BACHELOR'S DEGREE THESIS

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Title: Numerical Model of Cardiac Electrochemistry

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Thanks to the tutors of this thesis, Blas and Pablo, for the the opportunity and the guidance, for giving me their time and help whenever I needed.

To Fer, for reading my final degree thesis much more carefully, I have to admit, than I did with his, and for always supporting me.

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To Hel, actually my related sister, for the late night videos at the sofa during the lockdown and after. Together we will do a mathematician of you.

To my grandparents, for being extraordinary.

Abstract

Given the relevance of cardiac maladies in today's society, investigation driven towards the understanding of how our hearts work has been gaining importance. In this bachelor degree thesis we approach the matter by giving a numerical implementation of the ten Tusscher model of the heart's electrophysiology, a very complete and accurate model, even if it may be more complex and computationally expensive than others. We will also incorporate the model to work with the electrochemical problem for a single cardiac cell and for a cardiac tissue, giving a numerical implementation for both, using the Backward Euler method in the first case and a the Finite element method in the second one.

Keywords

Computational biophysics, Cardiac electrochemistry, Cardiac electrophysiology, Numerical implementation, Finite elements method, Backward Euler method

Contents

1. Introduction

Understanding how does our heart work has been a recurrent topic of multiple studies in the past few years. Since the cardiac issues represent around 30% of all deaths worldwide, the study and detailed comprehension of the human heart has become necessary to allow the scientific community to deal with the cardiac problems.

Besides the experimental data that can be obtained directly from working with human patients, it is possible to do a mathematical approach to model the functioning of our heart. With a mathematical model formulated it is possible to take advantage of the power of the computation using the numerical approaches to obtain results from simulations. If the modeling and the numerical implementation are accurate enough we will be capable of reproducing the human heart's electrochemical behaviour.

The first model of a cell's electrophysiology was proposed by Hodgkin and Huxley in [HH52]. Their modeling of the action potential in neurons was the basis to many other models for different types of cells, including the cardiomyocytes, the cardiac cells. We can check a few of the cardiac electrophysiology models in [FC08]. For this work we have chosen the ten Tusscher model exposed in [tTNNP04]. Although it is more complex and computationally more expensive than other models, it is also more complete and accurate. We will develop the model extensively in the following sections but for a first introduction this model takes into account 4 ion concentrations, 15 ionic currents and 13 gating variables to reproduce the electrophysiology of a cardiac human cell.

The objectives of this bachelor degree thesis are:

- First, to learn how to treat the electrical potential problem in a heart cell reducing it to a mathematical expression that we can work with.
- Second, to understand the workings of the ten Tusscher's model to reproduce the electrophysiology in the cardiac cells.
- Following this to implement a numerical code that adapt this mentioned model to obtain a complete simulation of electrochemistry for a single cardiac cell.
- Finally to extend the previous code to contemplate many cells attached forming a tridimensional piece of cardiac tissue.

With this goal in mind we are going to work at two levels. We will see then, throughout the project, that working at the level of a single cell will imply implementing a numerical scheme to solve an ordinary differential equation while working at the tissue level will imply adding to the single cell scheme a numerical method to work with a partial differential equation.

The project will be structured as follows:

- First there will be an explanation of the electrochemical model we are going to use. In this first section, the equations that model the electrical problem at both levels will be obtained and the details of the chemical model will be given.
- Following we will find the detailed explanation of the numerical methods we are going to use tho solve the cell problem, Backward Euler, and the tissue problem, Finite Elements Method.
- After that we will find the schemes used in the numerical implementation codes.

- Finally we will see some of the results obtained and will give the conclusions of the work.

This work has three appendixes, the first one to specify the formulas for some intermediate parameters needed in one of the variables we use, the gating variables, the second one to show the values obtained for the gating variables and the currents, both variables used in the simulation with the tissue and the final one to host the links to the repositories with the implementation codes.

Before the end of this introduction we are going to give some general details about how a human heart is and how it works.

1.1 A simple approach to a human heart

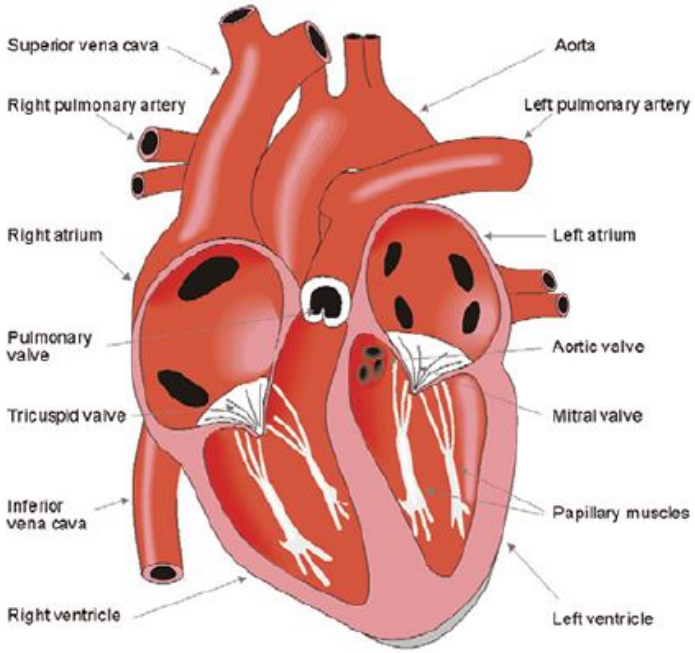

Figure 1: Scheme of the human heart. Image taken from [MP+95]

The human heart is a hollow organ about the size of a fist constituted by four chambers arranged two by two as is shown in Figure 1. It also has four valves, two called atrioventricular separating the atria from the ventricles and two more valves separating the ventricles from the principal arteries, the pulmonary and the aorta.

The walls of our heart are formed by thousands of cells, mostly muscular ones called cardiomyocytes. The union of all these cells forms the so-called cardiac tissue. This tissue is composed by the epicardium, the most external layer full with vessels, the myocardium, the middle tissue that is the muscle itself and the endocardium, the most internal of the three.

The cardiomyocytes are cells with a high resistance to fatigue. These cells answer to the electrical pulse contracting and relaxing, fact that allows circulation of blood around the body. The membrane of the cardiomyocytes has a selective permeability. That means that there is circulation of ions through ionic

gates that are open or close depending on the potential difference between the interior and the exterior of the cell.

Located in the wall of the right atrium we find a group of particular cells called the sinus node. These cells are capable of, spontaneously, generating an electric pulse. This pulse acts as a trigger, the stimulus increases the membrane potential above a threshold, and once exceeded, the response called action potential will begin with the final result of the muscle contraction. This kind of system is called excitable system and it has an attractive fixed point, the resting state, where it always returns to and where it has to remain for a while between stimulus.

2. Electrochemical model

As we have explained previously, the heart contraction is generated by a variation of the potential in the cell's membrane. Concretely, each cardiac cell membrane, works as a little capacitor. The main goal of this section is to model the change in the membrane potential with a mathematical equation. To do so, we start using the well known functioning of a capacitor.

We have two conductor surfaces separated by a dielectric material arranged so that the total amount of lines in the electric field go from one surface to the other. The result of this arrangement is that if there is difference in the potential, one of the surfaces acquires positive charge and the other acquires negative charge. Furthermore, we get that the charge stored in the capacitor directly depends on the difference of potential between the two surfaces. The specific formula detailing this interaction is the following simple equation:

$$C = \frac{Q}{V_1 - V_2} \tag{1}$$

where C is the capacitance, a constant related to the capacitor, Q is the stored charge and $V_1 - V_2$ is the potential difference between the two surfaces.

The membrane of the cardiomyocytes has multiple ionic channels that regulate the entrance and exit of the ionic currents in a binary manner: either the channel is open or it is closed. Another current arrives periodically coming form the sinus node which will act as a stimulus to open some of the gates of the channels, and doing so, some of the ionic current will start to flow through the membrane starting all the changes. Then, knowing that the total amount of charge has to be 0, we have that:

$$I_{ions} + I_{stim} + I_{stored} = 0 \tag{2}$$

where I_{ions} is the sum of the different ionic currents that affect the cell, fifteen in our model as mentioned before, I_{stim} is the stimulus current and I_{stored} is the charge stored in the membrane. Using that the electrical current is the variation of charge per unit of time we get the following equation:

$$I_{ions} + I_{stim} + I_{stored} = I_{ions} + I_{stim} + \frac{\delta(V_e - V_i)}{\delta t} C = 0 \tag{3}$$

From now on we are going to use $\Phi = V_e - V_i$ and we will note the time derivative as $\dot{\Phi}$.

$$\dot{\Phi} = -\frac{I_{ions} + I_{stim}}{C} \tag{4}$$

In addition, the sum of the currents is a function depending on the potential difference Φ, thirteen gating variables, noted as g_{gate}, and 4 ionic concentrations, noted as c_{ion}, all three being variables. Therefore we can rewrite our expression:

$$\dot{\Phi} = f(\phi, g_{gate}, c_{ion}) \tag{5}$$

The specific details of the function will be explained in the following subsection.

This last equation works for a single cell and depends only of the time, which means that it is an Ordinary Differential Equation (ODE). To deal with a piece of tissue, i.e. multiple cells, we have to take into account a correcting factor that will add the spatial dependence. This term will represent the

connection between cells and will transform our local equation into a more accurate expression to model the propagation of the electrical wave trough the fibers. The most common way to do so is adding the term $\nabla(D \cdot \nabla\phi)$. We will work assuming D, the diffusion, as a constant even if other works like [WGK11] assume D is a second order tensor.

So, we have finally obtained a Partial Differential Equation (PDE) that takes into account the time variable and the spatial structure to model the wave that goes through our heart to make it beat.

$$\dot{\phi} = \nabla(D \cdot \nabla\phi) + f(\phi, g_{gate}, c_{ion}) \tag{6}$$

In the following subsection we are going to discuss the details of the constitution of the function $f(\phi, g_{gate}, c_{ion})$.

2.1 Chemical problem

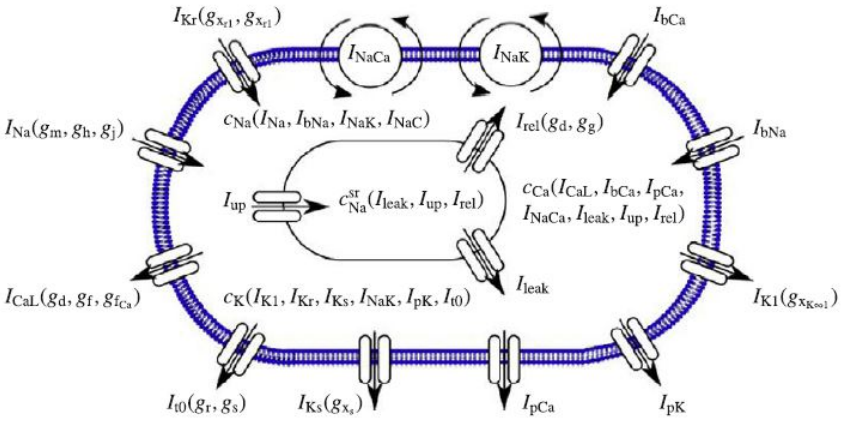

Figure 2: Scheme for currents, gates and concentrations in a cardiomyocytes. Image taken from [WGK11]

As we have mentioned before, we are following the ten Tusscher model of the electrophysiology of a human cardiomyocyte [tTNNP04]. In general terms this model describes the ionic scheme of the cardiac cells taking into account:

- 4 ion concentrations $\rightarrow c_{ion} = [c_K, c_{Na}, c_{Ca}, c_{Casr}]$.
- 15 ionic currents $\rightarrow I_{current} = [I_{Na}, I_{bNa}, I_{NaK}, I_{NaCa}, I_{K1}, I_{Kr}, I_{Ks}, I_{pK}, I_{t0}, I_{CaL}, I_{bCa}, I_{pCa}, I_{leak}, I_{up}, I_{rel}]$.
- 13 gating variables $\rightarrow g_{gate} = [g_m, g_h, g_j, g_{K1}, g_{xr1}, g_{xr2}, g_{xs}, g_r, g_s, g_d, g_f, g_{fCa}, g_g]$.

The function $f(\phi, g_{gate}, c_{ion})$ is defined as the negative sum of 12 of the previously mentioned currents:

$$f(\phi, g_{gate}, c_{ion}) = -[I_{Na} + I_{bNa} + I_{NaK} + I_{NaCa} + I_{K1}, I_{Kr} + I_{Ks} + I_{pK} + I_{t0} + I_{CaL} + I_{bCa} + I_{pCa}] \tag{7}$$

All the currents are obtained differently, the complete formulas will be written in the following section, but some of them take into account the gating variables and the ions concentrations.

The gating variables g_{gate} represent the ionic channels that control the entrance and exit of the currents in the cell. The equations that rule the state of the gates are ODEs of the time variable. We can divide the gates into sets according to the characteristics of their ODE:

- $g_{gateI} = [g_m, g_h, g_j, g_{xr1}, g_{xr2}, g_{xs}, g_r, g_s, g_d, g_f]$
- $g_{gateII} = [g_{K1}, g_{fCa}, g_g]$

The g_{gateI} differential equation only depends on the potential ϕ. So we have $\dot{g}_{gateI} := g_I(\phi, g_{gateI})$, and the concrete formula for g_I is the following one:

$$g_I(\phi, g_{gateI}) = \frac{1}{\tau_{gateI}(\phi)}[g^{\infty}_{gateI}(\phi) - g_{gateI}] \tag{8}$$

The g_{gateII} formula depends on the potential, ϕ, and on one of the concentrations c_{ion}. Then we note $\dot{g}_{gateII} := g_{II}(\phi, c_{ion}, g_{gateII})$, with the formula for g_{II} being:

$$g_{II}(\phi, c_{ion}, g_{gateII}) = \frac{1}{\tau_{gateII}(\phi)}[g^{\infty}_{gateII}(\phi, c_{ion}) - g_{gateII}] \tag{9}$$

This type of equations to model the gating variables follows the model of Hodgkin-Huxley [HH52]. $\tau_{gateI}(\phi)$ and $\tau_{gateII}(\phi)$ are mostly exponential functions that only depend of ϕ, constants in time. g^{∞}_{gateI} and g^{∞}_{gateII} represent the steady state value and are also commonly exponential functions of the membrane potential. The concrete formulas used for each g^{∞}_{gateI}, g^{∞}_{gateII}, $\tau_{gateI}(\phi)$ and $\tau_{gateII}(\phi)$ can be found on the Annex A. We can see, however, that the characteristics of the equations allow us to solve them analytically, so no numerical approximations will be necessary.

We also need to take into account the variation on the concentrations of the 3 most relevant ions found in the cardiomyocytes: K^+, Na^+, Ca^{2+}. We will note the K^+ concentration as c_K, the Na^+ concentration as c_{Na}, the total concentration of calcium as c_{Ca} and the calcium concentration on the sarcoplastic reticulum as c_{Casr}. The evolution of each one of the four concentrations will add to our scheme another set of ODEs dependents of the time. Therefore we have $\dot{c}_{ion} := h(c_{ion}, \phi, g_{gate})$ and more precisely, the 4 differential equations can be written in terms of the currents such follows:

$$\dot{c}_K = -\frac{C}{VF}[I_{K1} + I_{Kr} + I_{Ks} - 2I_{NaK} + I_{pK} + I_{t0}] \tag{10}$$

$$\dot{c}_{Na} = -\frac{C}{VF}[I_{Na} + I_{bNa} + 3I_{NaK} + 3I_{NaCa}] \tag{11}$$

$$\dot{c}_{Ca} = \gamma_{Ca}[-\frac{C}{2VF}[I_{CaL} + I_{bCa} + I_{pCa} - 2I_{NaCa}] + I_{leak} - I_{up} + Irel] \tag{12}$$

$$\dot{c}_{Casr} = \gamma_{Casr}\frac{V}{V_{sr}}[-I_{leak} + I_{up} - Irel] \tag{13}$$

To work with this 4 ODE we are going to use the backward Euler method. The details of the implementation will be explained in the next section.

3. Discrete problem of electrochemistry

This section is a necessary previous step to finally be able to obtain numerical solutions to our equations. It is going to be divided in two parts, the first one related to the local problem of the electrochemistry state of a single cell, and the second part related to the global problem of the electrochemistry state for a piece or cardiac tissue.

Each one of this subsection will be divided in 2 parts:

1. Technical explanation of the numerical method chosen to solve the problem in a general way.
2. Rewriting and discretitzation of our problem according to the method.

3.1 Working without the space variable: Backward Euler method

We have explained in the previous section that the cell electrochemistry works under different ODEs. We will explain the method we are going to use to work with them, Backward Euler, and then, apply it to our simplified problem (5).

Backward Euler to solve an ODE

We define a general ODE as $\frac{dy}{dt} = f(t, y(t))$ in a time domain $[0, T]$ with a discretization $[0, T] = \cup_{i=0}^{n-1}[t_i, t_{i+1}]$. We take the order 1 Taylor series expansion of $y(t)$: $y(t) = y(t_i) + \dot{y}(t_i)(t - t_i)$. If we evaluate the series expansion in t_{i+1} and reorganize the expression we obtain:

$$\dot{y}(t_{i+1}) = \frac{y(t_{i+1}) - y(t_i)}{t_{i+1} - t_i} = f(t_{i+1}, y(t_{i+1})) \tag{14}$$

$$y(t_{i+1}) - y(t_i) - f(t_{i+1}, y(t_{i+1}))(t_{i+1} - t_i) = 0 \tag{15}$$

We call (14) a backward approximation of the derivative. Once we have the expression (15), we can solve it with a Newton-Raphson method or other numerical method to find zeros on functions.

Backward Euler applied to our ODE problem

To use this implicit method the first step is discretize our time frame. We will work in the time interval $[0, T]$, where the $t_0 = 0$ corresponds to the resting state. Then we take $[0, T] = \cup_{i=0}^{n-1}[t_i, t_{i+1}]$ with n = number of time steps as our time discretization. It is trivial then that $T = n\Delta t$ being Δt the constant length of the intervals. Solve the problem then is finding ϕ such that:

$$\dot{\phi} = f(\phi, g_{gate}, c_{ion}) \quad in \quad [0, T] \tag{16}$$

We apply the Backward Euler scheme explained previously and we obtain:

$$\phi(t_{i+1}) - \phi(t_i) - \Delta t \cdot f(\phi(t_{i+1}), g_{gate}, c_{ion}) = 0 \tag{17}$$

From here we are going to use the Newton-Raphson method to obtain the membrane potential.

3.2 Working with the space variable: Finite elements method

Our ultimate goal is to implement a finite element method, FEM, to solve the space related problem of the equation (6) and to implement a finite difference numerical scheme to do the same with the related time one. In this subsection we are going to focus on laying the groundwork to implement the FEM method.

Finite elements method in three dimensions

This part of the work will be used to explain in general terms how to apply the FEM method.

We start having a PDE in a tridimensional space. We are going to work in a domain $\Omega \subset \mathbb{R}^3$, connex and Lipschitz. We note as $\delta\Omega$ the borders of our space and as $x = (x_1, x_2, x_3) \in \Omega$ a generic point on our domain.

First we will rewrite our equation to a suitable form: the weak form. To do it, the steps are as follows:

1. We suppose that exist a classical solution for our PDE in the Hilbert space $\mathcal{U} = \mathcal{H}^1(\Omega)$, our trial space. We are going to note this solution as $u := u(x, t) \in \mathcal{U}$.

2. We multiply both sides of our function for a so called test function, $v := v(x, t) \in \mathcal{C}_0^\infty$. We define $\mathcal{C}_0^\infty = \{f \in \mathcal{C}^\infty : f = 0 \ \ on \ \ \delta\Omega\}$. Then we integrate in each side of the equality.

3. We use the divergence theorem and we apply the boundary conditions to simplify our expression.

4. We change our initial $v \in \mathcal{C}_0^\infty$ for $v := v(x, t) \in \mathcal{V}$ taking $\mathcal{V} = \mathcal{H}_0^1(\Omega)$. Our new space, the test space, is a Hilbert space such that $\mathcal{H}_0^1(\Omega) := \{v \in \mathcal{H}^1 : v = 0 \ \ on \ \ \delta\Omega\}$

From this weak formulation we are going to obtain a weak solution of the original equation.

After reformulating our problem we proceed to discretize our domain. We have defined Ω such that it is possible to divide it in n finite subsets $\Omega = \cup_{e=1}^{ne} \Omega_e$, called finite elements. Each element is a compact subset with a Lipschitz border and we have that $\text{int}(\Omega_i) \cap \text{int}(\Omega_j) = \emptyset, \ \ i \neq j$. It is an extended practice to take all the elements with the same "shape", and the domain used as reference is called isoparametric domain. Common domains for a tridimensional space are tetrahedrons or hexahedrons. In each element we define a set of nodes, the points we are going to work with.

Finally, we have to transform our infinite test space $\mathcal{V}$ to a space with finite dimension. We take $\mathcal{V}^h \subset \mathcal{V}$, with $h > 0$ the size of the finite sub-spaces, such that $\mathcal{V}^h \xrightarrow{h \to 0} \mathcal{V}$. In this new space we choose a basis, usually conformed by polynomial functions, $\{N_1(x), ..., N_{nh}(x)\}$ being nh the dimension of $\mathcal{V}^h$. We will obtain the solution of our problem approximated with this basis:

$$u \approx u^h = \sum_{i=1}^{nh} u_i N_i(x) \tag{18}$$

We close this section and now we are going to apply the generic method to our concrete diffusion PDE.

Finite elements method applied to our diffusion problem

We start this part recovering the PDE (6) to work with the spatiotemporal problem.

As is usual in the cardiac models, we take homogeneous Neumann conditions in the border of the domain. Adding an initial value for the potential, solving the Cauchy problem for (6) is finding $\phi = \phi(x, t)$ such that:

$$\begin{cases} \dot{\phi} = \nabla(D \cdot \nabla\phi) + f(\phi, g_{gate}, c_{ion}) \quad in \quad \Omega \times (0, T] \\ \nabla(D \cdot \nabla\phi) = 0 \quad in \quad \delta\Omega \\ \phi_0 = \phi(x, 0) \quad in \quad \Omega \times (0, T] \end{cases} \tag{19}$$

We take $H = \{\phi = \phi(\cdot, t) \in \mathcal{H}^1(\Omega), t \in [0, T]\}$ as our trial space and, due the homogeneous Neumann boundary conditions in all of the border, we can take the same Hilbert space as our test space $\tilde{H}$. So, having $H = \tilde{H}$, we obtain the weak form of the PDE as follows:

$$\int_\Omega \tilde{\phi} \cdot \phi - \tilde{\phi} \cdot \nabla(D \cdot \nabla\phi) \quad d\Omega = \int_\Omega \tilde{\phi} \cdot f(\phi, g_{gate}, c_{ion}) \quad d\Omega \tag{20}$$

where $\tilde{\phi} \in \tilde{H}$.

In addition, we note $f := f(\phi, g_{gate}, c_{ion})$ and we apply the divergence theorem and the homogeneous Neumann conditions to obtain a simplified form of our equation.

$$\int_\Omega \tilde{\phi} \cdot \phi \ d\Omega + \int_\Omega \nabla\tilde{\phi} \cdot (D \cdot \nabla\phi) \ d\Omega = \int_\Omega \tilde{\phi} \cdot f \ d\Omega \tag{21}$$

The next step is discretize our domain into a collection of finite elements. We take $\Omega = \cup_{e=1}^{ne} \Omega_e$, with $\{x_j\}_{j=1}^{nen}$ nodes for each element, being *ne* the number of elements and *nen* the number of nodes per element from now on. In addition the shape of our isoparametric domain will be an hexaedron.

In this space we define the functions $N_i(x)$, with $i = 1 \div nen$, such that $N_i(x_j) = \delta_{ij}$. We can form now the linear polynomial basis $\{N_i(x)\}_{i=1}^{nen}$ and approximate the potential function in this new basis:

$$\phi\big|_{\Omega_e} \approx \phi^h\big|_{\Omega_e} = \sum_{i=1}^{nen} \phi_i N_i(x) \tag{22}$$

We are going to choose one of the functions of this basis as the trial function, $\tilde{\phi} = N_j(x)$. We will obtain a new form of our equation in terms of the new basis as follows:

$$\int_\Omega N_j(x) \sum_{i=1}^{nen} \dot{\phi}_i N_i(x) \ d\Omega + \int_\Omega \nabla N_j(x) \cdot (D\nabla \cdot \sum_{i=1}^{nen} \phi_i N_i(x)) \ d\Omega = \int_\Omega N_j(x) \cdot f \ d\Omega \tag{23}$$

We can reorganize the expression to obtain the integral terms only dependant of the basis functions:

$$\sum_{i=1}^{nen} \dot{\phi}_i \int_\Omega N_j(x) N_i(x) \ d\Omega + \sum_{i=1}^{nen} \phi_i \int_\Omega \nabla N_j(x) \cdot (D \cdot \nabla N_i(x)) \ d\Omega = \int_\Omega N_j(x) \cdot f \ d\Omega \tag{24}$$

Finally we are going to rewrite the expression with a more general notation:

$$K\dot{\phi} + L\phi = F \tag{25}$$

where:

$$K_{ij} = \int_{\Omega} N_j(x) N_i(x) \ d\Omega \tag{26}$$

$$L_{ij} = \int_{\Omega} \nabla N_j(x) \cdot (D \cdot \nabla N_i(x)) \ d\Omega \tag{27}$$

$$F_j = \int_{\Omega} N_j(x) \cdot f \ d\Omega \tag{28}$$

We want to compute integrals on polynomial functions element-by-element:

$$K_{ij} = \sum_{e=1}^{ne} \int_{\Omega_e} N_j(x) N_i(x) \ d\Omega \tag{29}$$

$$L_{ij} = \sum_{e=1}^{ne} \int_{\Omega_e} \nabla N_j(x) \cdot (D \cdot \nabla N_i(x)) \ d\Omega \tag{30}$$

$$F_j = \sum_{e=1}^{ne} \int_{\Omega_e} N_j(x) \cdot f \ d\Omega \tag{31}$$

So we have $K = A_e K_e$, $L = A_e L_e$, $F = A_e F_e$, where K_e, L_e, F_e are the integral matrix in the element e and A_e is the connectivity matrix that gives the equivalence between the number inside the element with the global number of the node. In each element we apply the Gauss quadrature to solve the integrals.

Our last step will be, as in the problem without the spatial variable, apply a backward Euler scheme to solve the time problem. We discretize our time frame $[0, T] = \cup_{i=0}^{n-1}[t_i, t_{i+1}]$ with n = number of time steps, and consequently $T = n\Delta t$ being Δt the constant length of the intervals.

$$K\frac{\phi^{n+1} - \phi^n}{\Delta t} + L\phi^{n+1} - F = 0 \tag{32}$$

From that we will use Newton-Raphson in each time step to actualize our membrane potential, that was indeed our primal goal.

4. Numerical implementation

In this section we are going to explain the details of the numerical implementation for our two exposed problems: the simple cell problem with only time dependence and the more complex expression for a tissue adding the space variable.

For the first problem we will obtain its own results but also we will be able to reuse the scheme at a local level for the second problem.

4.1 ODE numerical implementation

Table 1: Numerical implementation scheme for a single cell

Initialize ϕ at steady state value Initialize internal variables $g_{gateI}, g_{gateII}, c_{ion}$
Global Newton-Raphson iteration Update type I gating variables $g_{gateI} \leftarrow g_{gateI} + g_I \Delta t$ Initialize type II gating variables $g_{gateII} \leftarrow g_{gateII} + g_{II} \Delta t$ Initialize ionic currents $I_{current} \leftarrow I(\phi, g_{gate}, c_{ion})$ Local Newton-Raphson iteration Calculate the ion concentration residuals R_{ion} and the local iteration matrix $d_{c_{ion}} R_{ion}$ Update ion concentrations $c_{ion} \leftarrow c_{ion} - d_{c_{ion}} {R_{ion}}^{-1} R_{ion}$ Update type II of gating variables $g_{gateII} \leftarrow g_{gateII} + g_{II} \Delta t$ Update ionic currents $I_{current} \leftarrow I(\phi, g_{gate}, c_{ion})$ Calculate the residual R_{global} and its derivative $d_\phi R_{global}$
Update the membrane potential $\phi \leftarrow \phi - d_\phi R_{global}^{-1} R_{global}$

We start the procedure initializing $\phi, g_{gateI}, g_{gateII}, c_{ion}$ with the steady state values. We recover from the previous section the expression (17). With this residual form we can apply a Newton-Raphson scheme, with the dime discretization $[0, T] = \cup_{i=0}^{n-1} [t_i, t_{i+1}]$, and for each time step we actualize ϕ such follows:

$$R_{global} = \phi(t_{i+1}) - \phi(t_i) - \Delta t \cdot f(\phi(t_{i+1}), g_{gate}, c_{ion}) \tag{33}$$

$$d_\phi R_{global} = 1 - \Delta t \cdot df(\phi(t_{i+1}), g_{gate}, c_{ion}) \tag{34}$$

$$\phi(t_{i+1}) = \phi(t_i) - \frac{R_{global}}{d_\phi R_{global}} \tag{35}$$

In each time iteration we have to update f. To do so first, we update the g_{gateI} variables the with the previous step potential value. According to (8) we take the mentioned time discretization and apply a backward approximation of the derivative to obtain:

$$g_{gateI_{i+1}} = g_{gateI_i} + \frac{1}{\tau_{gateI}(\phi(t_i))} [g^{\infty}_{gateI}(\phi(t_i) - g_{gateI_{i+1}}] \Delta t \tag{36}$$

Then we update the g_{gateII} gating variables with the previous step concentrations and potential according to (9). We take, as with the g_{gateI} case, the mentioned time discretization and we apply the backward

approximation of the derivative:

$$g_{gateII_{i+1}} = g_{gateII_i} + \frac{1}{\tau_{gateII}(\phi(t_i))}[g^{\infty}_{gateII}(\phi(t_i, c_{ion}) - g_{gateII_{i+1}}]\Delta t \tag{37}$$

Both equations, 36 and 37, can be solved analytically.

Then we have to initialize the currents with the previous iteration values using the following equations:

$$\begin{aligned}
I_{Na} &= C_{max_{Na}} g_m^3 g_h g_j [\phi - \phi_{Na}] \\
I_{bNa} &= C_{max_{bNa}} [\phi - \phi_{Na}] \\
I_{NaK} &= \frac{I_{max_{NaK}}(c_{K0} c_{Na})}{[(c_{Na} + c_{NaK})(c_{K0} + c_{KNa})(1 + 0.1245 e^{-0.1\phi F(RT)^{-1}} + 0.0353 E^{-\phi F(RT)^{-1}})]} \\
I_{NaCa} &= \frac{I_{max_{NaCa}}(e^{\gamma\phi F(RT)^{-1}} c_{Na}^3 c_{Ca0} - e^{(\gamma-1)\phi F(RT)^{-1}} c_{Na0}^3 c_{Ca} \gamma_{NaCa})}{(c_{NaCa}^3 + c_{Na0}^3)(c_{CaNa} + c_{Ca0})(1 + K_{NaCa} e^{(\gamma-1)\phi F(RT)^{-1}})} \\
I_{K1} &= C_{max_{K1}} g_{K1} \left[\frac{c_{K0}}{5.4}\right]^{\frac{1}{2}} [\phi - \phi_K] \\
I_{Kr} &= C_{max_{Kr}} g_{xr1} g_{xr2} \left[\frac{c_{K0}}{5.4}\right]^{\frac{1}{2}} [\phi - \phi_K] \\
I_{Ks} &= C_{max_{Ks}} g_{xs}^2 [\phi - \phi_{Ks}] \\
I_{pK} &= C_{max_{pK}} \left[1 + e^{\frac{[25-\phi]}{5.98}}\right]^{-1} [\phi - \phi_{Ks}] \\
I_{t0} &= C_{max_{t0}} g_r g_s [\phi - \phi_K] \\
I_{CaL} &= \frac{C_{max_{CaL}} g_d g_f g_{fCa} (4\phi F^2)(c_{Ca} e^{2\phi F(RT)^{-1}} - 0.341 c_{Ca0})}{RT(e^{2\phi F(RT)^{-1}} - 1)} \\
I_{bCa} &= C_{max_{bCa}} [\phi - \phi_{Ca}] \\
I_{pCa} &= C_{max_{pCa}} c_{Ca} [c_{pCa} + c_{Ca}]^{-1} \\
I_{leak} &= I_{max\ leak} [c_{Casr} - c_{Ca}] \\
I_{up} &= I_{max\ up} \left[1 + \frac{c_{up}^2}{c_{Ca}^2}\right]^{-1} \\
I_{rel} &= I_{max\ rel} g_d g_g \left[1 + \frac{\gamma_{rel} c_{Casr}^2}{[c_{rel}^2 + c_{Casr}^2]}\right]
\end{aligned}$$

We denote as ϕ_{ion} the following expression:

$$\phi_{ion} = \frac{RT}{z_{ion} F} \log\left(\frac{c_{ion0}}{c_{ion}}\right) \tag{38}$$

Next, we recover the equations (10), (11), (12) and (13) to work with the concentrations problem. In each time step of the global Newton-Raphson we have to solve a system of 4 coupled ODEs. To do so, we use the same scheme as in the previous cases. We take a fixed number of steps and an appropriate Δh,

we apply a backward approximation of the derivative and we obtain the following residual expressions:

$$R_K = c_{K_{j+1}} - c_{K_j} + \frac{C}{VF}[I_{K1} + I_{Kr} + I_{Ks} - 2I_{NaK} + I_{pK} + I_{t0}]\Delta h \tag{39}$$

$$R_{Na} = c_{Na_{j+1}} - c_{Na_j} + \frac{C}{VF}[I_{Na} + I_{bNa} + 3I_{NaK} + 3I_{NaCa}]\Delta h \tag{40}$$

$$R_{Ca} = c_{Ca_{j+1}} - c_{Ca_j} + \gamma_{Ca}\left[-\frac{C}{2VF}[I_{CaL} + I_{bCa} + I_{pCa} - 2I_{NaCa}] + I_{leak} - I_{up} + Irel\right]\Delta h \tag{41}$$

$$R_{Casr} = c_{Casr_{j+1}} - c_{Casr_j} + \gamma_{Casr}\frac{V}{V_{sr}}[-I_{leak} + I_{up} - Irel]\Delta h \tag{42}$$

We have then the vector of concentrations $c_{ion} = [c_K, c_{Na}, c_{Ca}, c_{Casr}]$, the vector of local residuals $R_{ion} = [R_K, R_{Na}, R_{Ca}, R_{Casr}]$ and we build the matrix of derivatives to apply the Newton-Raphson scheme:

$$d_{c_{ion}}R_{ion} = \begin{bmatrix} d_{c_K}R_K & d_{c_{Na}}R_K & 0 & 0 \\ 0 & d_{c_{Na}}R_{Na} & d_{c_{Ca}}R_{Na} & 0 \\ 0 & d_{c_{Na}}R_{Ca} & d_{c_{Ca}}R_{Ca} & d_{c_{Casr}}R_{Ca} \\ 0 & 0 & d_{c_{Ca}}R_{Casr} & d_{c_{Casr}}R_{Casr} \end{bmatrix} \tag{43}$$

Now for each local iteration we update the vector c_{ion} as follows:

$$c_{ion_{j+1}} = c_{ion_j} - d_{c_{ion}}{R_{ion}}^{-1}R_{ion} \tag{44}$$

With the new values of c_{ion} we update the currents and the g_{gateII} variables.

When we obtain the final values for the currents, we can calculate f and df and update the membrane potential for the time step.

4.2 PDE numerical implementation

Table 2: PDE numerical implementation. Scheme proposed in [WGK11]

Initialize ϕ at steady state value Initialize internal variables $g_{gateI}, g_{gateII}, c_{ion}$
Global Newton-Raphson iteration
Loop over all elements
Loop over all integration points
Update type I gating variables $g_{gateI} \leftarrow g_{gateI} + g_I \Delta t$
Initialize type II gating variables $g_{gateII} \leftarrow g_{gateII} + g_{II} \Delta t$
Initialize ionic currents $I_{current} \leftarrow I(\phi, g_{gate}, c_{ion})$
Local Newton-Raphson iteration
Calculate the ion concentration residuals R_{ion} and the local iteration matrix $d_{c_{ion}} R_{ion}$
Update ion concentrations $c_{ion} \leftarrow c_{ion} - {d_{c_{ion}} R_{ion}}^{-1} R_{ion}$
Update type II of gating variables $g_{gateII} \leftarrow g_{gateII} + g_{II} \Delta t$
Update ionic currents $I_{current} \leftarrow I(\phi, g_{gate}, c_{ion})$
Calculate integration point residual R_{ipoint} and its derivative $d_\phi R_{ipoint}$
Calculate the element residuals R_{elem} and element matrices $d_\phi R_{elem}$
Calculate the global residuals R_{global} and global iteration matrix $d_\phi R_{global}$
Update the membrane potential $\phi \leftarrow \phi - d_\phi R_{global}^{-1} R_{global}$

We will add the spatial term and recover (6). The work done in the previous subsection will serve to implement the iterations at integration point level to obtain the g_{gate} and the c_{ion}. On the other hand our unknown, the membrane potential ϕ, will be treated globally.

We start, as in the one cell case, initializing the membrane potential and giving the internal variables the values in the steady state values. Parting from the expression (32) and taking the same time discretization $[0, T] = \cup_{i=0}^{n-1} [t_i, t_{i+1}]$ with the time interval Δt, we write the global time actualization for the membrane potential as follows:

$$R_{global} = K \frac{\phi^{n+1} - \phi^n}{\Delta t} + L\phi^{n+1} - F \tag{45}$$

$$d_\phi R_{global} = \frac{K}{\Delta t} + L - d_\phi F \tag{46}$$

$$\phi(t_{i+1}) = \phi(t_i) - {d_\phi R_{global}}^{1} R_{global} \tag{47}$$

For each time step we retake the space discretization explained in the section 3.2, and we iterate through each element and each integration point of the element. As it has been said previously, at the integration point level we use exactly the same scheme as in the previous subsection (we can see the repeated scheme colored in the Tables 1 and 2, we only have changed the notation R_{global} to R_{ipoint} and $d_\phi R_{global}$ to $d_\phi R_{ipoint}$). Finally, with the connectivity matrices we compose the global matrices to actualize our unknown potential ϕ.

5. Simulations

Table 3: Choice of parameters for the numerical implementation

Choice of parameters			
Extracellular concentrations (in mM)		Maximum conductance (in mm^3/μ Fs)	
c_{Na0}	140	$C_{max_{Cal}}$	0.175
c_{K0}	5.4	Half saturation constants (in mM)	
c_{Ca0}	2	c_{CaNa}	1.38
Elementary charge per ion		c_{NaCa}	87.5
z_{Na}	1	c_{KNa}	1
z_K	1	c_{NaK}	40
z_{Ca}	1	c_{pCa}	0.0005
Maximum currents (in pA/pF)		c_{up}	0.00025
$I_{max_{NaCa}}$	1000	c_{rel}	0.25
$I_{max_{NaK}}$	1.362	c_{buf}	0.001
Maximum currents (in mM/ms)		c_{srbuf}	0.3
$I_{max\ up}$	0.425/1000	Other parameters	
$I_{max\ rel}$	8.232/1000	K_{NaCa}	0.1
$I_{max\ leak}$	0.08/1000	P_{KNa}	0.03
Maximum conductances (in nS/pF)		C_{tot}	0.15
$C_{max_{Na}}$	14.838	C_{srtot}	10
$C_{max_{bNa}}$	0.00029	γ_{NaCa}	2.5
$C_{max_{bCa}}$	0.000592	γ	0.35
$C_{max_{pCa}}$	0.825	γ_{rel}	2
$C_{max_{K1}}$	5.405	Generic constants	
$C_{max_{Kr}}$	0.096	R	8.3143
$C_{max_{Ksepi}}$	0.245	F	96.4867
$C_{max_{Ksendo}}$	0.245	T	310
$C_{max_{Ksm}}$	0.062	C	185
$C_{max_{pK}}$	0.0146	V	16404
$C_{max_{t0epi}}$	0.294	V_{sr}	1094
$C_{max_{t0endo}}$	0.073		
$C_{max_{t0m}}$	0.294		

In this section we are going to simulate the variation of the potential in an epicardial cell and in a piece of epicardial tissue following the schemes we have presented. In both cases we will initialize our membrane potential at $\phi = -86$ mV; the initial values for the four ion concentrations will be $c_{Na} = 11.6$ mM, $c_K = 138.3$ mM, $c_{Ca} = 0.08\dot{1}0^{-3}$ mM and $c_{Casr} = 0.56$ mM; and we give the gating variables the initial values $g_m = 0$, $g_h = 0.75$, $g_j = 0.75$, $g_d = 0$, $g_f = 1$, $g_{fCa} = 1$, $g_r = 0$, $g_s = 1$, $g_{xs} = 0$, $g_{xr1} = 0$, $g_{xr2} = 0$, $g_{K1} = 0.5$ and $g_g = 1$. The constant values we are going to use are the ones in the Table 3. These values are the same used in [tTNNP04] and also in [WGK11]. The codes for both implementation can be found following the links in the Annex C. We can also obtain the results for an endocardial cell and an endocardial piece of tissue introducing the changes in g_s that can be checked in the Tables 4 and 5.

5.1 Simulation for a single epicardial cell

All the results that are shown in this subsection have been obtained using a time interval of one second (1000 ms) and a time step $\Delta t = 0.02$ ms.

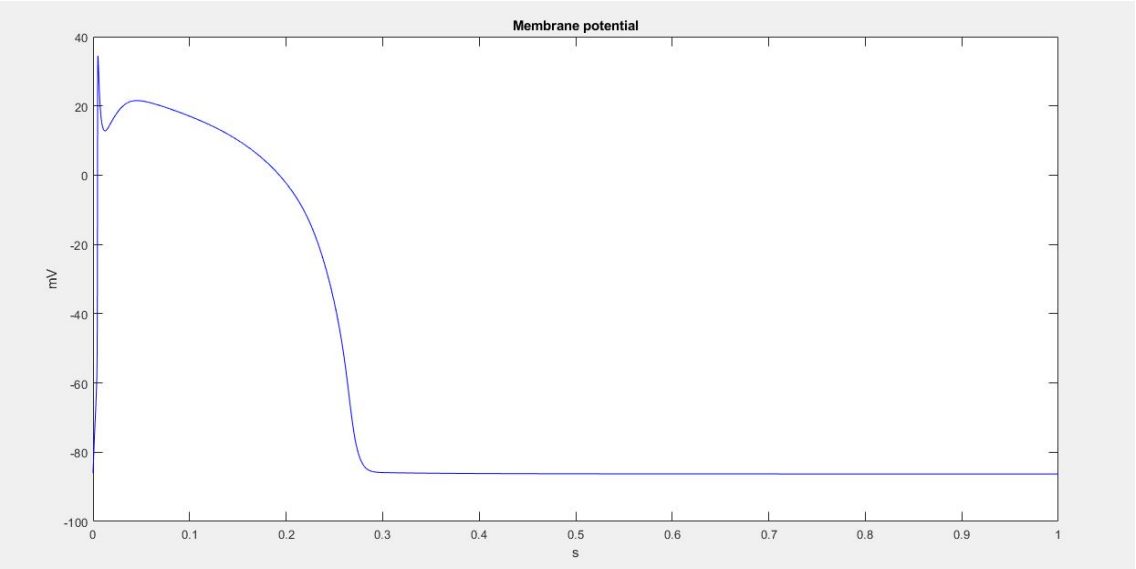

Figure 3: Membrane potential evolution for an epicardial cell

The normal functioning of the action potential starts with a rapid increase of the Na^+ ions due to an influx coming from the fast sodium channels followed by a repolarization caused by an efflux of K^+ ions. The concentration of Ca^{2+} influxed increases and is regulated again by the efflux of K^+ ions. The final repolarization is due to the lack of Ca^{2+} input compared to K^+ output. There is a rest period between the end of one cycle and the start of the next.

In Figure 3 we can see one cycle of this action potential. In less than 5ms the potential changes from the initial value, -86 mV, to almost 40 mV. This fast upstroke is due to the external impulse generated in the sinus node. This initial pulse will trigger the changes in the doors that affect the currents and consequently, the concentrations.

The graphics we can find in Figure 4 represent the evolution of the four ions concentrations through the evolution of membrane potential. We can see the fast increase of the sodium concentration quickly followed by the increase of the potassium and calcium concentrations. The four concentrations return to the initial state at the end of the cycle.

In Figures 5 and 6 we can see evolution of the 15 ionic currents I_{Na}, I_{bNa}, I_{NaK}, I_{NaCa}, I_{K1}, I_{Kr}, I_{Ks}, I_{pK}, I_{t0}, I_{CaL}, I_{bCa}, I_{pCa}, I_{leak}, I_{up} and I_{rel}, the 13 gating variables g_m, g_h, g_j, g_{K1}, g_{xr1}, g_{xr2}, g_{xs}, g_r, g_s, g_d, g_f, g_{fCa} and g_g through the interval chosen.

Finally, Figure 7 shows the time constants and the steady state values necessaries for the calculation of the gating variables through the changes of the potential. The exception is the gate g_{fca}^{∞} that is shown related to the variation of the concentration c_{Ca}.

The values we observe in the previous figures are pretty similar to the the ones in the work [WGK11] that reproduce the obtained experimental values. Then we can say that we have obtained consistent values for a human epicardial cell.

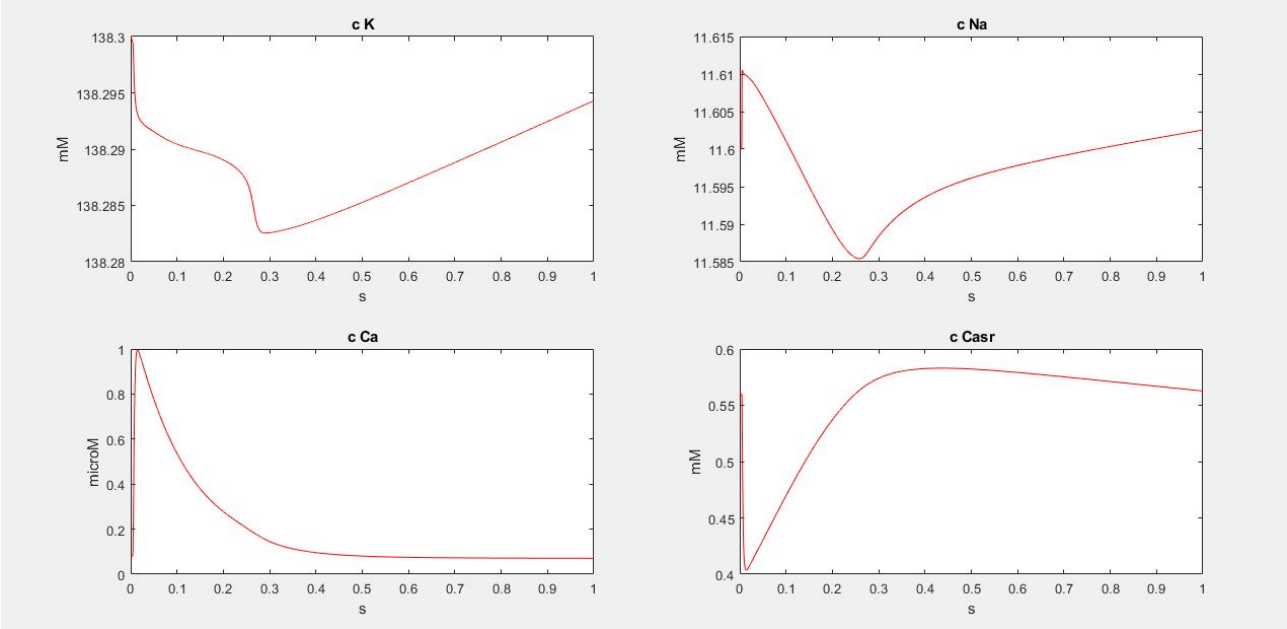

Figure 4: Ion concentrations evolution

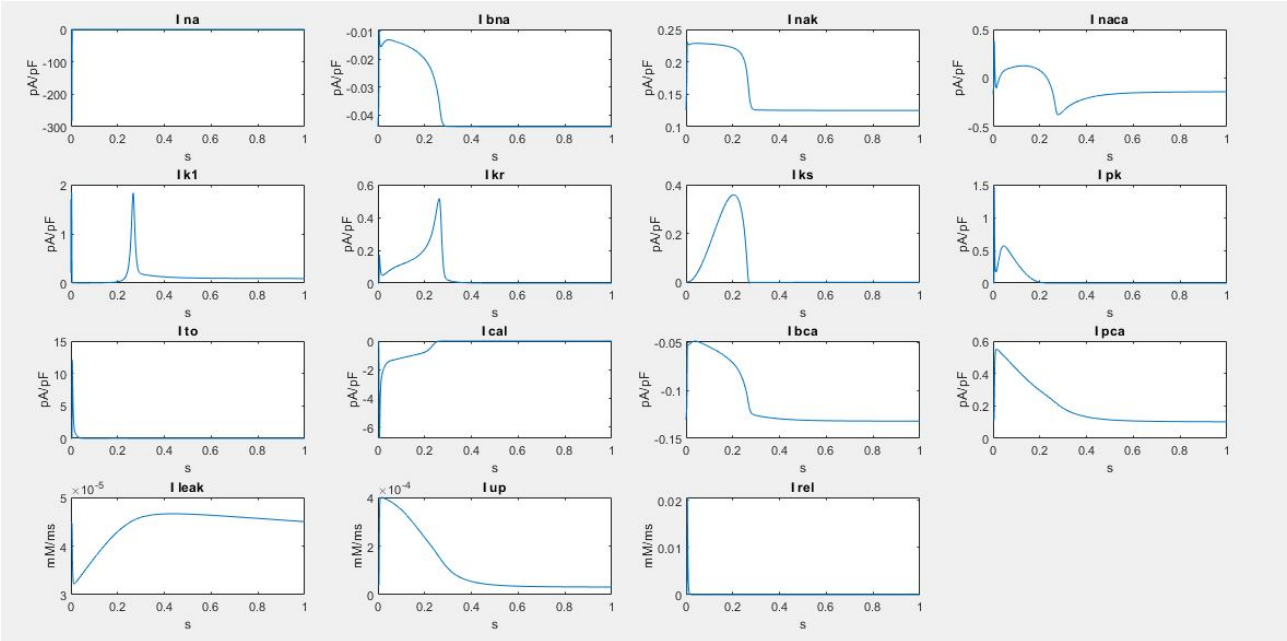

Figure 5: Ion currents evolution

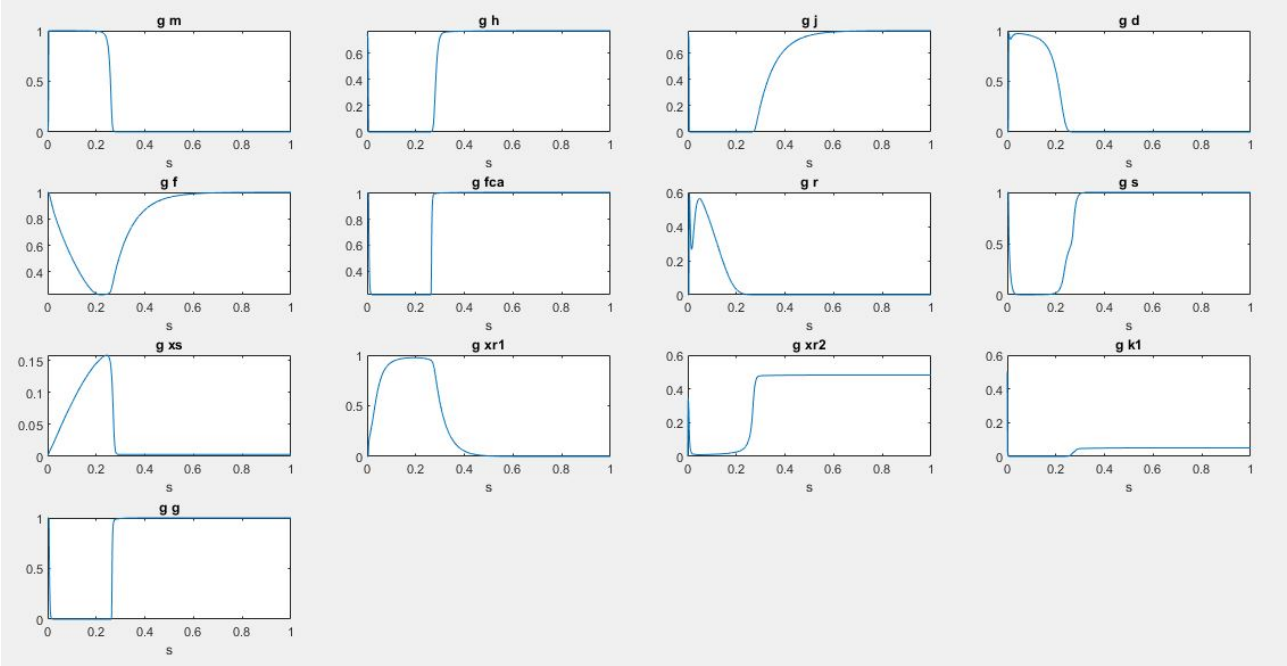

Figure 6: Gating variables evolution

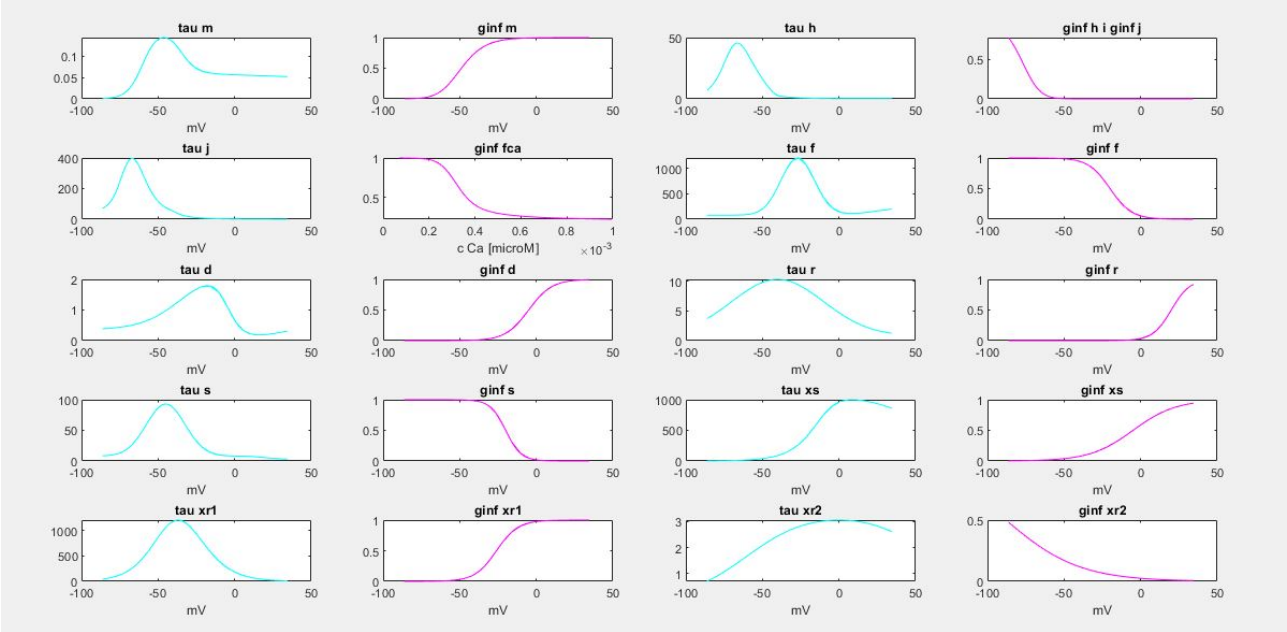

Figure 7: Time constants,τ_{gate}, and steady state values, g_{gate}

5.2 Simulation for a piece of epicardial tissue

To obtain the evolution of the potential in a piece of tissue we have used a time interval of 400 ms and a time step $\Delta t = 0.2$ ms. The mesh created for the simulation contains 64 nodes. As explained before, the FEM method operates by dividing the mesh into elements, and in our case the 64 nodes are divided in 24 tetrahedral elements. The diffusion used is $D = 0.5\ mm^2$. We have applied an external stimulus of 20 mV in the left part of the mesh.

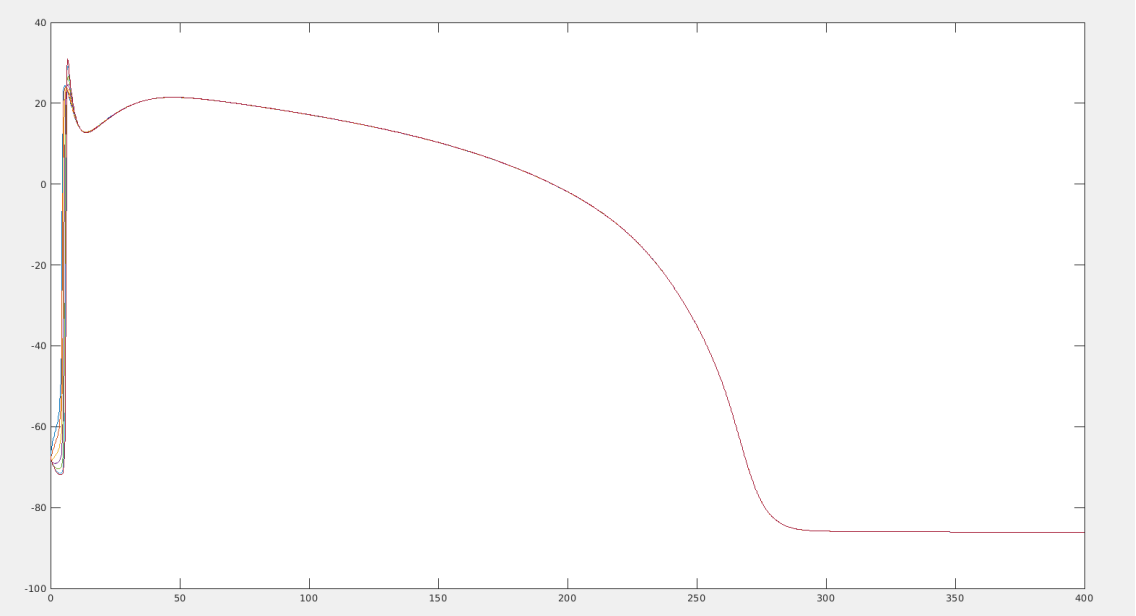

Figure 8: Membrane potential evolution for a piece of epicardial tissue

In Figure 8 is shown one cycle of the action potential obtained using the FEM method. We can see that the potential evolution obtained is the same as in the cell case. In Figure 9 we can see in more detail the fast upstroke of the potential and the slow decrease to the initial value on the three-dimensional mesh.

All the values obtained agree with the ones in the [WGK11]. In the Annex B are shown the values for the evolution of the gating variables and the currents obtained in this simulation of the tissue problem.

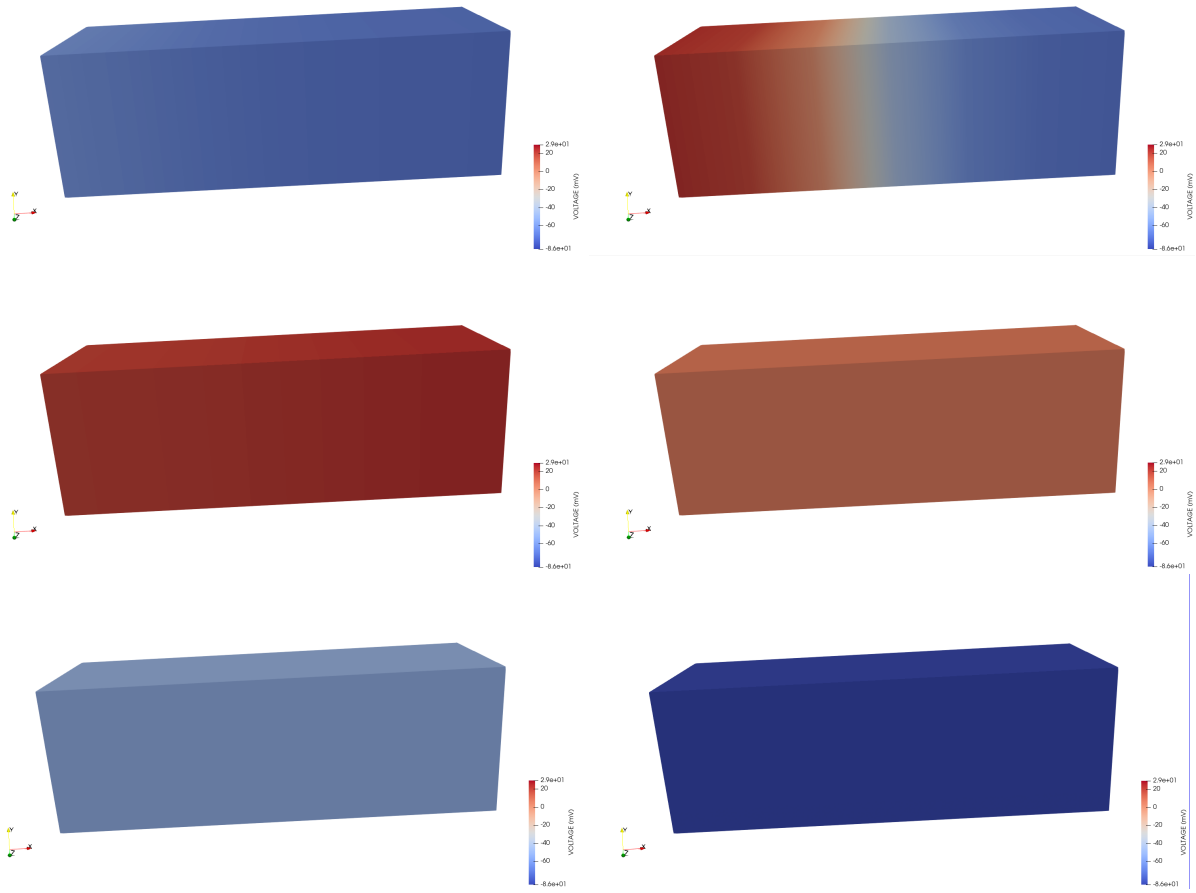

Figure 9: Action potential for a piece of epicardial tissue [2ms, 5ms, 8ms, 172ms, 261ms, 300ms]

6. Conclusions and future work

The beginning of this bachelor degree thesis is focused on developing the mathematical equations that rule the electrochemical behavior of a cardiac cell. We have obtained, after observing that the functioning of the cell membrane can be compared to a capacitor, two expressions, an ODE and a PDE, that allow us to follow the evolution of the potential in the membrane for a single cell and a tissue respectively thus achieving our first objective.

Following that we have an extended explanation of how the ten Tusscher model works. The complexity of the model is shown in the amount of variables that it takes into account, plus that the differential character of some of them requires the implementation of numerical methods in a local level. This understanding leads us to the achievement of our second main goal for this thesis.

Then, we have explained accurately the numerical methods necessaries to deal with the equations in our problems and we have described the schemes used in the implementation codes. The extension of this explanations in addition to the use of more visual schemes are meant to simplify the lecture and the comprehension of the code files that are publicly deposited for anyone to use.

The link to the full codes for both problems can be found in Annex C.

As we can see in the previous section we have been able to implement a completely functional code to simulate the single cell problem given by the ten Tusscher model for the electrophysiology of the cell. We have also been able to do the implementation for the tissue problem and we can see the results obtained with a small mesh. Due to the high computational cost of the program, a very powerful computer is required to use a larger mesh.

For future works, these codes can be used as a base to add variations that reproduce cardiac issues, like arrhythmia, and generate simulations that allow us to understand a little better the human heart, how it can malfunction and how to fix it.

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[WGK11] Jonathan Wong, Serdar Göktepe, and Ellen Kuhl, *Computational modeling of electrochemical coupling: a novel finite element approach towards ionic models for cardiac electrophysiology*, Computer methods in applied mechanics and engineering **200** (2011), no. 45-46, 3139–3158.

A. Parameters for the gating variables

In this Annex we will present the formulas for the τ_{gate} parameters, that denote the time associated to reaching the steady state, and the g_{gate}^{∞} parameters associated with the steady state necessaries to actualize the gating variables.

Table 4: Parameters τ_{gate}

$$\tau_h = \begin{cases} 0.1688\left(1+e^{-\frac{\phi+10.66}{11.1}}\right) & \text{if } \phi \geq -40 \\ \left(0.057\cdot e^{-\frac{\phi+80}{6.8}} + 2.7\cdot e^{0.079\phi} + 3.1\cdot 10^5\cdot e^{0.3485\phi}\right)^{-1} & \text{if } \phi < -40 \end{cases}$$

$$\tau_d = \left(1.4\cdot\left(1+e^{-\frac{\phi+35}{13}}\right)^{-1} + 0.25\right)\cdot\left(1.4\cdot\left(1+e^{\frac{\phi+5}{5}}\right)^{-1}\right)\cdot\left(1+e^{-\frac{\phi-50}{20}}\right)^{-1}$$

$$\tau_j = \begin{cases} 0.6\cdot e^{0.057\phi}\cdot\left(1+e^{-0.1(\phi+32)}\right)^{-1} & \text{if } \phi \geq -40 \\ \left(-2.5428\cdot 10^{-4}\cdot e^{0.2444\phi} - 6.948\cdot 10^{-6}\cdot e^{-0.04391\phi}\right)\cdot(\phi+37.78)\cdot\left(1+e^{0.311(\phi+79.23)}\right)^{-1} + & \\ +0.02424e^{-0.01052\phi}\cdot\left(1+e^{-0.1378(\phi+40.14)}\right)^{-1} & \text{if } \phi < -40 \end{cases}$$

$$\tau_m = 0.1\left(1+e^{-\frac{\phi+60}{5}}\right)^{-1}\left(\left(1+e^{\frac{\phi+35}{5}}\right)^{-1} + \left(1+e^{\frac{\phi-50}{200}}\right)^{-1}\right)$$

$$\tau_f = 1125\cdot e^{-\frac{(\phi+27)^2}{240}} + 165\left(1+e^{-\frac{\phi-25}{10}}\right)^{-1} + 80$$

$$\tau_r = 9.5\cdot e^{-\frac{(\phi+40)^2}{1800}} + 0.8$$

$$\tau_{s_{epi}} = 85\cdot e^{-\frac{(\phi+45)^2}{320}} + 5\left(1+e^{\frac{\phi-20}{5}}\right)^{-1} + 3$$

$$\tau_{s_{endo}} = 1000\cdot e^{-\frac{(\phi+67)^2}{1000}} + 8$$

$$\tau_{xr1} = 2700\left(1+e^{-\frac{\phi+45}{10}}\right)^{-1}\left(1+e^{\frac{\phi+30}{11.5}}\right)^{-1}$$

$$\tau_{xs} = 1100\left(1+e^{-\frac{\phi+10}{6}}\right)^{-\frac{1}{2}}\left(1+e^{\frac{\phi-60}{20}}\right)^{-1}$$

$$\tau_{xr2} = 3.36\left(1+e^{-\frac{\phi+60}{20}}\right)^{-1}\left(1+e^{\frac{\phi-60}{20}}\right)^{-1}$$

We will get that for any gate in the subset g_{gateI},

$$g_{gate_{j+1}} = \frac{g_{gate_j} + g_{gate}^{\infty}\frac{dt}{\tau_{gate}}}{1+\frac{dt}{\tau_{gate}}} \tag{48}$$

whereas for all gates in the subset g_{gateII} except g_{k1} we get $g_{gate_{j+1}} = g_{gate_j}$ if $g_{gate}^{\infty} > g_{gate_j}$ and $\phi < -60$, or

$$g_{gate_{j+1}} = \frac{g_{gate_j} + g_{gate}^{\infty}\frac{dt}{2}}{1+\frac{dt}{2}} \tag{49}$$

otherwise.

In the particular case of g_{k1} we have that

$$g_{k1_{j+1}} = \frac{0.1\left(1+e^{0.06(\phi-\phi_k-200)}\right)^{-1}}{0.1\left(1+e^{0.06(\phi-\phi_k-200)}\right)^{-1}+\left(3\cdot e^{0.0002(\phi-\phi_k+100)+e^{0.1(\phi-\phi_k-10)}}\right)\left(1+e^{-0.5(\phi-\phi_k)}\right)^{-1}}$$

Table 5: Parameters g^{∞}_{gate}

Gates in $\mathbf{g_{gatel}}$

$$g_h^{\infty} = \left(1+e^{\frac{\phi+71.55}{7.43}}\right)^{-2}$$
$$g_d^{\infty} = \left(1+e^{-\frac{\phi+5}{7.5}}\right)^{-1}$$
$$g_j^{\infty} = \left(1+e^{\frac{\phi+71.55}{7.43}}\right)^{-2}$$
$$g_m^{\infty} = \left(1+e^{-\frac{\phi+56.86}{9.03}}\right)^{-2}$$
$$g_f^{\infty} = \left(1+e^{-\frac{\phi+20}{7}}\right)^{-1}$$
$$g_r^{\infty} = \left(1+e^{-\frac{\phi-20}{6}}\right)^{-1}$$
$$g_{s_{epi}}^{\infty} = \left(1+e^{\frac{\phi+20}{5}}\right)^{-1}$$
$$g_{s_{endo}}^{\infty} = \left(1+e^{\frac{\phi+28}{5}}\right)^{-1}$$
$$g_{xr1}^{\infty} = \left(1+e^{-\frac{\phi+26}{7}}\right)^{-1}$$
$$g_{xs}^{\infty} = \left(1+e^{-\frac{\phi+5}{14}}\right)^{-1}$$
$$g_{xr2}^{\infty} = \left(1+e^{\frac{\phi+88}{24}}\right)^{-1}$$

Gates in $\mathbf{g_{gateII}}$

$$g_{fca}^{\infty} = 0.685\left(\left(1+\left(\frac{cant_{ca}}{0.000325}\right)^{8}\right)^{-1}+0.1\left(1+e^{\frac{cant_{ca}-0.0005}{0.0001}}\right)^{-1}+0.2\left(1+e^{\frac{cant_{ca}-0.00075}{0.0008}}\right)^{-1}+0.23\right)$$

$$g_g^{\infty} = \begin{cases} functional\left(1+\left(\frac{cant_{ca}}{0.00035}\right)^{6}\right)^{-1} & \text{if } cant_{ca} \leq 0.00035 \\ \left(1+\left(\frac{cant_{ca}}{0.00035}\right)^{16}\right)^{-1} & \text{else} \end{cases}$$

B. Gates and Currents of the tissue problem

In this annex we can see the values obtained for the gating variables and the currents in the simulation for the tissue problem.

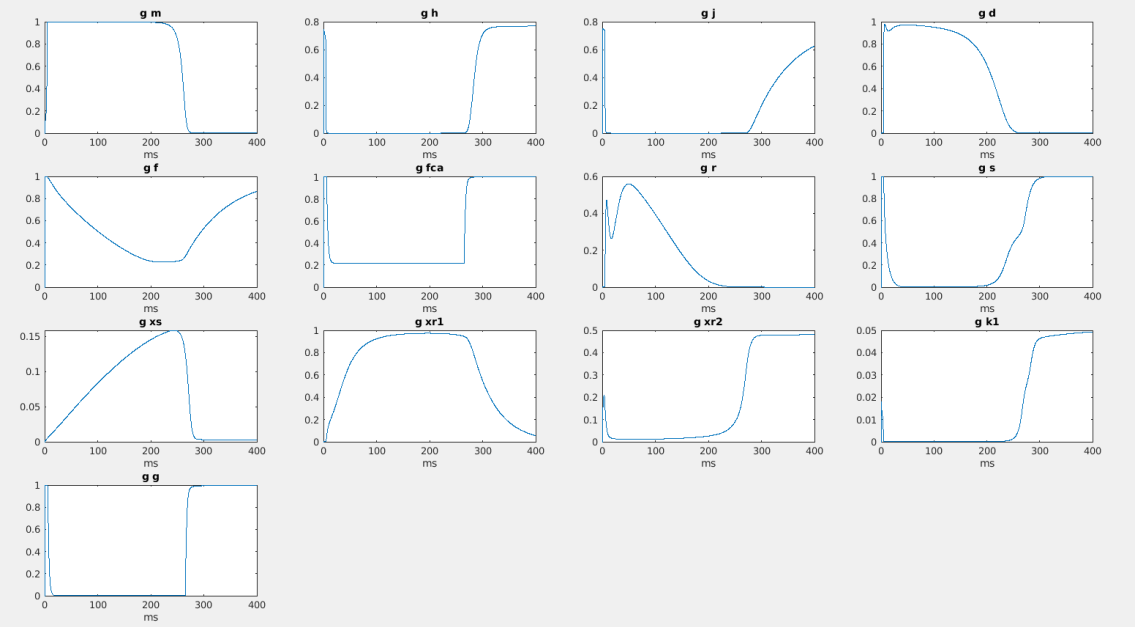

Figure 10: Gating variables evolution for a node with direct stimulus in a piece of epicardial tissue

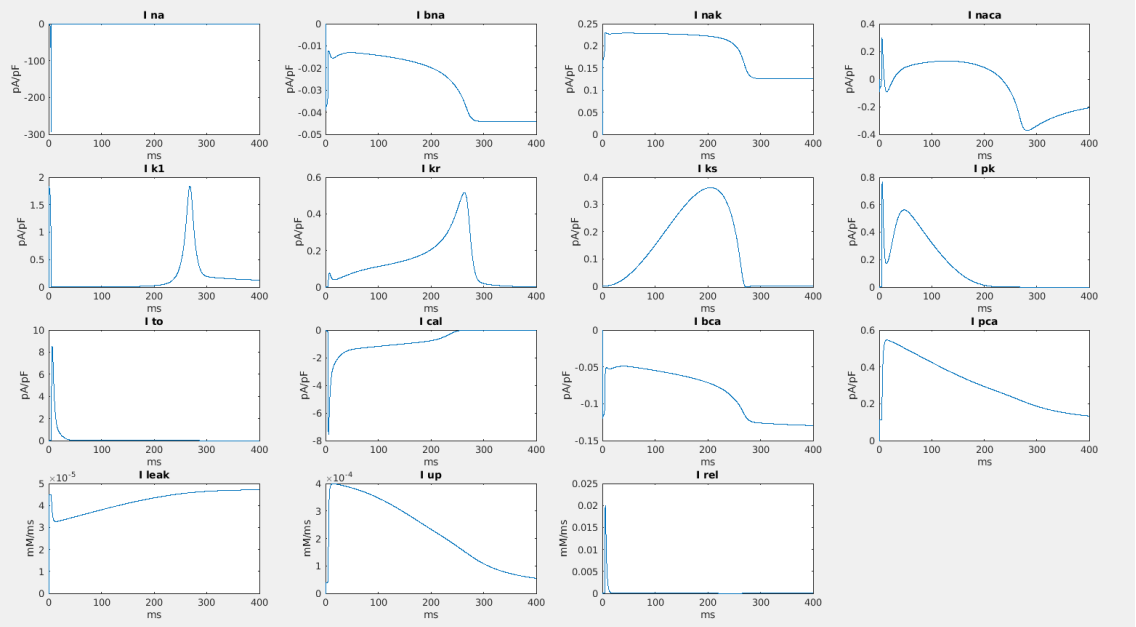

Figure 11: Currents evolution for a node with direct stimulus in a piece of epicardial tissue

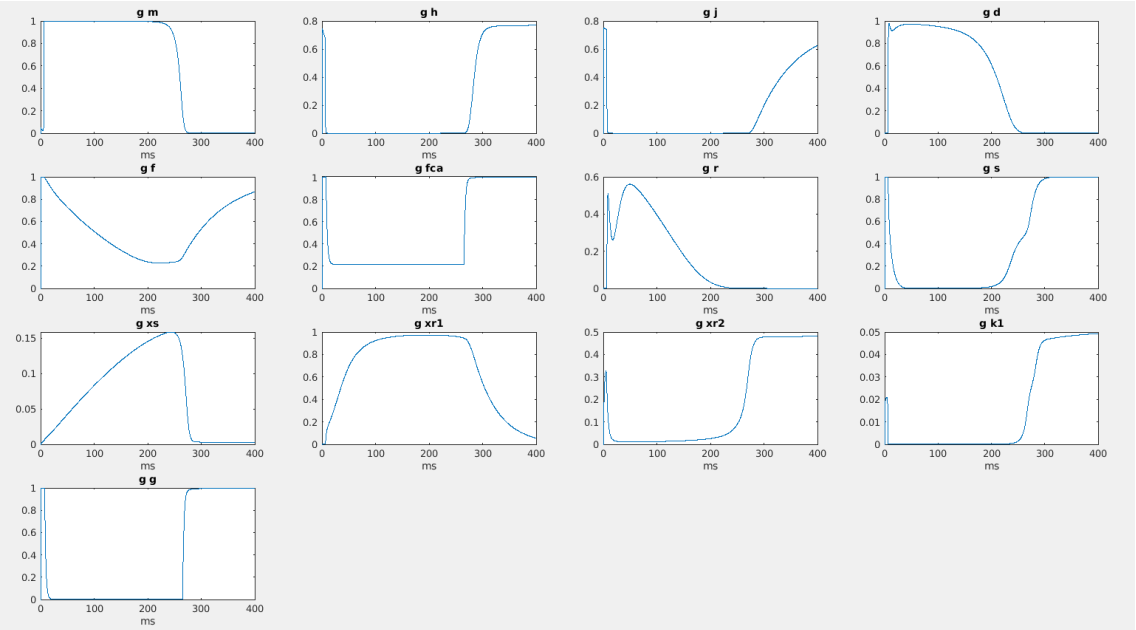

Figure 12: Gating variables evolution for a node with no direct stimulus in a piece of epicardial tissue

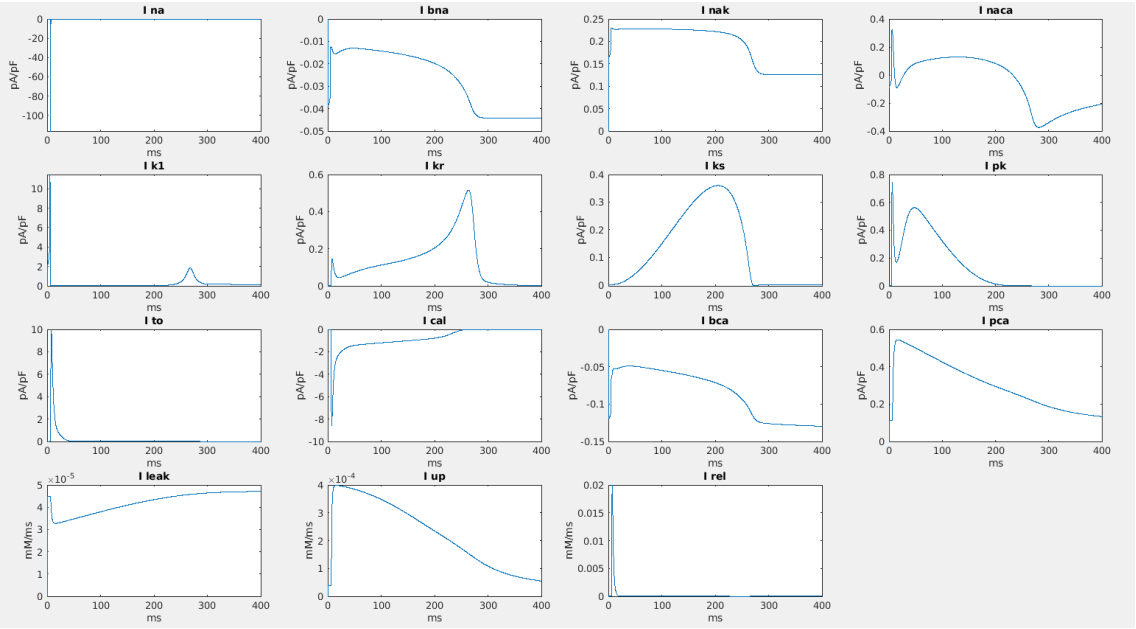

Figure 13: Currents evolution for a node with no direct stimulus in a piece of epicardial tissue

In Figures 10 and 11 is shown the evolution, in the 400 first milliseconds of the action potential, for the gates and currents, respectively, of a node with external stimulus applied directly. In Figures 12 and 13 is also shown the evolution for the gates and currents but this time of a node with no external stimulus applied directly. If we compare the results with the ones obtained in the simulation for a single cell we can see that the values obtained are the expected ones.

C. Links to the codes

Instead of including all the codes made for this project in an Annex we have created two repositories to store the code and make it accessible.

This is the link to the ODE implementation code: https://github.com/Anagdelgado/Numerical-model-of-cardiac-electrophysiology-ODE.git

This is the link to the PDE implementation code: https://github.com/Anagdelgado/Numerical-model-of-cardiac-electrophysiology-PDE.git