Abstract: Heart diseases are the major cause of deaths worldwide and within this context, the most common disease is cardiac arrhythmia. There is some evidence that the generation and maintenance of those arrhythmias might be related to the properties of the Purkinje system. Mostly because of its complex structure, which is thought to be the source of reentry activity, one of the precursors of dangerous arrhythmias. The objective of this work is to investigate how the morphology and properties of the Purkinje fibers of the heart may affect the electrical activation of the tissue. In order to build the Purkinje networks of this project, three different algorithms were used and their responses in activating the ventricular walls were compared. The monodomain equation was used to mathematically model the electrical activation and a parallel solver was used to speed up the numerical solution of the problem. The results of this work show that, together with the geometry of the Purkinje network, properties of the coupling between the terminals of the network and the ventricular tissue also affect the electrical activation by leading to conduction blocks.

Keywords: Electrophysiology. Purkinje fibers. Arrhythmia.

Resumo: Doenças cardíacas são a maior causa de mortes no mundo, e dentro deste contexto, a doença mais comum são as arritmias cardíacas. Existem evidências que a geração e manutenção de arritmias podem estar relacionadas a propriedades do sistema de Purkinje. Principalmente por possuir uma estrutura complexa, o que pode ser uma fonte de correntes reentrantes, um dos principais precursores das arritmias. O objetivo deste trabalho é a investigação de como a morfologia e as propriedades das fibras de Purkinje do coração podem afetar a ativação elétrica do tecido. Para a construção das redes de Purkinje deste projeto, três diferentes algoritmos foram utilizados e sua resposta na ativação das paredes dos ventrículos foram comparados. A equação do monodomínio foi usada para modelar matematicamente a ativação elétrica e um resolvido paralelo foi utilizado para agilizar a solução numérica do problema. Os resultados deste trabalho mostram que juntamente com a geometria da rede de Purkinje, propriedades relacionadas ao acoplamento entre os terminais da rede e o tecido do ventrículo também afetam a ativação elétrica através de bloqueios na condução do estímulo.


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1 INTRODUCTION

Cardiac diseases are still the main cause of deaths worldwide, counting up approximately 15.2 million of deaths in 2016. This not only represent a public health problem, but also an economical one, it is expected that the cost in cardiac diseases surpass 1044 billions of dollars by 2030 (WHO, 2018).

As a result of the severity of this problem, research in electrophysiology is essential to better understand this complex phenomena, which until now is not certain what are its main causes. Therefore, computational models that reproduce the electrophysiology of the heart began to be a valuable tool over the years by providing more knowledge about the processes that are responsible for causing these diseases. Furthermore, these studies also provide a way to reduce the cost of the clinical experiments. Within this context, most of the works aim to analyze the cardiac conduction system.

The cardiac conduction system is a group of specialized cardiac cells of the heart which sends electrical signals to the ventricular muscles, enabling them to contract in order to pump the blood from the ventricles to all parts of the body.

It is mainly composed by the sinoatrial node (SA node), the atrioventricular node (AV node), the bundle of His and the Purkinje fibers. The SA node is the natural pacemaker of the heart, on its normal state, it delivers stimulus to the system. After the stimulus pass through the AV node and the bundle of His, the signal reaches the Purkinje fibers, which are responsible for stimulating the ventricle tissue leading to a contraction of the muscle (CLAYTON et al., 2011).

There are several studies that relates problems in the cardiac conduction system and cardiac arrhythmias (DEO et al., 2010; BEHRADFAR; NYGREN; VIGMOND, 2014; QUAN; RUDY, 1990; BOYLE et al., 2010; OLIVEIRA et al., 2018a). In addition, other studies that mapped the electrical activity of dog and pig hearts, suggest that the Purkinje fibers play a important role in generating ventricular fibrillations at the junctions sites that link the fibers with the ventricular tissue (BEHRADFAR; NYGREN; VIGMOND, 2014; ALLISON et al., 2007; DOSDALL et al., 2008; LI et al., 2008). At these junctions, known as Purkinje-muscle junctions (PMJ’s), reentry currents could occur, which are a cyclic stimulation that happens over the tissue and it is normally triggered by an unidirectional block that occurs at some point of the cardiac conduction system (SIGG et al., 2010).

Also, it was demonstrated that the behavior of the Purkinje system changes when the fibers are couple to a large ventricular mass. There are electrotonic interactions between the fiber and the myocardium which makes the passage of the stimulus from one domain to the
another more difficult, leading to delays and even a complete propagation block (SANTOS et al., 2006). This condition is considered as a source-sink mismatch (OLIVEIRA et al., 2018a; XIE et al., 2010).

Moreover, the geometry of the Purkinje network is considered to be very irregular, as it has been verified in the recent studies from (DUAN et al., 2017), which analyzed the morphology of the Purkinje system on yak heart.

In the present work it is presented a study which analyzes how the Purkinje network geometry can affect the electrical stimulus over the ventricles by evaluating how the distribution of the branches of the tree affect the activation along the ventricular tissue. In order to build the networks three different algorithms were implemented and their response on activating the cells within the tissue were compared.

2 MATERIALS AND METHODS

2.1 Electrophysiology Modeling

The cardiac cells could only contract because of an electrical activation due to an action potential (AP), which is a depolarization current that rises the transmembrane potential of an excitable cell from its resting value, normally between -90 and -80 mV, to slightly positive values, ranging from 20 to 40 mV.

The propagation of the AP from one cell to another can only happen because of gap junctions, which are specialized proteins that enables the flux of ions between neighboring cells as represented by Figure 1.

![Figure 1: Representation of the electrical propagation through a bidimensional cardiac tissue.](image)

The difference in ionic concentration of the cell membrane generates a difference in the potential, which is responsible for triggering an AP, depolarizing the cell when it reaches a certain threshold. In addition, ions can pass from one cell to another by gap junctions, activating the adjacent cells in a wave-like form.
2.2 Monodomain Model

In order to mathematically reproduce the electrical propagation over the Purkinje fibers and also the ventricular tissue we use the monodomain model, which is a reaction-diffusion equation.

\[ \beta C_m \frac{\partial V}{\partial t} + \beta I_{ion}(V, \eta) = \nabla \cdot (\sigma \nabla V) + I_{stim}, \]  

(1)

\[ \frac{\partial \eta}{\partial t} = f(V, \eta), \]  

(2)

where \( V \) is the transmembrane potential; \( I_{ion} \) is the total ionic current that may also depend on gating variables \( \eta \); \( \beta \) is the surface-volume ratio; \( C_m \) is the membrane capacitance; \( I_{stim} \) is the current due to an external stimulus; and \( \sigma \) is the monodomain conductivity tensor. The model is further equipped with appropriate initial conditions and no-flux boundary conditions: \( \sigma \nabla V \cdot n = 0 \) on \( \partial \Omega \), where \( n \) is the normal vector of the surface, \( \partial \Omega \).

Regarding the Purkinje fibers, the unidimensional form of the monodomain equation was applied. On the other hand, for the ventricular tissue modeling, the bidimensional form of the equation (1) was used.

2.3 Purkinje Fibers

In this section we are going to describe each of the three algorithms implemented to build the Purkinje networks used to run our simulations.

2.3.1 Fractal

The usage of fractal trees to build Purkinje network have become a valuable option for automatically generate these structures for computer simulations. One of the main issues of these methods are that they not provide a control over the curvature of the branches, unabling its usage into both regular and irregular surface.

The main idea of this fractal method, which is proposed by (COSTABAL; HURTADO; KUHL, 2016), is to solve this limitation and also grant a tool to build networks under physiological and pathological conditions by keeping the network within a given surface, which in our case will be the ventricular tissue.

First of all, the method for constructing a two-dimensional fractal network starts by picking up a root point and then iteratively grow the branches of network by following the
generation rule given in (COSTABEL; HURTADO; KUHL, 2016). In summary, the fractal algorithm can be described as below:

**Result:** A fractal Purkinje network within a given surface

Pick up a root point;

**for Generations=1 to Number-of-Generations do**
  shuffle Branches-to-Grow;
  **for Mother-Branch in Branches-to-Grow do**
    **for Child=1 to Number-of-Children do**
      Create Branch;
      if Branch did not collide and is in the surface then
        add branch to Branches-to-Grow;
      end
    end
  end
end

**Algorithm 1:** Fractal network generation

2.3.2 L-system

The Purkinje network appears in histological images to be somewhat like a structure similar to tree-like structures (DUAN et al., 2017). The L-system algorithm is a famous fractal method that is able to capture this particular geometry. The L-system used in this work is based on the work of (IJIRI et al., 2008). It consists of an iterative growing process that starts at a given root node, where on each iteration a growing queue of nodes is processed by applying a set of rules, which try to spread the branches along the surface by avoiding collisions with other segments.

For each node in the queue, a new growing direction, vector $d$, is calculated by:

$$d = \frac{d_{ori} + w_1 d_{gra}}{||d_{ori} + w_1 d_{gra}||}. \quad (3)$$

In this expression $d_{ori}$ is the direction of the previous segment that ends in the parent node; $d_{gra}$ is the direction of a distance gradient, and $w_1$ is a weight specified by the user that controls by how much the gradient direction affects the direction of the new segment, $d$. Therefore, if the gradient direction is not taken into account, $d = d_{ori}$, i.e., the new segment direction is the same as the original one, or parent one.

One particularity of this method is that the value of $w_1$ plays an important role on the
distribution of the branches. By increasing $w_1$ the branches of the tree will become more separated from each other covering more homogeneously the surface where the tree is growing.

### 2.3.3 Constructive Optimization

The Constructive Optimization (CO) algorithm for generating a Purkinje network relies on an optimization method. The Purkinje network is generated considering that the tree is represented as a binary branching network of segments, i.e., as a binary tree. The model generation starts at the first segment by specifying a root point and it successively bifurcates down to terminal segments while the algorithm attempts to minimize the total length of the tree.

$$T = \sum_{i=1}^{k_{tot}} l_i,$$

where $k_{tot}$ is the total number of segments in the model and $l_i$ is the length of segment $i$. The optimization procedure may consider constraints. In this work we used this to include morphological features in the generation of the Purkinje network.

More detailed informations about the implementation of the CO algorithm can be found on the work of (ULYSSES et al., 2018).

### 2.4 Numerical Solution

To solve the monodomain equations and simulate the action potential propagation in both the Purkinje fibers and the ventricular tissue, we used the MonoAlg3D, which is an efficient parallel cardiac solver (OLIVEIRA et al., 2018b). This particular solver can handle non-uniform, non-conforming adaptive meshes and most important, use the GPU power to speedup the solution of the reaction term associated with equation (2). The source code of the solver is freely available online at <https://github.com/bergolho/MonoAlg3D_C>.

To solve the partial differential equation (PDE) given by (1) the Finite Volume Method (FVM) was used. Regarding the ionic current $I_{ion}$ from the reaction term, which is given by equation (2), we use the ten Tusscher model of human ventricle myocyte (TUSSCHER; PANFILOV, 2006) for both the Purkinje fibers and the ventricular tissue. The Rush-Larsen method was implemented to numerically solve the ordinary differential equations (ODE) associated with the ionic currents $I_{ion}$ and the time discretization for both the PDE and the ODE’s was set to be 0.02 ms.
3 RESULTS AND DISCUSSIONS

In this study, we consider the ventricular tissue to be model as a rectangular slab with 20000 x 20000 $\mu m$ dimension, where the space discretization of this domain was set to be 200 $\mu m$ on both $x$ and $y$ directions. The conductivities we consider $\sigma_x = 0.00001334$ mS/cm and $\sigma_y = 0.0000176$ mS/cm. With respect to the Purkinje fibers, we set the position of the root point in all the three algorithms to be (10000, 20000, 0). The space discretization for the Purkinje fibers was set to 100$\mu m$ and the conductivity of the fibers were set to be $\sigma_x = 0.0004$ mS/cm. In addition, the simulation time was set to be 400 ms and the monodomain parameters were set as $C_m = 1.0 \mu F/cm^2$ and $\beta = 0.14 cm^2$.

Regarding the stimulation protocol, we first run a simulation applying a stimulus over the first 5 cells from the Purkinje network, simulating the activation of the His-Bundle. Moreover, after the stimulus reach the terminal points of the Purkinje network, we save all the activation times of those points. Next, we run a second simulation by loading the positions and the activation times of the terminals, so that those points will be the source of stimulation for the ventricular tissue.

Furthermore, we were interested in analyzing the source-sink mismatch that can happen on the coupling between the two different domains that we considered. Thus, we define that the source of stimulation on the ventricular domain will be given from within a circle of radius equals to 500 $\mu m$, where its center will be the position of each terminal point from the Purkinje network. Fig. 2 represent this process.

![Figure 2: Source of stimulation from the ventricular tissue comes from circles with radius $R = 500 \mu m$, where its center position is a terminal location from the Purkinje network.](image)

After generating three different Purkinje networks using each of the three algorithms we perform a simulation to evaluate the activation of the ventricular tissue.
Figure 3: Comparison between the activation map from the three different Purkinje network generation algorithms when the time of the simulation was $t = 10$ ms. Fig. 3a represents the network generated by the Fractal approach, Fig. 3b the Purkinje system from the L-System algorithm and Fig. 3c the tree that was constructed by following the CO procedure.

From the results of Fig. 3 it was observed that the distribution of the branches along the ventricular domain can affect the activation of the tissue. In all the three scenarios we could see that the only sites that were activated by the Purkinje fibers were located where there was a concentration of branches. This behavior mainly occurs because of the source-sink mismatch that happens at the coupling sites. Conduction blocks were observed when a single branch try to stimulate the tissue. However, when a set of branches were very close to each other an AP could be trigger over the tissue. Moreover, given the three algorithms we could also see that the CO approach was the one that was able to activate more sites and the main reason for this was that the branches of the Purkinje network from Fig. 3c, were more close to each other, which makes sense since the minimization function that we use relies on minimizing the total length of the network.

For example, in Fig. 4 we analyze the AP over two different terminals from the Purkinje network generated by the Fractal algorithm (Fig. 3a) considering one that was activated and another one which suffers a block.

Figure 4: Action potential from two points of the ventricular tissue. Where the green line represents the cell with index 3004 and the red line the cell index 7575.
From the above figure we could see that after 10 ms, only the cell with index 3004 was able to trigger an AP from the Purkinje fiber. On the other hand, the cell with index 7575 could only trigger an AP after a part of the ventricular tissue was already activated and the activation wave reached its location.

4 CONCLUSIONS

In this work, we presented a comparison between different Purkinje network generation methods and we compared their response on activating a rectangular ventricular tissue. From the results it was observed that the distribution of the branches of the Purkinje network plays an important role on properly activating the ventricular tissue in a synchronous way, indicating that in fact the Purkinje system might be the source of some types of cardiac arrhythmias.

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