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Executive Summary of the Thesis

Semi-automatic generation of the Purkinje network and simulations of the electrical activity of the ventricles

Laurea Magistrale in Ingegneria Biomedica - Biomedical Engineering

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1. Introduction

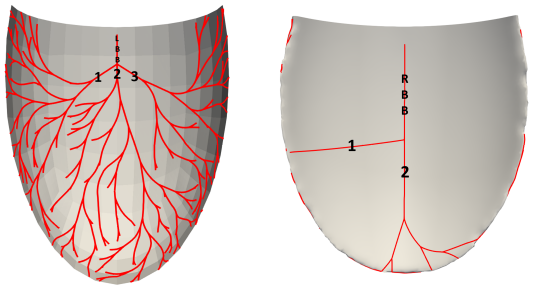
The electrical activation of the heart is triggered by a heterogeneous complex network, that combines subendocardial and free-running fibers, forming the so-called cardiac conduction system (CCS). The ventricular portion of the CCS, the His-Purkinje system, ensures the coordinated activation of the ventricular myocardium to achieve the most efficient pumping activity. The bundle of His is a cordal structure collocated in the interventricular septum, which proceeds towards the ventricles, dividing into the main bundle branches, commonly called the left and right bundle branches (LBB and RBB), bringing the signal to the left and right ventricles, respectively. Both bundle branches descend into the septum and from its lower part they start branching, forming a complex subendocardial net of conductive tissue called Purkinje network. The Purkinje system is composed by highly specialised fibers for a rapid conduction (2-4 m/s) of the action potential, and it is isolated from surrounding myocardium by connective tissue sheaths, with the exception of its terminal portion, the Purkinje-muscle junctions (PMJs). In normal case (i.e. orthodromic propagation), the electrical signal travels from the Purkinje fibers to the endocardium, after suffering a suitable delay of 5-15 ms at the PMJs. However, in pathological cases, the depolarization front may propagate from the myocardium to the Purkinje network (antidromic propagation), with a shorter delay of 2-3 ms.

In order to describe properly the electrical activity of the myocardium and considering its fundamental role in physiological and pathological scenarios (such as during ventricular tachyarrhythmias or ventricular fibrillation), the integration of the Purkinje network, in computational models of ventricular electrophysiology (EP), is mandatory. Nevertheless, the characterization or reconstruction of the Purkinje network from patient-specific human data is a challenging problem. In fact, the dimension of the fibers is in the cell order, thus the modern imaging techniques are not able to distinguish them from the surrounding myocardium. Therefore, to suitably represent the morphology of the Purkinje network, several computational models, able to reproduce the topography of the network, have been developed. Moreover, it is important to adequately model the physiological Purkinje-myocardium coupling which is present at the PMJs.

The aim of this thesis is to implement an effective numerical strategy to model the Purkinje-myocardium coupling, with the integration of the Purkinje network's generation, in the case of normal electric propagation.

2. Semi-automatic generation of the Purkinje network

In this thesis, the morphological model of the Purkinje network was generated exploiting the semi-automatic algorithm proposed by Costabal *et al.* in [1]. Unlike the others models based on a fractal law, this algorithm allows the generation of the network on both smooth and irregular ventricular surfaces [1]. The network is generated by means of a series of parameters, defined by the user, and by various randomness sources. In particular, the code provides for three cinematic parameters that directly affect the geometry of the generated network: the mean length of the branches, the branch angle and the repulsion parameter. In this thesis, the algorithm was used to reproduce the Purkinje network on several ventricular endocardium geometries, modeled as surfaces discretized by triangles. In particular, the network was built on an ideal left ventricle (LV) mesh, on three real LV mesh of three patients (p2, p8 and p11) from Santa Maria del Carmine hospital of Rovereto, on one ideal biventricular (BIV) mesh and finally on one opensource real BIV mesh.
Several histological studies highlight the presence of three branches of the left bundle branch: the anterior fascicle directed toward the anterior papillary muscle, the septal fascicle directed to the apex of the ventricle, and the posterior fascicle directed to the posterior papillary muscle [4, 5]. Thus, for the anatomically relevant construction of the left Purkinje network, the three branches of the left bundle branch (LBB) was generated, as well as the distal part of the network, and the algorithm's parameters setting was done according to the *in vivo* measurements driven by several authors in literature [5]. Unlike the LBB, the right bundle branch (RBB) remains unbranched almost until the apex of the right ventricle, where it splits in a branch directed to the anterior papillary muscle [4]. Unfortunately, in literature there are not several geometrical data of the right ventricle's (RV) Purkinje network. Therefore, for its generation, the parameters of the algorithm were chosen in order to fit the visible anatomy of the real network. The Figure 1 shows both results.

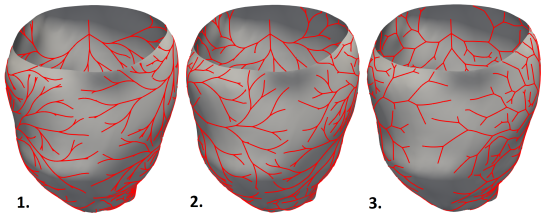


(a) (b)

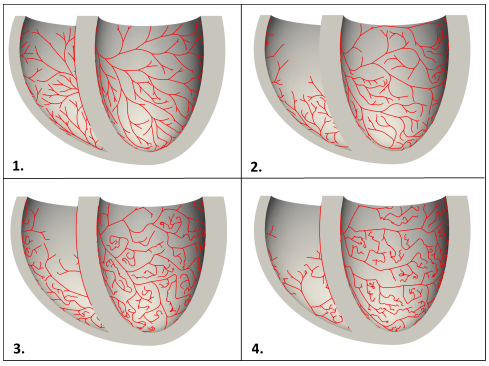
Figure 1: (a) Model of the three branches of the left bundle branch (LBB). **1.** Anterior fascicle. **2.** Septal fascicle. **3.** Posterior fascicle. (b) Model of the the two branches of the right bundle branch (RBB). **1.** Branch directed to the anterior papillary muscle. **2.** Branch directed to the apex of the ventricle.

One of this thesis' purposes is to investigate the influence of the three cinematic parameters on the geometry of the generated network. Hence, the effect of the branch length was questioned in the case of the ideal LV, choosing three different values of that parameter: 6 mm, 8 mm and 10 mm, accordingly to the real values find in literature [5]. It was possible to trivially conclude that the higher such parameter was, the greater was the branch length. Therefore, for the generation of the Purkinje network, the value of the mean length was chosen according to the geometry at hand. The influence of the branch angle was investigated in the case of the three real LV geometries. In this case, four different values of the angle were chosen: 0.15 rad, 0.30 rad, 0.60 rad and 1.2 rad, consonant to the real values find in literature [5]. The higher was the angle, the greater was the dispersion of the branches, that spread more evenly on the surface. In the end, only three values of the analyzed angles were selected for the generation of the Purkinje networks used in the following Purkinje-myocardium coupling simulations (Figure 2a). Finally, the influence of the repulsion parameter, which rules how much the branches repel each others, was analyzed in the case of the ideal BIV mesh. In this way, it was possible to prove that higher values of such parameter caused the

branches to form non-physiological patterns similar to spirals (Figure 2b). For that reason, only the lowest value of the repulsion parameter was considered.



(a)



(b)

Figure 2: (a) The Purkinje network of the real LV p2, with three different values of branch angle. **1.** branch angle = 0.15 *rad*. **2.** branch angle = 0.30 *rad*. **3.** branch angle = 0.60 *rad*. (b) The Purkinje network of the ideal BIV mesh with four different values of the repulsion parameter. **1.** repulsion parameter = 0.1. **2.** repulsion parameter = 0.3. **3.** repulsion parameter = 0.7. **4.** repulsion parameter = 1.0.

3. Electrophysiology modeling

The electrical activity of the ventricular myocardium was modeled by means of the partial differential equation (PDE) of the *monodomain model*, in which the trans-membrane potential is the only unknown. Let Ω_{mus} be the 3D myocardium, for each $t > 0$, find the trans-membrane potential V_m such that:

$$\chi_m c_m \frac{\partial V_m}{\partial t} - \nabla(\Sigma \nabla V_m) + \chi_m I_{ion} = I^{ext} \quad (1)$$

where χ_m is the surface area-to-volume ratio, c_m is the membrane capacitance, I^{ext} is the applied current per unit volume, V_m is the transmembrane potential, I_{ion} is the ionic current, and Σ is the effective conductivity tensor. Furthermore, a ventricular cell model was needed to provide the ionic current I_{ion}. In this thesis, we chose the human ventricular ten Tusscher-Panfilov model, which is composed by 12 gating variables and 6 ionic concentrations.

On the other hand, in order to model the electrical activity of the Purkinje network, we used the easier 1D *isotropic eikonal model*, which ignores the kinetics of the cardiomyocytes and only permits to compute the activation times. Let Ω_p be the one-dimensional Purkinje network and $u_p(\mathbf{x})$ the unknown activation times in the network. Then, the eikonal model reads:

$$\begin{cases} V_p \left| \dfrac{\partial u_p}{\partial s} \right| = 1 & \mathbf{x} \in \Omega_p \quad (2a) \\ u_p(\mathbf{x}) = u_{p,0}(\mathbf{x}) & \mathbf{x} \in \Gamma_p \quad (2b) \end{cases}$$

where $V_p = V_p(\mathbf{x})$ is the conduction velocity of the network, s is the curvilinear coordinate along the network, Γ_p is the set of points generating the front in the network, and $u_{p,0}(\mathbf{x})$ is the value of the activation times on Γ_p.

To numerically solve the continuous problem (1), we used the first order *finite element* approximation and the second order *Backward Differentiation Formula* (BDF2). In particular, we chose a implicit-explicit (IMEX) scheme, where the diffusion term is treated implicitly, whereas the ionic and reaction terms explicitly. Furthermore, this scheme adopts an explicit handling of the ionic concentrations, and an implicit handling of the gating variables. The discretization of the ionic current term I_{ion} is performed following the *Ionic Current Interpolation* approach. The time resolution was imposed equal to 0.05 ms, while the space resolution was 0.8 mm in the case of the ideal and real LV, 2.5 mm in the case of the ideal BIV mesh, and 1.2 mm in the case of the real BIV mesh.

To computationally solve the eikonal model (2) in the network, we implemented an algorithm belonging to the class of the *Fast Marching Methods* (FMM), based on a finite difference approximation scheme. Such methods are founded on the observation that the information propagates only from smaller to larger values of the unknown.

The Purkinje-myocardium coupling was modeled in terms of exchange of currents [3]. The PMJ act as sources for the endocardium through regions of influence modeled as spheres of radius

r, centered at each PMJ. In practice:

1. Thanks to FM, the algorithm computes the activation times of the Purkinje network and identifies the positions of the terminal points of the network (i.e. PMJs). Subsequently the code adds 10 ms delay at each PMJ, in order to model the physiological case of the orthodromic propagation.
2. At the time instant in which each PMJ is activated (including the delay), the algorithm imposes some spherical current impulses, of certain intensity and radius, centered at each PMJ, on the endocardium surface.
3. The algorithm solves the continuous problem (1) discretized by means of the finite element in space and by BDF2 in time, in order to compute the trans-membrane potential and the activation times in the myocardium.

The Purkinje-myocardium coupling, modeled in terms of an Eikonal/Monodomain (EM) strategy, was computationally simulated in each previously mentioned ventricular geometry. The EM coupling was implemented in `life`^{x}, a high-performance finite element library, mainly focused on mathematical models and numerical methods for cardiac applications. In particular, the algorithm that solves the monodomain model has already been implemented in `life`^{x}, whereas the FM method to solve the eikonal model was developed from scratch. All the numerical results were obtained using the available HPC resource at MOX Laboratory, Politecnico di Milano.

4. Simulations results

In the case of the ideal LV, three simulations were performed with the same Purkinje network, but with different network's conduction velocity. In fact, the velocity of the Purkinje network was set equal to 3 m/s, to 3.5 m/s and to 4 m/s, in order to investigate the conduction velocity's influence on the activation of the network itself and of the ideal ventricle. The results were not surprising: the higher was the conduction velocity, the lower was the time the network and the myocardium needed to completely activate. In particular, the activation of the Purkinje network alone required 30 ms in the fastest case, while in the slower case, the electrical activation was completed in 39 ms. Whereas, in the myocardium, the total activation time was around 80 ms in each of the three cases, consonant to the value reported in literature for the ventricular activation. The electric front propagated from the endocardium towards the epicardium, and the last region reached by the activation wave was the basal part of the ventricular septum, according to what reported by the authors in [4].

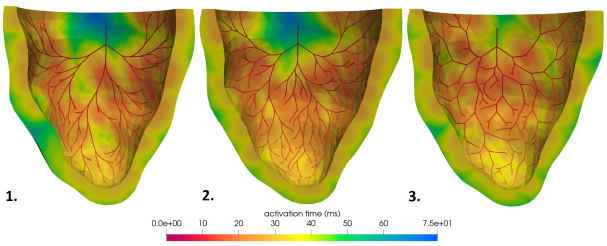


Figure 3: Activation times of the Purkinje network and myocardium in the real LV p8. **1.** Purkinje network's branch angle = 0.15 rad. **2.** Purkinje network's branch angle = 0.30 rad. **3.** Purkinje network's branch angle = 0.60 rad.

The influence of the branch angle, on the network and myocardium activation, was questioned in the case of the three real LVs (Figure 3). In particular, for each of the real geometries, three values of the branch angle were chosen: 0.15 rad, 0.30 rad, and 0.60 rad, and overall, nine different scenarios were simulated, with the same network's conduction velocity equal to 4 m/s. In general, it seems that the greater was the value of the angle, the higher was the activation time the Purkinje network required for its activation. Vice versa, the higher was the angle, the fastest was the activation of the myocardium. This trend can be explain considering that the branch angle influences the dispersion of the branches. Therefore, if the angle is high, the branches are more separated and they are able to cover more endocardial surface. Furthermore, the last part of the myocardium reached by the activation front was the basal septum, in the case of the branch angle equal to 0.15 rad and to 0.30 rad, while in the case of the highest angle, was the basal free wall of the ventricle.
To perform the EP simulation in the case of the ideal BIV mesh, the Purkinje network's conduction velocity was set to 4 m/s, while the branch angle was equal to 0.30 rad. The Purkinje net-

work needed almost 45 ms to activate, in particular, the activation of the left part of the network required 30 ms, while the right part took 10 ms longer, because of the morphology of the network itself. This difference is fundamental in order to ensure the delay of 5-10 ms, which is present between the beginning of the activation of the left and of the right endocardium, measured in literature [2]. The simulation performed on the ideal BIV mesh (Figure 4) was able to reproduce the physiological activation sequence of the two ventricles: the mid-left septal surface showed the greatest activity early, and the wave on this septal surface moved toward the right [2, 4]; 5-10 ms after it began on the left, the electrical activity started on the right endocardial surface, near the anterior papillary muscle [2]; once the left and right endocardium were mainly activated, the electrical front propagated toward the epicardium. In this case, the last part of the BIV mesh to be activated was the basal septum, because Purkinje fibers are not widely distributed to the basal wall or to the basal septum [4], and the total BIV mesh activation ended in 130 ms.

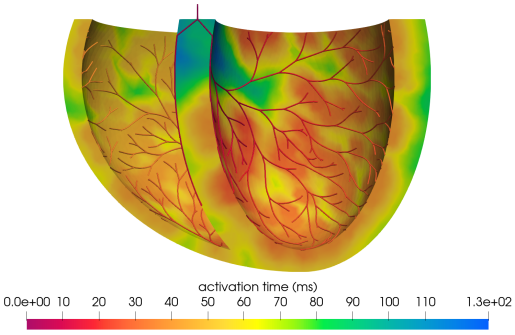


Figure 4: Activation times of the Purkinje network and myocardium in the ideal BIV geometry.

In the case of the real BIV mesh, two Purkinje networks with two different values of branch angle (0.30 and 0.60 rad), and the same conduction velocity (4 m/s), were used in order to perform EP simulations of the Purkinje-myocardium coupling. In both cases, the activation of the network required almost 45 ms, in good agreement with what was observed in the ideal BIV mesh. Furthermore, the electrical activation of the myocardium seemed to be independent from the value of the branch angle, in fact, the time required for the total activation of the real BIV mesh was almost equal in both cases: 98 ms for the highest angle, and 100 ms for the lowest. Also in the real BIV mesh, the simulations performed were able to reproduce the physiological activation of the ventricles (Figure 5). The only difference with the ideal case was that the last part of the real BIV mesh to be activated was the basal part of the right ventricle, consonant to what reported in [2].

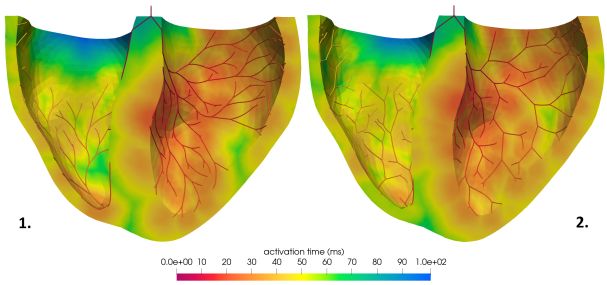


Figure 5: Activation times of the Purkinje network and myocardium in the real BIV geometry. **1.** Purkinje network's branch angle = 0.30 rad. **2.** Purkinje network's branch angle = 0.60 rad.

In all the simulations, the trend of the transmembrane potential mirrored the electrical activation, and the values of the potential were within the range of -85 mV, as the minimum, to the maximum of 30 mV.
In the end, we simulated also the activation of the Purkinje-myocardium coupled system in the case of myocardial ischemia, in one of the real LV geometry. Since we did not have real clinical data for the patient at hand related to a myocardial ischemia, we assumed to know the ischemic region location and we modeled it as sphere of radius equal to 0.01 m. In this region the myocardium is no longer excitable, and accordingly we set the conductivity of the muscle equal to zero. Whereas we assumed that the portion of the Purkinje network belonging to that region is characterized by a reduced conduction velocity, since also the cells of the network are supposed to die under the reduced blood supply. In particular, we reduced the conduction velocity of the network to 0.4 m/s. In this pathological case, the ischemic PMJs could be activated either by the network (orthodromic propagation) or by the healthy nearby PMJs, since the electrical signal could travel through the muscle (antidromic propagation). The algorithm com-

puted both the activation times of the ischemic PMJs as if they were activated by the network or by the muscle, and it considered only the lowest value. Since the implemented method, used to model the Purkinje-myocardium coupling, does not describe the antidromic propagation, the latter was model exploiting an approximation. The results of the EP simulation proved that the myocardium remained inactivated, while the muscular region beyond the ischemia showed a slower activation than the normal case.

5. Conclusions and Limitations

In general, the numerical strategy presented in this thesis proved to be sufficiently robust to simulate Purkinje-myocardium coupling in different ventricular geometries, both ideal and real, in the case of orthodromic propagation. In particular, the algorithm exploited to generate the Purkinje network is very simple to use, and allows the effortless semi-automatic generation of the network in all the geometries. Furthermore, modifying the algorithm's parameters, it is possible to generate a network whose branch lengths and angles match to the real ones, including also the branching of the LBB and the RBB.

The EP simulations were able to reproduce the physiological activation of the ventricles, as well as the values of the activation times and of the trans-membrane potential. Not surprisingly, it was proved that the greater is the conduction velocity of the Purkinje network, the lower was the time required for the activation of both the network and the myocardium. Moreover, since the value of the branch angle influences the branches distribution, the higher was the angle, the slowest was the activation of the Purkinje network, while the fastest was the activation of the myocardium.

The main limitations of the proposed method are:

1. The method does not model the antidromic propagation, but the orthodromic one exclusively.
2. The spatial resolution of the performed EP simulations is not suitable for the EP standards (h<0.3mm).

Once the limitations will be fixed, the subject of future works could be the extension of the proposed method to scenarios in which more accurate models are used, such as for example the monodomain model, to describe the electrical activity of the Purkinje fibers, or the bidomain model, for the activation of the myocardium. Furthermore, it could be interesting to evaluate the validity of the strategy even in cases of conduction block, such as bundle branch blocks, also simulating a possible His pacing. Finally, for the sake of completeness, the method could also be exploited to simulate conditions of myocardial ischemia in which real patient data are available.

In conclusion, the method proposed in this thesis not only gives importance to the inclusion of the Purkinje network in computational models of ventricular EP, but it proves to be very versatile, as it is able to adapt to different ideal and real ventricular geometries. Furthermore, for the first time, it allows to run simulations of the Purkinje-myocardium coupling in the `life`^{x} library, in the case of orthodromic propagation.

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