UNIVERSITÉ DE TOULON

Numerical study of the models which describe the heart rhythm

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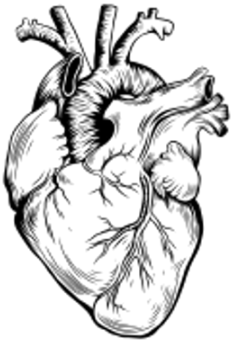

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2021

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1 Introduction

The human heart is a finely-tuned instrument that serves the whole body. It is a muscular organ around the size of a closed fist, and it sits in the chest, slightly to the left of center.

The heart beats around 100,000 times a day, pumping approximately 8 pints of blood throughout the body 24/7. This delivers oxygen- and nutrient-rich blood to tissues and organs and carries away waste.

The heart sends deoxygenated blood to the lungs, where the blood loads up with oxygen and unloads carbon dioxide, a waste product of metabolism.

We can bring out two parts in the heart: the left and the right. Each of these parts has a well-defined role:

- the right heart pumps blood directly into the lungs in order to eject it towards the left heart;

- the left heart, which receives blood from the right, ejects it through the aorta throughout the body.

Each part of the heart, i.e. left and right, splits into two parts and thus forms cavities: the atrium and the ventricle. The function of the heart to pump is ensured by these parts thanks to regular rhythmic contractions coordinated by these sub-parts. The heart can therefore propel oxygenated blood - about 8,000 liters of blood pumped each day.

This project will mostly focus on the study of the existing models to describe the heart rhythms of miocard.
In the first part of this report, we present a brief description of the heart components and chemical and physical processes occurring and causing the heartbeat.
In the second part we will consider the existing types of models for describing the heartbeat and give some examples for each one.
In the third part, we will consider the numerical description of the Aliev-Panfilov model in 1D and 2D dimensions.
Also we used Python to clearly show some obtained results of my research.

2 Anatomy and function of the Heart

2.1 The heart cell

The heart muscle is characterized by its ability to contract rhythmically and spontaneously. It is made up of a complex network of interconnected cardiomyocytes in three dimensions. The cardiomyocyte is able to contract constantly without getting tired during the approximately three billion heartbeats in an individual's lifetime. These cylindrical cells interconnect at the bifurcations they present at their ends.

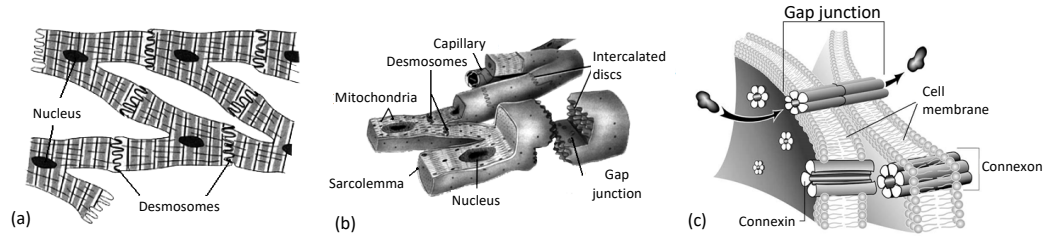

Figure 1: (a) cardiomyocyte interconnections, (b) elements of cardiomyocytes, (c) gap junction

Figure 1 (a) shows the arrangement and interconnection of cardiomyocytes with each other. Figure 1 (b) shows a section of a cardiomyocyte and illustrates the aspect of the gap junction which allows ion exchange as well as fixation between cardiomyocytes. Figure 1 (c) shows the structure and elements of the gap junction between two cardiomyocytes. Bifurcation in the form of cardiomyocytes allows, in addition to longitudinal connections, cross connections with adjacent myocardial cells. The tissue thus formed is capable of conducting excitation transversely and longitudinally. Several studies have shown the importance of connections in the proper functioning of the heart.

At the Figure 1 (c) there are the gap junctions. They are made up of tens to a few thousand channels grouped together in junctional plates and crossing the two cell membranes. The channels are formed by two connexons, one for each membrane. Connexons are assemblages of proteins called connexins. The opening of the channels is controlled by gradients of ionic or electrical concentrations, or by pH. There are several types of channels, they are permeable to one type of ion in particular or to several (example: sodium, calcium, potassium). The transport of ions against a gradient (electrical or concentration) on either side of the membrane is provided by ion pumps.

2.2 The cell membrane

The majority of biological cells have in common a structure combining three basic elements; a nucleus, a cytoplasm and a membrane. There are two types of membranes. The cytoplasmic membranes which separate the environments inside and outside the cell and the membranes specific to the organelles which animate and compose the cell. In the following, we are only interested in the cytoplasmic membrane.

2.3 The Membrane potential and Action potential

Membrane potential is the difference in electrical potential between the inner and outer parts of a biological cell. The concentration gradient is the difference in concentrations of the substance on both sides of the membrane.

The potential of the membrane is due to the transmembrane gradients of ion concentrations and to its almost exclusive permeability to K^+ (50 to 100 times more) compared to Na^+. There is 10 times more Na^+ in the extracellular environment than in the cell, and there is 30 times more K^+ in the intracellular environment than outside. These gradients are maintained by the $Na^+/\ K^+$ pump which behaves like a generator pump. By releasing three Na^+ ions to bring in two K^+ ions, the pump directly participates in the electronegativity of the membrane. This phenomenon is known as the Goldman potential.

As it was said, on both sides of the membrane there are ions, mainly Na^+, K^+, Ca^{2+} and Cl^-, at different concentrations. The difference in concentration leads to a change in the membrane potential difference in response to an exciting stimulus. It is called action potential. The spread of excitement in nerve and muscle fibers is caused by an electric current.

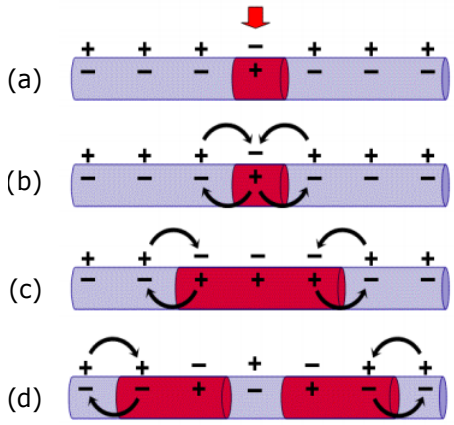

Figure 2: Diffusion. (a) the spread of excitement in nerve and muscle fibers is caused by an electric current; (b) - (d) the stimulus causes an initial depolarization at the site of its application. Ring currents begin between this area and the neighboring ones, which are depolarized; then everything repeats.

The action potential consists of 5 phases, which are well shown in the inserted figure.

Another phenomenon participates more weakly in the transmembrane potential. This is the presence of negatively ionized intracellular proteins that create the Donnan potential at about 12 mV. The membrane potential reaches about -90 mV at rest and changes suddenly when the cell is excited. The changes in transmembrane potential following arousal describe a particular course called the action potential. Each cell reacts according to its state and interactions with other cells. When a stimulus is given to the cell via

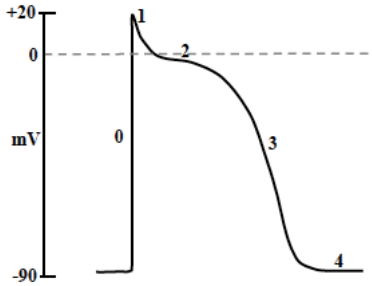

Figure 3: Action potential of a cardiac muscle cell. There are four phases typical: 0. Rapid depolarization, 1. Rapid initial repolarization, 2. Plateau phase, 3. Repolarization final.

an electric current or extracellular ionic charges, it changes state to become excited and trigger an action potential.

3 Overview of existing models for describing the heart rhytms

Numerical modeling of biological cells makes it possible to understand certain aspects of their activity. These models simplify cellular behavior by reducing the number or type of mechanisms taken into account. Over the course of history, these models have been enriched by the knowledge acquired from the study of living tissues and organs. Their growing complexity is supported by the constant evolution of simulation tools, especially computer science. In the field of electrophysiology, mathematical models focus on the dynamics of the action potential.

Previous decades brought many models so that in 2013 there were several hundred models involving heart cells (ventricular, atrial, nodal). Advances in computing now allow a number of variables to be taken into account increasing.

3.1 First models

The first models appear in the middle of the 20th century and do not yet integrate physiological notions. They are systems of equations. They tend to reproduce the shape of the potential curves resulting from experiments. There is a flip side to this simplification. The choice to cover only part of the aspects of cellular dynamics moves digital models away from reality. Complexity is inherent in non-linear biological systems and arises from a set of interactions.

3.1.1 Hodgkin and Huxley model

In 1952, Hodgkin and Huxley (HH) developed an ionic model of the excitable membrane. In this study, the initiation and propagation of an action potential in the giant squid

axon is described by an analogy of the membrane with an electrical circuit. All cells in animal body tissues are electrically polarized. That means that there is voltage difference V across the cell's membrane (membrane potential). This electrical polarization results from different Na, Ca and K ions consentrations inside and outside cells (due to the electrochemical gradient). Polarization is maintaining by voltage-gated protein structures embedded in the membrane called ion pumps and ion channels. The Hodgkin-Huxley model describes how action potentials in neurons are initiated and propagated.

$$C_m \frac{dV}{dt} = -(g_{Na}(V - V_{Na}) + g_K(V - V_K) + g_L(V - V_L) + i_{stim}),$$

where
- V is a potential difference;
- V_{Na}, V_K, V_L are transmembrane potentials of Na, K and leak;
- g_{Na}, g_K, g_L are membrane conductivities.

Another form of this equation is

$$C_m \frac{dV}{dt} = -g(V - V_{eq}) - i_{stim},$$

where
- $g = g_{Na} + g_K + g_L$ is an effective membrane conductivity;
- $V_{eq} = \frac{g_{Na}V_{Na} + g_K V_K + g_L V_L}{g}$ is an equilibrium potential;
- V is potential difference across the membrane taking into account the transmitted current i_{stim};

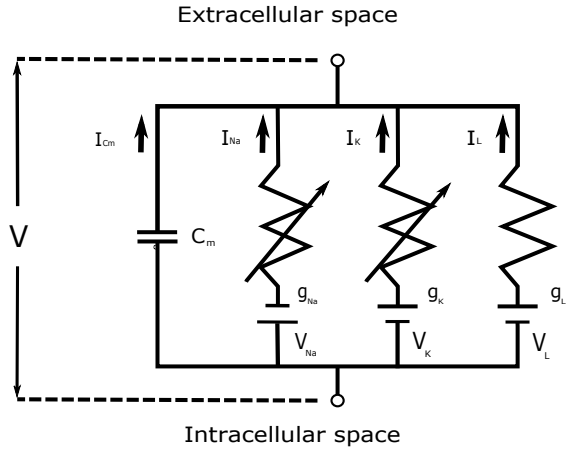

Figure 4: Electrical representation of the plasma membrane

Description of potassium conductivity in Hodgkin-Huxley models

The formal assumptions used to describe the potassium conductance are:

$$g_K = \bar{g}_K n^4,$$

where
- $\bar{g}_K$ is a maximum channel conductivity, constant;
- n is the probability of some control particle to be in a condition that ensures the opening of the potassium channel;

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n, \tag{1}$$

- α_n, β_n are rate constants which vary with voltage but not with time;

Description of sodium conductivity in Hodgkin-Huxley models

$$g_{Na} = \bar{g}_{Na} m^3 h,$$

where
- $\bar{g}_{Na}$ is a maximum channel conductivity, constant;
- m is the probability that the activation particle is in a state corresponding to an open channel;
- m is the probability that the inactivation particle does not block the channel.

Kinetic Equations for Control Variables

$$\begin{cases} \frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m \\ \frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h, \end{cases} \tag{2}$$

where
- $\alpha_m, \alpha_h, \beta_m, \beta_h$ are membrane potential functions;
- Experimental values of the parameters of the conductivity of channels m, h, α, β depending on the membrane potential.

Complete system of model equations Hodgkin-Huxley action potential

$$\begin{cases} C_m \frac{dV}{dt} = -\left(\bar{g}_{Na} m^3 h(V - V_{Na}) + \bar{g}_K n^4 (V - V_K) + g_L(V - V_L) + i_{stim}\right) \\ I_{Na} = \bar{g}_{Na} m^3 h(V - V_{Na}) \\ I_K = \bar{g}_K n^4 (V - V_K) \\ I_L = g_L(V - V_L) \end{cases}$$

Many ionic models appeared after HH, they integrate the notion of equilibrium of electric currents on both sides of the membrane as well as their stochastic nature. Their

dynamics and sizing are based on the results of experiments on transmembrane ion currents.

3.2 Ionic models

Ionic models accurately reproduce most of the basic properties of cardiac tissue. These include the depolarization and repolarization phases of the action potential, restitution properties, dynamical changes in ionic concentration, etc. Such models are suitable for modeling solitary myocites, myocardiac fibers and even synthytium, which may consist of up to tens of thousands of myocardiac cells. The most well-known Ionic models are: Noble model, Beeler-Reuter model, Luo-Rudy model, Tusscher-Noble-Noble-Panfilov model.

3.2.1 Noble model

The Noble model (1962) was the first mathematical model of cardiac action potentials V dynamics. It was a development from the mentioned above Hodgkin-Huxley model. The electrical potential V across the membrane is changing due to the ionic currents

$$C_m \frac{dV}{dt} = (I_K + I_{Na} + I_{An}),$$

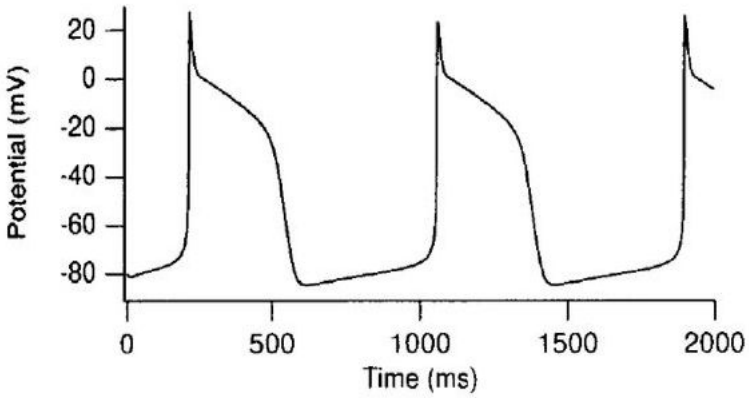

Figure 5: Noble model. $V(t)$ dynamics.

Sodium current

The formulation for the sodium current was taken from the Hodgkin-Huxley model, but the time constants were changed. The equation (2) is used here with

$$\alpha_m(V) = \frac{100(-V-48)}{\exp\left(\frac{-V-48}{15}\right)-1}, \quad \beta_m(V) = \frac{120(V+8)}{\exp\left(\frac{V+8}{5}\right)-1}$$

$$\alpha_h(V) = 170\exp\left(\frac{-V-90}{20},\right) \quad \beta_h(V) = \frac{1000}{1+\exp\left(\frac{-V-42}{10}\right)}$$

$$I_{Na} = (400000m^3h + 140)(V - E_{Na}),$$

where the reversal potential $E_{Na} = 40$.

Potassium current

Potassium current was split into an instantaneous current I_{K1} and a slowly activating I_{K2} current.

$$I_{K1} = (1200\exp\left(\frac{-V-90}{50}\right) + 15\exp\left(\frac{V+90}{60}\right))(V - E_K),$$

where the reversal potential $E_K = -100$.

Talking about the slowly activating current I_{K2}, in (2) let

$$\alpha_n = \frac{0.1(-V-50)}{\exp\left(\frac{-V-50}{10},\right)-1}, \quad \beta_n = 2\exp\left(\frac{-V-90}{80},\right),$$

then

$$I_{K2} = 1200n^4(V - E_K).$$

Furthermore, a current of anions (chloride) was introduced

$$I_{An} = 75(V - E_{An}), \quad E_{An} = -60.$$

However, ionic models are not very suitable for modeling many important problems, such as the problem of re-entrant cardiac arrhythmias. The main difficulty is that small space and time steps are required to integrate ionic models, whereas re-entry occurs only in quite large spatial regions of cardiac tissue. For example, the usual value for the spatial integration step for the Beeler-Reuter model is about 0.1 mm; this means that at least one million cells are needed to represent each cubic centimeter of cardiac tissue.

3.3 Simplified heart tissue models

To avoid computational difficulties researchers often use other models of cardiac tissue. These models belong to the group of simplified or so-called analytical models, which are based on the chemical reaction in the heart tissue. These are notably the first models to have been created and which do not incorporate a physiological basis. FitzHugh-Nagumo model, Aliev-Panfilov model, Karma model, Bueno-Orovio - Cherry - Fenton model are all simplified heart tissue models.

3.3.1 FitzHugh-Nagumo model

This model follows from the Hodgkin-Huxley model. The Fitzhugh-Nagumo model (FHN) belongs to a general class of reaction-diffusion equations. This model has different versions and was originally developed as a generic model for signal propagation along a nerve fibre.

One of its variations is described by the following system (3) with diffusion

$$\begin{cases} \partial_t u = d\triangle u + f(u,v), \;\; d > 0 \\ \partial_t v = g(u,v) \end{cases} \tag{3}$$

and without diffusion (4),

$$\begin{cases} \partial_t u = f(u,v) \\ \partial_t v = g(u,v) \end{cases} \tag{4}$$

$$f(u,v) = -k_u u(u-1)(u-a) - v, \quad g(u,v) = \epsilon(lu - v),$$

where:
- u is a fast variable acoounting for transmembrane potential, v is the recovery current that restores the restingstate of the model;
- k_u is the membrane conductance;
- d is a coefficient of diffusion;
- ϵ specifies the recovery rate constant;
- l is the positive slope of the $v-$nullcline;
- $\triangle$ is the Laplacian operator;
- The variable u describes the transmembrane potential (fast process of the ascending curve) and v represents the slow variable (refractory period due to potassium gates);
- a and k are constants with $0 < a < \frac{1}{2}$ and $k > 0$.

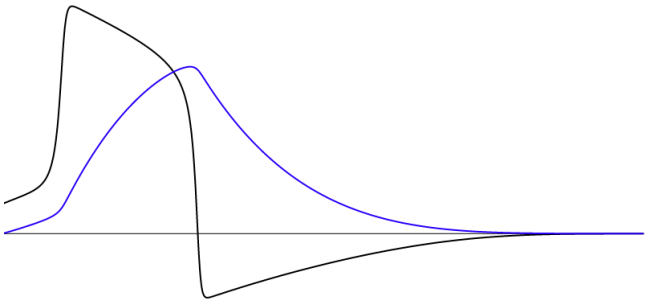

Figure 6: FitzHugh-Nagumo model. $u(t)$ excitation (black) and $v(t)$ recovery (blue) variables.

3.3.2 Dynamics of the FHN system and stability

In FHN model u and v represent the activator and the inhibitor respectively. The FHN patterns are based on the excitable dynamics from the reaction terms. By ignoring the diffusion terms, the dynamics of this system can be nicely described by the two nullclines describing excitable system on the (u, v) axis.
By ignoring the diffusion terms, lets consider the above system 4. It has fixed points which are defined by the intersections of the two nullclines $f(u, v) = 0$ and $g(u, v) = 0$. These nullclines may intersect never, once, or more than once. If the nullclines never intersect, then the system has no finite steady-state solutions. If there is one point of intersection, then there is only one steady-state solution. Linear systems have at most one steady-state solution. Nonlinear systems, however, can have any number of steady-state values. According to the nature of the intersections, the kinetic system can be classified as excitable, bistable or oscillatory.

We can make our system 4 excitable, bistable or oscillatory by simply making some changings in coefficients.

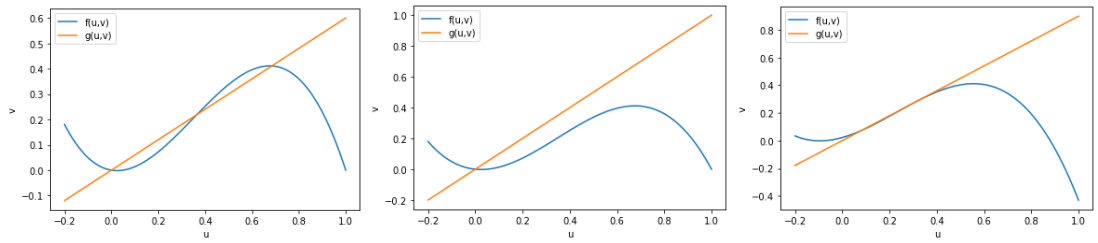

Figure 7: The two nullclines of the FHN model describing excitable, bistable and oscillatory systems on the (u, v) axis of system 4.

Here the blue curve is the cubic nullcline, that is when $f(u, v) = 0$. The orange curve is the linear nullcline, that is when $g(u, v) = 0$.

The only equilibrium point, in Figure 3.13, is the origin. We want to show that this is stable. We investigate the stability of this equilibrium point. To do so, we need to calculate the Jacobian matrix at this point. This is written as

$$J = \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix},$$

where $f_u = -k_u a, f_v = -1, g_u = l\epsilon, g_v = -\epsilon$. The trace and the determinant, computed at the origin, are defined as

$$trace = f_u + g_v = -k_u a - \epsilon < 0,$$

$$det = f_u g_v - f_v g_u = k_u a + l > 0.$$

This shows that the origin is stable.

3.3.3 Aliev-Panfilov model

Aliev Panfilov's model was developed to describe the qualitative behavior of cardiac tissue by a lightweight computer model. It builds on the FHN model and maintains its simplicity by more accurately describing the propagation of impulses in a set of heart cells. The Aliev Panfilov model tends to reproduce the pulse shape and restorative properties of the myocardium. It is described by the following system of equations with diffusion (5):

$$\begin{cases} \epsilon \partial_t u = \epsilon^2 d \triangle u + f(u,v), \quad d > 0 \\ \partial_t v = g(u,v) \end{cases} \tag{5}$$

and without diffusion (6)

$$\begin{cases} \epsilon \partial_t u = f(u,v) \\ \partial_t v = g(u,v) \end{cases} \tag{6}$$

with

$$f(u,v) = -ku(u-1)(u-a) - uv, \qquad g(u,v) = ku(1+a-u) - v,$$

where

- u is a fast variable acoounting for transmembrane potential, v is the recovery current that restores the restingstate of the model;
- d is a diffusion coefficient accounting for the macroscopic conductivity of the intracellular medium.;
- ϵ, k, a are positive constants with $a < \frac{1}{2}$ is the threshold for excitation, k controls the magnitude of the transmembrane current and $\epsilon \ll 1$.

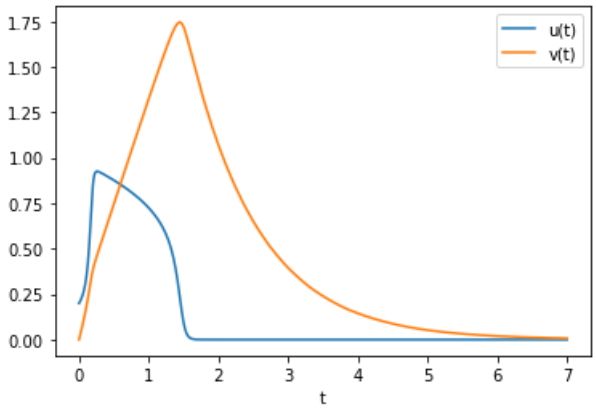

Figure 8: Aliev-Panfilov model without diffusion.

3.4 Mechanical models

The following model is used to describe the formation of a pacemaker in Aliev-Panfilov model with non-oscillating kinetics. Pacemaking activity occurs because the contraction of the medium that follows a propagating wave of excitation subsequently stretches the medium in the neighborhood of the initiation site. This stretch induces a depolarizing stretch activated current Is that initiates a subsequent excitation wave.

3.4.1 Excitation-contraction coupling model

We consider 1D lattice that consists of material points located at x_i connected by springs. All springs follow Hooke's force-displacement relation and may produce additional active contraction forces

$$\begin{cases} f_i^+ = \frac{c(x_{i+1}-x_i-l_0)}{l_0} + Ta_i = c\delta_i + Ta_i \\ f_i^- = -c\delta_{i-1} - Ta_{i-1}, \end{cases}$$

where
- l_0 and c are the spring length and stiffness;
- Ta_i is the value of variable Ta at mass point i, which modulates the active contraction force to associated mass points of the medium

$$\frac{dTa}{dt} = \epsilon(u)(k_T u - Ta),$$

where the parameter k_T controls the amplitude of the contraction twitch;

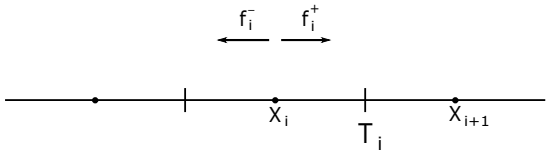

Figure 9: 1D lattice

Elastostatics is assumed in this model, i.e. the stationary deformations corresponding to each given configuration of active forces and boundary conditions are computed. In mechanical equilibrium

$$f_i^+ + f_i^- = 0 \quad \Rightarrow \quad \delta_i - \delta_{i-1} = -(Ta_i - Ta_{i-1}), \;\; \delta_i = Ta_{av} - Ta_i, \;\; Ta_{av} = \sum_i Ta_i$$

Physiological influence of contraction on cardiac tissue is given by a depolarising stretch-activated current Is through stretch activated channels

$$Is = Gs((1-\delta)^{1/2} - 1)(u - Es),$$

$Gs = 1,5, Es = 1$ are the maximal conductance and reversal potential of the stretch activated channels. The stretch activated current is active only if $\delta > 0$

4 Numerical description of Aliev-Panfilov model

4.1 Aliev-Panfilov 1D model

We are going to consider the equations representing the propagation of the cardiac action potential (5) with the Aliev Panfilov reaction terms with the diffusion, described above.

The boundary conditions we use are the Neumann homogen conditions in 0 and 1

$$\partial_x u(0) = 0, \;\; \partial_x u(1) = 0$$

and initial conditions

$$u(x,0) = u_0(x), \;\; v(x,0) = v_0(x).$$

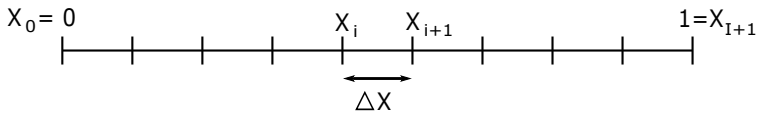

Figure 10: Discretization of 1D space

Here we chose "un schéma explicite" and the discretization of equation (1) on a regular admissible mesh of segment [0, 1] in N cells of measure $\triangle x = \frac{1}{I+1}$ is written:

$$\begin{cases} \epsilon \frac{u_j^{n+1} - u_j^n}{\triangle t} = \frac{\epsilon^2 d}{\triangle x^2} A u^n + f(u_j^n, v_j^n) \\ \frac{v_j^{n+1} - v_j^n}{\triangle t} = g(u_j^n, v_j^n) \end{cases} \tag{7}$$

where

$$A = \begin{pmatrix} -1 & 1 & & & \\ 1 & -2 & 1 & & \\ & \ddots & \ddots & \ddots & \\ & & 1 & -2 & 1 \\ & & & 1 & -1 \end{pmatrix}$$

We therefore have a nonlinear system of I equations with I unknowns to solve at each time step.

4.2 Aliev-Panfilov 2D model

We discretize $\Omega = [0,1] \times [0,1]$. Let $I, J \in \mathbb{N}^*$, we pose $\triangle x = \frac{1}{I+1}$ and $\triangle y = \frac{1}{J+1}$. Also we discretise the time with a step $\triangle t$. Thus, we note $u_{i,j}^n, i = 1 \ldots, I, j = 1 \ldots, J, n \in \mathbb{N}$ the approximationa of the $u(i\triangle x, j\triangle y, n\triangle t)$.

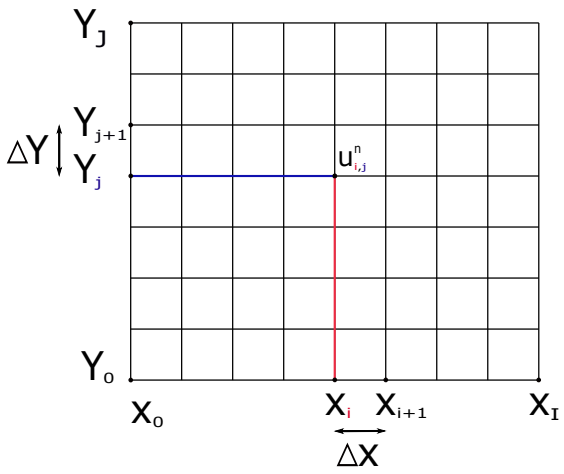

Figure 11: Discretization of 2D space

This problem discretized under the implicit Euler scheme can be written that way:

for $i = 1$ and $j = 1$ or $i = I + 1$ and $j = J + 1$:

$$\begin{cases} \epsilon \frac{u_{i,j}^{n+1} - u_{i,j}^n}{\triangle t} = \epsilon^2 d \frac{u_{i+1,j}^n - u_{i,j}^n}{\triangle x} + \epsilon^2 d \frac{u_{i,j+1}^n - u_{i,j}^n}{\triangle y} + f(u_{i,j}^n, v_{i,j}^n) \\ \frac{v_{i,j}^{n+1} - v_{i,j}^n}{\triangle t} = g(u_{i,j}^n, v_{i,j}^n) \end{cases} \tag{8}$$

for $1 < i < I + 1$ and $1 < j < J + 1$:

$$\begin{cases} \epsilon \frac{u_{i,j}^{n+1} - u_{i,j}^n}{\triangle t} = \epsilon^2 d \frac{u_{i-1,j}^n - 2u_{i,j}^n + u_{i+1,j}^n}{\triangle x} + \epsilon^2 d \frac{u_{i,j-1}^n - 2u_{i,j}^n + u_{i,j+1}^n}{\triangle y} + f(u_{i,j}^n, v_{i,j}^n) \\ \frac{v_{i,j}^{n+1} - v_{i,j}^n}{\triangle t} = g(u_{i,j}^n, v_{i,j}^n) \end{cases} \tag{9}$$

5 Reaction-Diffusion Equations

5.1 General form of equations

In this chapter we discuss some real biological pattern formation problems and show how the modelling discussed above, has been applied.

Reaction-diffusion equations describe the behaviour of a large range of chemical systems where diffusion of material competes with the production of that material by some form of chemical reaction. Many other kinds of systems are described by the same type of relation. Thus systems where heat (or fluid) is produced and diffuses away from the heat (or fluid) production site are described by the same form of equation. For chemical

systems the rate of change of the concentration, c, of a chemical component, consists of a diffusive term and a production/consumption term:

$$\begin{bmatrix} Time\ rate\ of \\ change \\ of\ concentration \\ of\ chemical\ component \end{bmatrix} = \begin{bmatrix} Change\ in \\ component \\ due\ to \\ diffusion \end{bmatrix} + \begin{bmatrix} Rate\ of\ formation \\ of\ component \end{bmatrix} - \begin{bmatrix} Rate\ of \\ cosumption \\ of\ component \end{bmatrix}$$

Mathematically reaction-diffusion equations can be in general represented in such way:

$$\partial_t u = D\triangle u + f(u),$$

where:
- as it was mentiones below, $u = u(x,t)$ is the rate of change of the concentration, of a chemical component;
- $\triangle$ denotes the Laplace operator;
- D is the diffusivity of chemical component;
- $f(u)$ is a smooth function, which describes processes with really "change" the present u, i.e. something happens to it (chemical reaction, ...), not just diffuse in the space.

We have already considered some reaction-diffusion equations in this work. In particular, Aliev-Panfilov 5 and FitzHugh-Nagumo 3 belong to such models.

The most natural application of the nonlinear diffusion equation is the study of chemical reactions taking place in the environment or in living organisms.

Reaction diffusion equations also are used to describe the population dynamics and ecology . Indeed they are at the basis of many studies ranging from the rate of advance of invading species to human genetics and expansion.

Finally, it is important to mention that RD systems do not only give rise to propagation phenomena but also to standing-patterns. Steady heterogeneous spatial structures, or patterns, appear in nature running from the very small scales, like in colonies of bacteria, to astronomical ones, like the spiral structure of some galaxies. The interest is then in understanding pattern formation.

Mammals exhibit extremely varied and complex fur patterns. These motifs have been the subject of many zoological studies which have noted the incredible variety of shapes and figures present in the animal world. Murray, in his book Mathematical biology, studied the formation of these patterns and according to him most of the observed shapes could be caused by a single phenomenon. The pigmentation of the skin and hair is due to the melanin produced by the melanocytes, cells dedicated to the production of this melanin. This production is linked to the genetic heritage (different animal species) and

to the environment (UV exposure in humans, for example). The model is based on the assumption that mammalian fur patterns only reflect spatial and temporal disparities in morphogen concentrations in the epidermis (for the color of skin and hair). Morphogens are fundamental molecules in cell development because they allow the specification of the different types of cells in an organism, their localization in space as well as their orientation, it is also a form of biological spatial spotting.

5.2 Reaction-diffusion equations and the spots

Murray uses a reaction-diffusion system (which can be unstable) and explains the spacing of spots in the coats by the existing pre-patterns of morphogen distributions. That is, genetic predispositions create a form of sketch of the shape of the spots during the embryonic period; then, the melanin, whose concentration is subjected to the phenomena of reaction-diffusion, disperses and diffuses to obtain the patterns which one observes in nature. To form patterns in the fur, this reaction-diffusion system is applied to two morphogens involved in the production (or not production) of melanin in melanocytes: oxygen substrates and uricase enzymes. They play the role of activator and inhibitor, respectively, in the chemical reactions that govern the production of melanin.

This dimensionless reaction-diffusion system is then written as follows:

$$\begin{cases} \partial_t u = \triangle u + f(u,v) \\ \partial_t v = d\triangle v + g(u,v), \end{cases} \tag{10}$$

with

$$f(u,v) = \gamma\left(a - u - \frac{\rho u v}{1+u+Ku^2}\right)$$
$$g(u,v) = \gamma\left(\alpha(b-v) - \frac{\rho u v}{1+u+Ku^2}\right),$$

where
- u is proportional to the oxygen substrate concentration and v to the uricase enzyme concentration ;
- α, a, b, ρ are positive constants;
- $d > 0$ is the term of diffusion "relative";
- $K > 0$ is a positive term describing the strength of the inhibitory character of v ;
- γ is a positive parameter proportional to the square of the area of the domain, it is the term which allows to size the study domain;

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