, $\text{Na}^+$, $\text{K}^+$). This procedure is called *retroperfusion*, which stands for Tyrode flowing in the opposite direction to the normal circulation of blood: it perfuses from the aorta to the ventricle and then up to the ventricle through the valves, by overcoming the pressure those valves can stand. Once cannulated and perfused we check if there is any Tyrode escape, meaning there is an undesired hole on the organ caused when cutting off the organ from the animal, by measuring the pressure. If any, we clamp it so that perfusion works correctly. Then, we perfuse dyes (they will be explained in the following subsection) both for calcium and membrane voltage as well as blebbistatin, a drug that kills contraction but doesn't affect the electrophysiology, so that motion doesn't affect data acquirement. At that time, the organ is ready for the optical mapping.

![Fig. 11. GPU acceleration mechanism.](image)
3.2.1 Optical Mapping: membrane potential and Ca\(^{2+}\)

The optical mapping technique relies on fluorescence of dyes. Dyes are indicators that attach to a target molecule and when absorbing light, they emit in a particular spectrum of wavelengths. They can be used to track a specific molecule along its trajectory, for example. In particular, for membrane potential and Ca\(^{2+}\), there exist dyes that will shift their emission spectrum as a function of the value of the membrane potential or the calcium concentration, which turns out to be a useful procedure to get data from a tissue.

For membrane potential, the most common dye used is di-8-ANEPPS (di-8-butyl-amino-napthyl-ethylene-pyridinium-propyl-sulfonate). It attaches to the outer leaflet of the membrane, excites between 400-550nm and emits between 570-700nm [Quantitative Cardiac Physiology, Candido Cabo & David S. Rosenbaum].

Depending on the value of the AP both the spectrum of excitation and emission will shift and give rise to the calculation of \(\Delta F/F\), the fractional fluorescence changes for the dye.

In our case [Figure 12], we are using di-4-ANBDQPQ dye for AP instead of di-8-ANEPPS, because its wavelength emission spectrum is >700nm (red) instead of being around 630nm (redish). The reason for that is the possibility to obtain data both from calcium and AP simultaneously due to the emission spectrum of the Ca dye Rhod-2, which is between 560-615nm (green), through an optical acquirement of data which changes its filters as well as the wavelength of the radiation absorbed by the organ at a frame rate of 4ms. That would be the exposure time between changes. Also, the resolution of the camera is between 100-300µm, so it can give information about single cells.

![Fig. 12. Experimental setup for optical mapping.](image-url)
3.2.2 MRI (Magnetic Resonance Image)

There is another experimental technique that has been indirectly used in simulations: MRI (Magnetic Resonance Image). It is a medical imaging technique used in radiology to image the anatomy and the physiological processes of the body in both health and disease. MRI scanners use strong magnetic fields, radio waves, and field gradients to form images of the body. For our purposes, we could get a data file containing the structure of a human atria as a result of an MRI in the form of a phase field: a 3D mesh filled with values ranging from 0 to 1 where 1 means there is atrial tissue and 0 means there is not. The values between 0 and 1 are the result of a smoothed curve in order not to have computational problems of divergence, they are contained on the surface of the atria representation.
Chapter 4

The Model

The recent development of models of atrial cellular dynamics and of realistic atrial anatomic structures has enabled modeling and computer simulation to become important research tools in the analysis of atrial arrhythmias. The cell model includes membrane potential, transmembrane ionic currents and ion concentrations. The tissue model describes the overall geometric structure of the tissue as well as how cells are interconnected. For these studies, the mechanical properties of the heart are decoupled and only the electrical properties are considered. Several models have been published on that basis, the most relevant ones referring to complex models of human atria are the Courtemanche et al. model in 1998 [15] and the Nygren et al. model that same year [1]. The model that will be used in this project is a variation of the Nygren et al. model made by C. Lugo et al. in 2014 [2]. Subsequently, the Nygren model will be explained as well as why was it needed and where it comes from, to then explain the modifications and distinctions Lugo et al. introduced and the reason for those.

4.1 Nygren Model

During the years before the Nygren model came to light, many laboratories published action potential data from isolated human atrial myocytes. On the basis of that data, as well as other published results, Nygren et al. developed the first comprehensive mathematical model of the electrophysiological responses of a representative human atrial cell based on a previous rabbit model motivated by the differences in the repolarizing currents, such as sustained outward K\(^+\) current (I\(_{sus}\)) which determines the human atrial APD. Their goal was to develop a model that is sufficiently accurate to have predictive capabilities for selected aspects of the electrophysiological responses in human atrium.
4.1.1 Assumptions

The model consists of a Hodgkin-Huxley–type (explained in the introduction) electrical equivalent circuit for the sarcolemma coupled with a fluid compartment model [Figure 13]. The dimensions of the human atrial myocyte are assumed identical to those of the rabbit atrial cell in the LMCG model [16]. These dimensions (cylindrical geometry of 130µm length and 11µm diameter) are very close to the dimensions of human atrial myocytes (i.e., 120µm length and 10-15µm diameter). Additionally, they used a total cell capacitance of 50 pF, which agrees very well with experimental observations for human atrial myocytes (51.9±3.5 pF, n=52).

Fig. 13. Schematic representation of the mathematical model of the human atrial cell. A, Electrical equivalent circuit for the sarcolemma. B, Fluid compartment model, including intracellular, cleft, and extracellular spaces.
4.1.2 Currents

In figure 13A one can see all the currents taken into account in the membrane equivalent circuit between the intracellular space and the cleft space. We will briefly introduce the most complex ones and then explain any additional information needed, e.g. the AP threshold. For a biological explanation of the currents, go to section Biological Scope.

- Time-Dependent Currents

- Sodium Current: \( I_{Na} \)

The sodium current gives rise to the upstroke, in this case with an AP threshold at around -55mV agreeing with experimental observations. This threshold is given by the steady-state activation curve \( \tilde{m}(V) \) and the steady-state inactivation curve \( \tilde{h}(V) \). The current depends on time, voltage, temperature and \( Na^+ \) concentration in the cleft space and in the intracellular media. Time dependence is due to the dependence on sodium concentration, as well as on \( m(V,t) \) and \( h_1(V,t) \), which are activation and inactivation gates respectively, depending on their time constants (these time constants represent the kinetics of activation and inactivation). Overall, the processes of activation and inactivation are described by the sum of a fast and a slow exponential.

\( \tilde{m}(V) \) is the permeability of the membrane to \( Na^+ \), \( F \) is the Faraday's constant and \( E_{Na} \) is the Nernst (equilibrium) potential of sodium.

- L-type Calcium Current: \( I_{Ca,L} \)

This current is open during the plateau phase, and activates the SR through calcium induced-calcium release. It has an activation threshold near -40 mV, its peak at approximately 0 mV, and an apparent reversal potential of 50 to 60 mV. The latter one will be fixed at \( E_{Ca,app} = 60mV \) instead of being a Nernst potential, i.e. a function of the concentration of \( Ca^{2+} \), in order to fit experimental data. \( I_{Ca,L} \) depends on time, non-linearly on voltage due to the activation and inactivation gates, and on calcium concentration in the restricted subsarcolemmal space. This calcium concentration in the restricted subsarcolemmal space \( [Ca^{2+}]_d \) is located between the L-type Ca channels and the peripheral junctional SR and may reach much higher levels than in the whole cytosol. It slows considerably the inactivation process, as seen in \( f_{Ca} \) in the equation. The rest of the parameters follow the same reasoning as in the sodium current, meaning one activation time and voltage dependent gate \( d_L \) and two inactivation time and voltage dependent gates \( f_{1,L} \) and \( f_{2,L} \) with their respective time constants and steady-state activation/inactivation curves, but with different values so that they correspond to the appropriate phase of each period.

- Transient and Sustained Outward K\(^+\) Currents: \( I_t \) and \( I_{sus} \)
These two currents will be explained at the same time because they are both responsible for repolarization in human atrial myocytes. $I_t$ is the transient current that activates rapidly on depolarization and $I_{sus}$ is the sustained one that will slowly inactivate once the previous one has decayed. They both have the same structure: a maximum conductance value $\bar{g}$, an activation gate $r$ and an inactivation gate $s$ with the corresponding steady-state activation/inactivation curve $\bar{r}$ and $\bar{s}$ and time constants $\tau_r$ and $\tau_s$.

- Delayed Rectifier $K^+$ Currents: $I_{K,r}$ and $I_{K,s}$

These currents follow the same structure as the ones before. However, we can find some differences worth mentioning: the inactivation gate $p_i$ in the fast delayed rectifier current is only voltage-dependent and modeled as being instantaneous because of being much faster than the activation. Moreover, the slow delayed rectifier current $I_{K,s}$ has a single activation gate. Remarkably, this differentiation between the fast and slow components of the current is significant at fast pacing rates: the slow current could build up progressively from cycle to cycle as a result of residual activation, meaning that it could fail to decay completely between cycles.

- Time-Independent Currents: $I_{K1}$, $I_{B,Na}$, $I_{B,Ca}$, $I_{NaK}$, $I_{NaCa}$, $I_{CaP}$

In the absence of reliable published data from human atrial cells for these currents, the expressions used were very similar to the ones in the LMCG model mentioned previously. The ones that have not been explained or mentioned before are $I_{B,Na}$, $I_{B,Ca}$ and $I_{CaP}$. The first ones ($I_{B,Na}$, $I_{B,Ca}$) correspond to the sodium and calcium background currents, fluxes caused due to the difference between the AP and the Nernst potential. The latter one $I_{CaP}$ is the sarcolemmal calcium pump current.

4.1.3 Ionic Concentrations

The ionic concentration variations over time has been introduced through the fluid compartment model. It is divided in three compartments: the extracellular or bulk space, in which concentrations are assumed to be constant, cleft space and intracellular space (see Fig.13B). The latter one contains the SR, intracellular space calcium buffering (troponin and calmodulin) and the restricted subsarcolemmal space previously mentioned.

The cleft space is a small restricted area surrounding the cell in which accumulation or depletion of ions may occur. Ions are exchanged between the cleft space and the bulk space by diffusion due to concentration gradients of ions. All constants have been adjusted to reproduce oscillations of potassium in cleft space similar to those in experimental data. Also, the model includes an electroneutral flux of inward sodium
ions to the such that ionic concentrations do not change from cycle to cycle, providing the possibility to run long simulations over time.

Additionally, referring to the SR, the addition of the restricted subsarcolemmal space where calcium can accumulate gives rise to a calcium induced-calcium release (CICR) mechanism to trigger the release of calcium from the SR into the intracellular media instead of having a voltage-dependent term. The concept of having two separate units for calcium concentration inside the cell makes it possible for the released calcium from the SR into the cytoplasm not to interfere with the calcium in the restricted subsarcolemmal space, i.e., having a triggering signal that is independent of the calcium concentration "far from the SR".

4.2 Lugo et al. Model

The aim of the modifications applied by C. Lugo et al. in the Nygren model is to reproduce calcium alternans in the intracellular media. An explanation for this arrhythmic mechanism is the sarco(endo)plasmic reticulum Ca\(^{2+}\)-ATPase (SERCA) not having enough time to refill the SR calcium content completely at every beat so that it fluctuates from one excitation to the next one giving rise to a bigger-smaller calcium release from the SR to the cytoplasm. However, Bers et al. [17] showed through experiments that alternans may occur without that fluctuation in SR Ca concentration.

An alternative mechanism was proposed by C. Lugo et al.: instead of the previous mechanism, they superposed a dysfunction on the RyR2 by applying an adjustable parameter for refractoriness. That is, the SR refills completely at every beat but it does not release all of its content due to a slow refractoriness caused by diseased RyR2.

They prove that this is a valid alternative explanation in a single cell Nygren modified model. The modifications are the following: 1) incorporating a four state description of the RyR2 dynamics with a Markovian chain in the same way as previously done by Stern et al. [18,19]. This provides the possibility to change the refractoriness of the type-II ryanodine receptors by changing the recovery rate, i.e. the inverse of recovery time from inactivation, in the Markovian chain; 2) In the fluid compartment model, a different unit from the ones in Nygren model is added. The restricted subsarcolemmal space where \([Ca^{2+}_d]\) triggered the CICR will be referred as Dyadic Space from now on (subscript \(d\)) and the subsarcolemmal space (subscript \(s\)) will now refer to the space between the intracellular media and the cleft space far from the SR and the RyR2. This way, the L-type calcium current will be modeled to flow from the cleft space to the dyadic space, and other currents such as the background calcium current, the Na-Ca pump or the Ca SR pump will flow from the subsarcolemmal space to the cleft space.

Figure 14 shows a schematic representation of the modified fluid compartment model containing the rest of the currents. Additionally, absence of t-tubules in atrial cells is
assumed (even if it is still a controversial topic). This makes cells distribute calcium concentration through saltatory conduction as explained in the *Biological Scope* section, resulting in a non-simultaneous rise in calcium concentration in all the cell. Thus, a distinction is made between the *Junctional SR* (JSR) and the *Nonjunctional SR* (CSR), such that the CICR will start in the peripheral region JSR and will rise in the CSR with a delay.

Moreover, new currents have been modeled and some others have been changed in order to fit data for a single cell. The modifications on currents are due to the change in volumes of the intracellular media and the addition of new units. The contribution of the buffers in the intracellular calcium will change as a function of the values that take part (intracellular and subsarcolemmal). Also the calsequestrin buffering, the calcium concentration in the SR, $I_{rel}$ and $I_{tr}$ will now have two components: one referring to the JSR and the other one to CSR. There will also be diffusive currents between the new spaces, naming $I_{ds}$ for dyadic-subsarcolemmal calcium current and $I_{si}$ for subsarcolemmal-intracellular. Additionally, there are new equations for the calcium concentration evolution over time in the dyadic space and in the subsarcolemmal space. The equations can be found in Appendix A.

To end with this section, we will explain the Markovian chain applied to describe the RyR2 dynamics [Figure 15]. It consists of a four state description, open (O), closed (C) and two inactivated states ($I_1$ and $I_2$), with their corresponding reversible state transition equations. This will affect the SR release current, which will now be a function of the fraction of ryanodine receptors in the open state. The parameter that will be changed in

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**Fig. 14.** Sketch of the different compartments used in the cell model. In italics we show the changes with respect to the original model by Nygren et al.
simulations is $\tau_r = 1/k_{-B}$, the recovery (activation) time constant from the second inactivated state to the open state. Equations, initial values and parameter values can be found in Appendix A.

Fig. 15. Diagram of the Markov model for the state of the ryanodine receptor (RyR2). The dynamics of activation (opening), inactivation and recovery of the RyR2 is given by the rates $k_A$, $k_{-A}$ and $k_{-B}$. The recovery time is defined as the inverse of the recovery rate $\tau_r = 1/k_{-B}$. The subindex $k$ in Ca refers to the dyadic or bulk cytosolic space.
Chapter 5

Simulations

The aim of these simulations is to compare and contrast the different phenomena that show up when going from single cell to a higher dimension, i.e., a cable (1D) and why. Also, to see the coupling effect and how it affects the model, as well as changes in parameters. Then, to check where calcium alternans appears and if it is different from the one in 0D (in terms of the cause, but also in terms of shape) as well as to identify if they give rise to APD alternans or APA alternans (Action Potential Amplitude). Furthermore, we will analyze conduction block and dynamic fast-slow discordant alternans as a function of SR refractoriness. Experimental results will also be shown. Finally, we will show the computational time required for these simulations both in GPU and CPU to observe if GPU is faster than CPU.

5.1 $P_{Na}$, Coupling and Calcium Alternans

First we will list the main differences in AP shape, calcium concentration (intracellular and in the CSR) and some currents between the 0D model and the 1D model. For the first one, we have done simulations comparing the 0D Nygren model and the 0D Lugo et al. model [2]. As can be seen in Fig. 16, the coupling effect is remarkable considering the results in Lugo et al. model, i.e., when adding diffusion to the equation for membrane voltage the amplitude of the AP decreases appreciably (maximum goes from 40mV to 10mV approximately), causing the other voltage dependent currents and gates not to activate properly because of having threshold fitted to single cell data. In order to change the amplitude of the AP, sodium permeability has been increased by a factor of 3.125 resulting in a similar AP amplitude to that of Lugo et al. model [Figure 17]. However, when changing the $P_{Na}$ parameter only the $I_{NaCa}$ current changes, being similar to the one in Lugo et al. model. The rest of currents remain the same except for the sodium current $I_{Na}$ which doubles in amplitude with respect to both the Nygren
model and this model with the original sodium permeability (the Nygren model and this one show the same $I_{Na}$). To solve the whole problem one should change all the equations in terms of thresholds and activation gates, giving rise to a new multidimensional model. All of these simulations have been shown for the stationary regime (the reason why data rendering starts at $t=30s$, transients are very long), with a period $T=1000ms$ and an SR recovery constant of $\tau_r = 650ms$.

Fig. 16. The coupling effect. $P_{Na} = 0.0016nL/s$ (original value from Lugo et al.). From top to bottom and from left to right: membrane voltage, maximum decreases from 40mV to 10mV; intracellular calcium concentration, peak decreases from 1.4µmol/L to 0.5µmol/L; L-type calcium current, minimum increases from -6pA/pF to -3pA/pF; CSR calcium concentration, maximum decreases from 0.5mmol/L to 0.4mmol/L and minimum decreases from 0.25mmol/L to 0.15mmol/L; sodium-calcium pump current, maximum decreases from 1.5pA/pF to 0.5pA/pF.
For a single cell, both APD alternans and Ca alternans are sustained at $T=400\text{ms}$ and $\tau_r = 650\text{ms}$ in simulations and in experiments [Blas model]. When applying the model in a multidimensional scope these results change: for $P_{Na} = 0.0016\text{nL/s}$ calcium alternans appears but it is not sustained, that is, the difference in intracellular calcium concentration from beat to beat decreases over time until in the stationary regime no alternans is seen. Transient calcium alternans gives rise to a small transient APA (action potential amplitude) alternans disappears eventually. The reason for this alternans to be small and also for an APD alternans not to appear could be a result of the intracellular calcium concentration being too small (in single cell the maximum value is $0.7\mu\text{mol}/L$ while in tissue it goes down to $0.3\mu\text{mol}/L$) [Figure 18]. Additionally, RyR2 intracellular calcium fills up completely during these time windows but does not fully release its calcium content at every beat: it fully releases every two beats like in the single cell case, meaning that SR refractoriness is the phenomenon that gives rise to calcium alternans. If the value of the sodium permeability is now changed to $P_{Na} = 0.005\text{nL/s}$, results change again [Figure 19]: a transient non-sustained calcium alternans now appears sooner (time window shifts from 80-90s to 20-40s) and lasts shorter (for $P_{Na} = 0.0016\text{nL/s}$ it disappears at $t=170\text{s}$). Moreover, the beat-to-beat calcium difference is bigger than in the previous case and leads both to APD and APA alternans for this short time window. The SR intracellular calcium concentration proceeds the same way as in the previous case with different values.
Fig. 18. Intracellular calcium transient alternans leading to small APA alternans. $T=400\text{ms}$ and $\tau_r = 650\text{ms}$. It will not be sustained (disappears at $t=170\text{s}$), as opposed to Lugo et al. single cell results. CSR calcium concentration fills completely but fully releases every two beats similarly to Lugo et al.
From now on, the permeability of sodium will be $P_{Na} = 0.0016 nL/s$. For a stimulation period of $T=100ms$, which is in the lower limit of possible biologically meaningful values, AF may occur. This may be caused by conduction block, i.e., a cell or a cluster of cells cannot excite due to refractoriness or other phenomena. In our case, we compared two long simulations (400s) for $\tau_r = 600ms$ and $\tau_r = 700ms$ [Figure 20].

5.2 SR Refractoriness & Conduction Block

Fig. 19. Intracellular calcium transient alternans leading to APD alternans and small APA alternans. $T=400ms$ and $\tau_r = 650ms$. It will not be sustained (disappears at $t=40s$), as opposed to Lugo et al. single cell results. CSR calcium concentration fills completely but fully releases every two beats similarly to Lugo et al.
There is a remarkable difference between the results: for the first case, total or "partial" conduction block occurs during the first and last 50s (we cannot talk about transient and stationary). However, when increasing the SR recovery time constant, conduction block happens during all the time window. This could be the effect of adding both AP refractoriness (remember the period is very small) and SR refractoriness leading to an even smaller Ca release.

Fig. 20. Conduction block. Top: T=100ms and $\tau_r = 600\, ms$. Partial conduction block occurs during the first and last 50s of simulation, i.e., the membrane potential does not reach its maximum value (white vertical lines). Bottom: T=100ms and $\tau_r = 700\, ms$. Conduction block occurs during all the simulation, i.e., the cell does not excite (white vertical lines).
5.3 SR Refractoriness & Dynamic Discordant Alternans

As explained in the *Biological Scope* section, discordant alternans can lead to conduction block. Additionally, this phenomenon can have a dynamic behavior: apart from having an APD or APA map that is out of phase in different parts of the tissue, this map could change in time such that when measuring a single cell one will not see an APD or APA that alternates between two values but between several more. In some cases, dynamic discordant alternans could give rise to a periodic AP that alternates, undergoes a conduction block and restarts. This is a possible explanation for the voltage found at T=300ms [Figure 21]. Also, we compared these simulations in the case of $\tau_r = 400\text{ms}$ and $\tau_r = 900\text{ms}$, and found that the conduction block period shortens for higher SR recovery time from inactivation.

![Figure 21](image.png)

Fig. 21. Dynamic discordant alternans giving rise to a periodic AP that alternates, undergoes a partial conduction block and restarts. Top: T=300ms and $\tau_r = 400\text{ms}$. Longer dynamic discordant alternans period. Bottom: T=300ms and $\tau_r = 900\text{ms}$. Shorter dynamic discordant alternans period.
5.4 Experimental Data

Experimental data has been obtained using optical mapping, following the steps explained in the GPU & Optical Mapping section. Results come from applying stimulation periods from 1000ms to 200ms (decrements of 25ms) for a rabbit atrium, stimulating with an external current of 9mA for a duration of 40ms at every period. First we measured data for stimulation periods starting at 350ms due to the natural SA pacemakers pacing at $T=400ms$ approximately, causing higher periods not to induce any propagation. Once the natural pacing was gone, we could measure the higher ones starting at 1000ms. We observed calcium alternans at some of the external pacing periods, however using this technique the amplitude of the AP or the value of the calcium concentration cannot be measured or extracted. No remarkable APD alternans was observed. For examples of experimental data for intracellular calcium with and without alternans, see Fig. 22.

![Fig. 22. Experimentally measured intracellular calcium concentration for a rabbit atrium, stimulating with an external current of 9mA for a duration of 40ms at every period. Top: $T=650ms$, intracellular calcium alternans. Bottom: $T=700ms$, absence of intracellular calcium alternans. Intracellular calcium concentration numeric value cannot be extracted from optical mapping, just its shape.](image-url)
5.5 CPU vs GPU

Because of the complexity of the model, it takes a long computational time to run simulations. In order to speed up the code OpenACC routines have been applied to the code so that loops are parallelized in the GPU, using a PGI compiler for Fortran routines. We have calculated the computational time that it takes to run a 2D code as a function of dimensions of the mesh both in CPU (with ftn95 compiler) and GPU. Codes have been executed in a personal laptop that is designed to be fast for CPU calculations (i5 with SSD), but is rather inefficient in terms of GPU performance. Even with that, GPU parallelized codes turned out to be faster by a factor of 1.5 in the case of the most expensive 2D model, which makes it a very powerful tool due to the long computational times for such a complex model [Figure 23].

Fig. 23. CPU vs GPU computational time as a function of the dimensions of the mesh. Top: 2D model. Bottom: 3D model. Better performance for GPU in both cases.
Chapter 6

Conclusions

Biological systems are described by complex models that contain non-linear relations between multiple parameters. This results in a big number of calculations as well as an extensive amount of data. Moreover, the mathematical treatment for modeling is intrinsically complex and can lead to multiple outputs. However, it gives rise to fruitful discussions and multidisciplinary cooperative work when tackling questions that remain unsolved in this contemporary research field. Understanding the underlying mechanisms of cardiovascular disease through mathematical models is not only a challenging task and a crucial medical aid, but also a path to reduce animal experiments and a launching pad for several intervening fields of study such as biotechnology, computer science, medicine, electrical engineering or physics.

This work shows the importance of understanding biological facts and aims to take profit of them: it pretends to go one step closer to clinical applications of cardiophysiology by using detailed descriptions for macrosystems. Understanding specific mechanisms such as SR refractoriness means stepping up a long staircase that leads to a better comprehension of the system as a whole.

Short-term future work is understanding calcium alternans, conduction block and APA and APD alternans by calculating the conduction velocity, a restitution curve and bifurcation diagrams on a 2D mesh that exceeds the wavelength of the propagating wave in order to see whether spiral wave dynamics can occur as well as study if they can break into atrial fibrillation. After that, using MRI data to add a phase field to a 3D code that has already been started to have a realistic model for atria and see if any differences are observable.

For long-term future work, the first obstacle to be overcome comes from the relevance of the coupling effect when dimensionalizing a model that is used to describe a specific phenomenon while it keeps working for the rest of them, adapting the equations and
parameter values for different thresholds and activations. The following would be using faster GPUs with more optimized codes through far-reaching programming languages (like WebGL) so that a patient-oriented user-friendly interface permits non-expert clinical professionals test their hypothesis in real time. It could be applied to personalized 3D simulations based on data obtained from a patient's MRI.
Appendix A

Model Equations

This appendix contains all the equations, parameter values, and initial conditions necessary to carry out the simulations presented in this article. Unless otherwise noticed, the units are as follows: time in seconds (s), voltage in millivolts (mV), concentration in millimoles/liter (mmol/L), current in picoamperes (pA), conductance in nanosiemens (nS), capacitance in nanofarads (nF), volume in nanoliters (nL), and temperature in kelvin (K). The stimulus used to evoke an action potential consists of a rectangular current pulse \( I_{\text{stim}} \) with an amplitude of 1.14 µA and duration of 3 ms.

**Membrane Voltage: \( V \)**

\[
\frac{dV}{dt} = \frac{I_{Na} + I_{Ca,L} + I_t + I_{sus} + I_{K1} + I_{Kr} + I_{Ks} + I_{B,Na} + I_{B,Ca} + I_{NaK} + I_{CaP} + I_{NaCa} - I_{\text{stim}}}{-C_m} + \nabla^2 V
\]

---

**Na\(^+\) Current: \( I_{Na} \)**

\[
I_{Na} = P_{Na} m^3 (h_1 + 0.1 h_2) [Na^+]_e \frac{F^2 e^{(V - E_{Na})/RT}}{RT} \frac{e^{V/RT} - 1.0}{e^{V/RT} - 1.0}
\]

\[
\bar{m} = \frac{1.0}{1.0 + e^{(V+27.12)/-8.21}}
\]

\[
\frac{dm}{dt} = \frac{\bar{m} - m}{\tau_m}
\]

\[
h_1 = \frac{1.0}{1.0 + e^{(V+63.6)/5.5}}
\]

\[
\frac{dh_1}{dt} = \frac{\bar{h}_1 - h_1}{\tau_{h_1}}
\]

\[
h_2 = \frac{0.000042 e^{-(V+25.57)/28.8} + 0.000024}{1.0 + e^{(V+35.1)/3.2} + 0.0003}
\]

\[
\frac{dh_2}{dt} = \frac{\bar{h}_2 - h_2}{\tau_{h_2}}
\]

\[
E_{Na} = \frac{RT}{F} \log \frac{[Na^+]_e}{[Na^+]_i}
\]
\[ I_{\text{Ca,L}} = g_{\text{Ca,L}} d_1 I_1 \left( f_{\text{Ca}} f_{\text{L1}} + (1 - f_{\text{Ca}}) f_{\text{L2}} \right) (V - E_{\text{Ca,app}}) \]

\[
\begin{align*}
\bar{d}_1 &= \frac{1.0}{1.0 + e^{(V+9.0)/-5.0}} \\
\frac{dd_1}{dt} &= \frac{\bar{d}_1 - d_1}{\tau_{d_1}} \\
\frac{df_{\text{L1}}}{dt} &= \frac{\bar{f}_1 - f_{\text{L1}}}{\tau_{f_{\text{L1}}}} \\
\frac{df_{\text{L2}}}{dt} &= \frac{\bar{f}_1 - f_{\text{L2}}}{\tau_{f_{\text{L2}}}} \\
\frac{f_{\text{Ca}}}{f_{\text{Ca}}} &= \frac{[\text{Ca}^{2+}]_d}{[\text{Ca}^{2+}]_d + k_{\text{Ca}}} \\
\bar{f}_1 &= \frac{1.0}{1.0 + e^{(V+27.4)/7.1}} \\
\tau_{d_1} &= 0.0027 e^{-((V+35.0)/30.0)^2} + 0.002 \\
\tau_{f_{\text{L1}}} &= 0.161 e^{-((V+40.0)/14.4)^2} + 0.010 \\
\tau_{f_{\text{L2}}} &= 1.3323 e^{-((V+40.0)/14.2)^2} + 0.0626
\end{align*}
\]

**Transient and Sustained Outward K+ Currents: \( I_t \) and \( I_{\text{sus}} \)**

\[ I_t = g_{rs}(V - E_K) \]

\[
\begin{align*}
\bar{r} &= \frac{1.0}{1.0 + e^{(V-1.0)/-11.0}} \\
\frac{dr}{dt} &= \frac{\bar{r} - r}{\tau_r} \\
\frac{ds}{dt} &= \frac{\bar{s} - s}{\tau_s} \\
\tau_r &= 0.0035 e^{-((V/30.0)^2)} + 0.0015 \\
\tau_s &= 0.4812 e^{-((V+52.45)/14.97)^2} + 0.01414
\end{align*}
\]

\[ I_{\text{sus}} = g_{\text{sus}} r_{\text{sus}} s_{\text{sus}} (V - E_K) \]

\[
\begin{align*}
\bar{r}_{\text{sus}} &= \frac{1.0}{1.0 + e^{(V+4.5)/-8.0}} \\
\frac{dr_{\text{sus}}}{dt} &= \frac{\bar{r}_{\text{sus}} - r_{\text{sus}}}{\tau_{r_{\text{sus}}}} \\
\frac{ds_{\text{sus}}}{dt} &= \frac{\bar{s}_{\text{sus}} - s_{\text{sus}}}{\tau_{s_{\text{sus}}}} \\
\tau_{r_{\text{sus}}} &= 0.4 \frac{1.0 + e^{(V+20.0)/10.0}}{1.0 + e^{(V+20.0)/10.0}} + 0.6 \\
\tau_{s_{\text{sus}}} &= 0.009 \frac{1.0 + e^{(V+5.0)/12.0}}{1.0 + e^{(V+5.0)/12.0}} + 0.0005 \\
\tau_{n_{\text{sus}}} &= 0.047 \frac{1.0 + e^{(V+60.0)/10.0}}{1.0 + e^{(V+60.0)/10.0}} + 0.300
\end{align*}
\]

\[ E_K = \frac{RT}{F} \log \frac{[K^+]_c}{[K^+]_i} \]
**Delayed Rectifier K⁺ Currents: \(k_{\text{D}}\) and \(k_{\text{T}}\)**

\[
I_{K,n} = \bar{g}_{K,n} n (V - E_K)
\]

\[
\bar{n} = \frac{1.0}{1.0 + e^{(V - 19.9)/-12.7}}
\]

\[
\frac{\text{d}n}{\text{d}t} = \frac{\bar{n} - n}{\tau_n}
\]

\[
\tau_n = 0.7 + 0.4 e^{-((V - 20.0)/20.0)^2}
\]

\[
I_{K,t} = \bar{g}_{K,t} p_t p_i (V - E_K)
\]

\[
\bar{p}_t = \frac{1.0}{1.0 + e^{(V + 15.0)/-6.0}}
\]

\[
\frac{\text{d}p_t}{\text{d}t} = \frac{\bar{p}_t - p_t}{\tau_{p_t}}
\]

\[
\tau_{p_t} = 0.03118 + 0.21718 e^{-((V + 20.1376)/22.1996)^2}
\]

**Inward Rectifier K⁺ Current: \(k_{\text{I}}\)**

\[
I_{K,I} = \bar{g}_{K,I} [K^+]_{\text{e}}^{0.4457} \frac{V - E_K}{1.0 + e^{3(V - 66.48)/RT}}
\]

\[
E_K = \frac{RT}{F} \log \frac{[K^+]_i}{[K^+]_{\text{e}}}
\]

**Background Inward Currents: \(I_{B,Na}\) and \(I_{B,Na}\)**

\[
I_{B,Na} = \bar{g}_{B,Na} (V - E_{Na})
\]

\[
I_{B,Na} = \bar{g}_{B,Na} (V - E_{Ca})
\]

\[
E_{Na} = \frac{RT}{F} \log \frac{[Na^+]_i}{[Na^+]_{\text{e}}}
\]

\[
E_{Ca} = \frac{RT}{2F} \log \frac{[Ca^{2+}]_i}{[Ca^{2+}]_{\text{e}}}
\]

**Pump and Exchanger Currents: \(I_{NaK}, I_{CaP},\) and \(I_{NaCa}\)**

\[
I_{NaK} = \bar{I}_{NaK} \left[ \frac{[K^+]_c}{[K^+]_{\text{e}}} + k_{NaK,K} \right] \left[ \frac{[Na^+]_i^{1.5}}{[Na^+]_c^{1.5} + k_{NaK,Na}^{1.5}} \right] \cdot \frac{V + 150.0}{V + 200.0}
\]

\[
I_{CaP} = \bar{I}_{CaP} \frac{[Ca^{2+}]_s}{[Ca^{2+}]_{\text{e}}} + k_{CaP}
\]

\[
I_{NaCa} = k_{NaCa} \frac{[Na^+]_i^3 [Ca^{2+}]_s \left( e^{yVF/RT} - [Na^+]_c^5 [Ca^{2+}]_i e^{y1.0VF/RT} \right)}{1.0 + d_{NaCa} [Na^+]_c^3 [Ca^{2+}]_i^3 + [Na^+]_c^3 [Ca^{2+}]_i}
\]
Intracellular Ion Concentrations: $[\text{Na}^+]_i$, $[\text{K}^+]_i$, and $[\text{Ca}^{2+}]_i$

\[
\frac{d[\text{Na}^+]_i}{dt} = -\frac{I_{\text{Na}} + I_{B,\text{Na}} + 3I_{\text{NaK}} + 3I_{\text{NaCa}} - I_{\text{stim}}}{V_{\text{ol}i}F}
\]

\[
\frac{d[\text{K}^+]_i}{dt} = -\frac{I_{k} + I_{\text{st}} + I_{K,1} + I_{K,s} + I_{K,t} - 2I_{\text{NaK}}}{V_{\text{ol}i}F}
\]

\[
\frac{d[\text{Ca}^{2+}]_i}{dt} = I_{\text{si}} + I_{\text{rel},i} - I_{\text{up}} - 0.454\frac{dO}{dt} - \frac{d[\text{Ca}^{2+}]_d}{2FV_{\text{ol}i}}
\]

\[
\frac{d[\text{Ca}^{2+}]_d}{dt} = \frac{I_{\text{Cal}} + I_{\text{ds}} - I_{\text{rel},d}}{2FV_{\text{ol}d}}
\]

\[
\frac{d[\text{Ca}^{2+}]_s}{dt} = -\frac{I_{\text{ds}} + I_{B,\text{Ca}} + I_{\text{CaP}} - 2I_{\text{NaCa}} + I_{\text{si}}}{2FV_{\text{ol}i}}
\]

\[
I_{\text{ds}} = \frac{2FV_{\text{ol}d}(\text{[Ca}^{2+}]_d - \text{[Ca}^{2+}]_s)}{\tau_{\text{ds}}}
\]

\[
I_{\text{si}} = \frac{2FV_{\text{ol}i}(\text{[Ca}^{2+}]_s - \text{[Ca}^{2+}]_i)}{\tau_{\text{si}}}
\]

Intracellular Ca$^{2+}$ Buffering

\[
\frac{dO_{\text{C}}}{dt} = 200000.[\text{Ca}^{2+}]_i(1.0 - O_{\text{C}}) - 476.0O_{\text{C}}
\]

\[
\frac{dO_{\text{TC}}}{dt} = 78400.0[\text{Ca}^{2+}]_i(1.0 - O_{\text{TC}}) - 392.0O_{\text{TC}}
\]

\[
\frac{dO_{\text{TMgC}}}{dt} = 20000.0[\text{Ca}^{2+}]_i(1.0 - O_{\text{TMgC}} - O_{\text{TMgMg}})
\]

\[
- 6.6O_{\text{TMgC}}
\]

\[
\frac{dO_{\text{TMgMg}}}{dt} = 2000.0[\text{Mg}^{2+}]_i(1.0 - O_{\text{TMgC}} - O_{\text{TMgMg}})
\]

\[
- 666.0O_{\text{TMgMg}}
\]
Cleft Space Ion Concentrations: \([\text{Na}^+]_c\), \([\text{K}^+]_c\), and \([\text{Ca}^{2+}]_c\)

\[
\frac{d[\text{Na}^+]_c}{dt} = \frac{[\text{Na}^+]_b - [\text{Na}^+]_c}{\tau_{\text{Na}}} + \frac{I_{\text{Na}} + I_{B,\text{Na}} + 3I_{\text{NaK}} + 3I_{\text{NaCa}} - I_{\text{stim}}}{\text{Vol}_cF}
\]

\[
\frac{d[\text{K}^+]_c}{dt} = \frac{[\text{K}^+]_b - [\text{K}^+]_c}{\tau_{\text{K}}} + \frac{I_{\text{t}} + I_{\text{gs}} + I_{k_1} + I_{k_{\text{t}}} + I_{k_{\text{r}}} - 2I_{\text{NaK}}}{\text{Vol}_cF}
\]

\[
\frac{d[\text{Ca}^{2+}]_c}{dt} = \frac{[\text{Ca}^{2+}]_b - [\text{Ca}^{2+}]_c}{\tau_{\text{Ca}}} + \frac{I_{\text{Ca.L}} + I_{B,\text{Ca}} + I_{\text{CaP}} - 2I_{\text{NaCa}}}{2.0 \text{ Vol}_cF}
\]

**Ca^{2+} Handling by the Sarcoplasmic Reticulum**

\[
I_{\text{up}} = \frac{[\text{Ca}^{2+}]_b/\kappa_{\text{cyc}} - k_{\text{rel}}[\text{Ca}^{2+}]_{\text{app}}/k_{\text{rel}}}{([\text{Ca}^{2+}]_b + k_{\text{cyc}})/\kappa_{\text{cyc}} + k_{\text{rel}}([\text{Ca}^{2+}]_{\text{app}} + k_{\text{rel}})/k_{\text{rel}}}
\]

\[
I_{\text{rel},k} = \frac{2F\text{Vol}_{\text{rel,k}}}{\tau_{\text{tr}}}([\text{Ca}^{2+}]_{\text{app}} - [\text{Ca}^{2+}]_{\text{rel,k}}), \text{ where } k = i, d.
\]

\[
\frac{dO_\text{CSQ,k}}{dt} = 0.48[\text{Ca}^{2+}]_{\text{rel,k}}(1.0 - O_\text{CSQ,k}) - 0.40O_\text{CSQ,k}
\]

\[
\frac{d[\text{Ca}^{2+}]_{\text{rel,k}}}{dt} = \frac{I_{\text{up}} - I_{\text{rel,j}} - I_{\text{rel,d}}}{2F\text{Vol}_{\text{rel,k}}}
\]

\[
\frac{d[\text{Ca}^{2+}]_{\text{app}}}{dt} = \frac{I_{\text{up}} - I_{\text{tr},i} - I_{\text{tr},d}}{2F\text{Vol}_{\text{app}}}
\]

\[
\dot{X}_{\text{Ck}} = k_{\text{A}}X_{\text{ok}} - c_k^2k_AX_{\text{Ck}} + k_{\text{B}}X_{\text{11k}} - c_kk_BX_{\text{Ck}}
\]

\[
\dot{X}_{\text{ok}} = c_k^2k_AX_{\text{Ck}} - k_{\text{A}}X_{\text{ok}} + k_{\text{B}}X_{\text{12k}} - c_kk_BX_{\text{ok}}
\]

\[
\dot{X}_{\text{12k}} = c_kk_BX_{\text{ok}} - k_{\text{B}}X_{\text{12k}} + c_k^2k_AX_{\text{11k}} - k_{\text{A}}X_{\text{12k}}
\]

\[
\dot{X}_{\text{11k}} = k_{\text{A}}X_{\text{12k}} - c_k^2k_AX_{\text{11k}} + k_{\text{B}}X_{\text{Ck}} - k_{\text{B}}X_{\text{11k}}
\]

where \(c_k = [\text{Ca}^{2+}]_k\), \(k = i, d\).
### Parameter Values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\text{Na}^+]_b$</td>
<td>130.0 mmol/L</td>
</tr>
<tr>
<td>$[\text{K}^+]_b$</td>
<td>5.4 mmol/L</td>
</tr>
<tr>
<td>$[\text{Ca}^{2+}]_b$</td>
<td>1.8 mmol/L</td>
</tr>
<tr>
<td>$[\text{Mg}^{2+}]_i$</td>
<td>2.5 mmol/L</td>
</tr>
<tr>
<td>$E_{\text{Ca,app}}$</td>
<td>60.0 mV</td>
</tr>
<tr>
<td>$k_{\text{Ca}}$</td>
<td>0.25 mmol/L</td>
</tr>
<tr>
<td>$R$</td>
<td>8314.0 mJ/molK</td>
</tr>
<tr>
<td>$T$</td>
<td>306.15 K (=33°C)</td>
</tr>
<tr>
<td>$F$</td>
<td>96487.0 C/mol</td>
</tr>
<tr>
<td>$C_m$</td>
<td>0.05 nF</td>
</tr>
<tr>
<td>$Vol_i$</td>
<td>0.005884 nL</td>
</tr>
<tr>
<td>$Vol_{rel,d}$</td>
<td>0.0000441 nL</td>
</tr>
<tr>
<td>$Vol_c$</td>
<td>13.6% $Vol_i$</td>
</tr>
<tr>
<td>$Vol_{rel}$</td>
<td>2% $Vol_i$</td>
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<tr>
<td>$Vol_s$</td>
<td>10% $Vol_i$</td>
</tr>
<tr>
<td>$Vol_{up}$</td>
<td>0.000477 nL</td>
</tr>
<tr>
<td>$Vol_{rel,i}$</td>
<td>0.000441 nL</td>
</tr>
<tr>
<td>$\tau_{\text{Na}}$</td>
<td>14.3 s</td>
</tr>
<tr>
<td>$\tau_{\text{K}}$</td>
<td>10.0 s</td>
</tr>
<tr>
<td>$\tau_{\text{Ca}}$</td>
<td>24.7 s</td>
</tr>
<tr>
<td>$\tau_{\text{dr}}$</td>
<td>0.01 ms</td>
</tr>
<tr>
<td>$\tau_{\text{si}}$</td>
<td>0.1 ms</td>
</tr>
<tr>
<td>$\tau_{\text{Na}}$</td>
<td>70.8253 pA</td>
</tr>
<tr>
<td>$k_{\text{Na,K}}$</td>
<td>1.0 mmol/L</td>
</tr>
<tr>
<td>$k_{\text{Na,Na}}$</td>
<td>11.0 mmol/L</td>
</tr>
<tr>
<td>$l_{\text{Ca}}$</td>
<td>4.0 pA</td>
</tr>
<tr>
<td>$k_{\text{Ca}}$</td>
<td>0.0002 mmol/L</td>
</tr>
<tr>
<td>$k_{\text{NaCa}}$</td>
<td>0.0374842 pA/(mmol/L)$^4$</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.45</td>
</tr>
<tr>
<td>$d_{\text{NaCa}}$</td>
<td>0.0003 (mmol/L)$^{-4}$</td>
</tr>
<tr>
<td>$\Phi_{\text{Na,ion}}$</td>
<td>0</td>
</tr>
<tr>
<td>$l_{\text{up}}$</td>
<td>2800.0 pA</td>
</tr>
<tr>
<td>$k_{\text{QfCa}}$</td>
<td>0.0003 mmol/L</td>
</tr>
<tr>
<td>$k_{\text{QfCa}}$</td>
<td>0.5 mmol/L</td>
</tr>
<tr>
<td>$k_{\text{C}}$</td>
<td>0.4</td>
</tr>
<tr>
<td>$\tau_{\text{B}}$</td>
<td>0.01 s</td>
</tr>
<tr>
<td>$a_{\text{rel}}$</td>
<td>0.39 ms$^{-1}$</td>
</tr>
<tr>
<td>$k_A$</td>
<td>$22.10^4$ mM$^{-2}$ ms$^{-1}$</td>
</tr>
<tr>
<td>$k_B$</td>
<td>$21$ mM$^{-1}$ ms$^{-1}$</td>
</tr>
<tr>
<td>$k_{-A}$</td>
<td>0.06 ms$^{-1}$</td>
</tr>
<tr>
<td>$k_{-B}$</td>
<td>1.0/200 ms$^{-1}$</td>
</tr>
</tbody>
</table>

### Maximum Conductance Values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_m$</td>
<td>0.0016 nS</td>
</tr>
<tr>
<td>$g_{\text{Ca}}$</td>
<td>4.05 nS</td>
</tr>
<tr>
<td>$g_s$</td>
<td>7.5 nS</td>
</tr>
<tr>
<td>$g_{\text{Na}}$</td>
<td>2.75 nS</td>
</tr>
<tr>
<td>$g_{\text{K}}$</td>
<td>1.0 nS</td>
</tr>
<tr>
<td>$g_{\text{K,s}}$</td>
<td>0.5 nS</td>
</tr>
<tr>
<td>$g_{\text{K,s}}$</td>
<td>3.0 nS</td>
</tr>
<tr>
<td>$g_{\text{Na}}$</td>
<td>0.060599 nS</td>
</tr>
<tr>
<td>$g_{\text{Ca}}$</td>
<td>0.078631 nS</td>
</tr>
</tbody>
</table>
### Initial Conditions

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V$</td>
<td>$-74.2525$ mV</td>
</tr>
<tr>
<td>$[Na^+]_i$</td>
<td>$130.0110$ mmol/L</td>
</tr>
<tr>
<td>$[K^+]_e$</td>
<td>$5.3581$ mmol/L</td>
</tr>
<tr>
<td>$[Ca^{2+}]_e$</td>
<td>$1.8147$ mmol/L</td>
</tr>
<tr>
<td>$[Na^+]_e$</td>
<td>$8.5547$ mmol/L</td>
</tr>
<tr>
<td>$[K^+]_i$</td>
<td>$129.4350$ mmol/L</td>
</tr>
<tr>
<td>$[Ca^{2+}]_i$</td>
<td>$6.7290 \times 10^{-5}$ mmol/L</td>
</tr>
<tr>
<td>$[Ca^{2+}]_a$</td>
<td>$7.2495 \times 10^{-5}$ mmol/L</td>
</tr>
<tr>
<td>$[Ca^{2+}]_{aq}$</td>
<td>$0.6646$ mmol/L</td>
</tr>
<tr>
<td>$m$</td>
<td>$3.2017 \times 10^{-3}$</td>
</tr>
<tr>
<td>$h_1$</td>
<td>$0.8814$</td>
</tr>
<tr>
<td>$h_2$</td>
<td>$0.8742$</td>
</tr>
<tr>
<td>$a_1$</td>
<td>$1.3005 \times 10^{-5}$</td>
</tr>
<tr>
<td>$f_{l_1}$</td>
<td>$0.9986$</td>
</tr>
</tbody>
</table>

Where $[Ca^{2+}]_s = [Ca^{2+}]_i$, $[Ca^{2+}]_{rel} = [Ca^{2+}]_{rel,i} = [Ca^{2+}]_{rel}$ and $O_{Calse,i} = O_{Calse,s} = O_{Calse}$
Bibliography


