Comparison of Phenomenological and Biophysical Cardiac Models Coupled with Heterogenous Structures for Prediction of Electrical Activation Sequence

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Abstract

The electrical activation sequence of the ventricles follows a complex pattern which ensures an efficient contraction and subsequent blood pumping. Today, electrical therapies are often used to correct those behaviors, although a-priori it is unknown how the activation sequence will change. In this paper, we study changes in the activation pattern using electrical simulations based on both phenomenological and biophysical models. The complex electrophysiological modeling takes into account the cell specific ion kinetic and reaction-diffusion equations for tissue propagation, whereas the simple modeling is based on Eikonal equation. The computational model includes the specialized electrical structures in the ventricles. Simulation outcomes were compared by looking at the local activation times (LAT) and following total activation time (TAT). Results show that the inclusion of a biophysically based conduction system on a phenomenological model reduces the differences with fully biophysical models, requiring short computational times.

1. Introduction

Computational biophysical models have been used as tools to investigate electrophysiological cardiac phenomena such as cardiac arrhythmia or fibrillation, which requires to explicitly model membrane ionic currents [1]. These models have the potential to reproduce with a high degree of detail the cardiac electrophysiology at cell and tissue levels. One of the final goals of such models is to predict the electrical activity of a given heart under normal conditions and after complex procedures such as Cardiac Resynchronization Therapy (CRT) [2]. Biophysical models use equations that approximate the cardiac electrical properties based on the representation of the tissue as a functional syncytium [1]. This includes detailed information about the cell level electrophysiological function of tissue into the model. Nonetheless, the level of the detail required to model the dynamics of action potential propagation in ventricular tissue depends highly on the ultimate target application [3]. This is the case of simple tissue level wavefront propagation models that are designed for fast intra-operative decision making and are based on the assumption that the speed of propagation varies more slowly and over much larger spatial scales than the transmembrane potential.

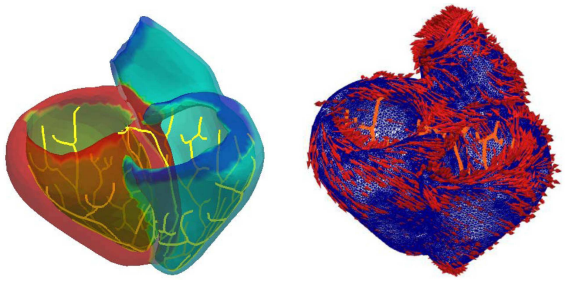
In addition to the physical models, it is also important to accurately model the cardiac domain, with particular emphasis on its heterogeneous structures. Those structures have known differences at various levels and are responsible for the correct performance of the heart. One of the most important influences on cardiac electrophysiology is due to the cardiac conduction system (CCS). The CCS has differentiated sections with specific conduction features, and its effect on the sequence of activation is determinant for the proper heart function. Therefore, it is important to specifically model each part using different cellular, tissue and morphological models.

In this study we analyze the difference between simulations performed using detailed biophysical models and phenomenological models in a human biventricular anatomy model, but considering a morphological and electrical model of the CCS. For this personalized biventricular geometry we will report the procedure of applying the coupled model and then will study the effect from phenomenological and biophysical modeling on the electrophysiological propagation in the domains.

2. Methods

2.1. Anatomical model

The biventricular geometry used here was segmented in a previous work [4]. In that study, an active shape model was used to obtain the inner and outer ventricular sur-



(a) (b)

Figure 1. Construction of geometrical model, (a) surface mesh of LV and RV including CCS structure and (b) fiber direction distribution in the domain.

faces, that allowed the automatic transfer of a number of functional substructures incorporated in an atlas. Tetrahedral elements were used to generate the computational domain for myocardium tissue. The segmented surface was meshed with TetGen to generate volumetric linear tetrahedral elements. Different resolutions were used for the same mesh as indicated in table below:

	No Element	No Node	Mesh size*	Model type
1	11820	3813	5.0	phenomenological
2	43488	13192	3.0	phenomenological
3	157575	36599	2.0	phenomenological
4	592340	122172	1.2	phenomenological
5	1042800	206974	1.0	phenomenological
6	14937781	2450389	0.5	biophysical

*Average internodal distance, unit in *mm*

The anatomical model for the CCS was the same described in [4]. Its structure was manually delineated by following a deterministic approach and consists of a branching network built with linear splines, which are distributed on the endocardial surface of left and right ventricles (Fig. 1(a)). The independent elements of CCS are then mapped to the surface of the segmented biventricular model. The resulting CSS consisted of 100 branches, along with the right and left bundle branches that originated approximately on the AV node.

Myocardium fiber structure, a critical element for electrophysiological wave propagation, was included using a mathematical model that was adjusted to the measurements form Streeter [5]. Fiber orientation in the left and right ventricular free wall varied from -60 degrees at the epicardium to +50 degrees at the endocardium, whereas in the septal wall the fiber angle ranged from approximately +50 degrees at the right ventricular endocardium to around -60 degrees at the left ventricular endocardium (Fig. 1(b)).

2.2. Electrophysiological models

All the numerical calculations that used biophysical models are based on a previous work [6]. In this study Ten Tusscher-Panfilov model was used to simulate the cellular ion kinetics in the bulk myocardium coupled to the monodomain formulation for the propagation of the electrical impulse in the cardiac tissue. DiFrancesco-Noble model was used [7] for electrical propagation in the CCS. The simulations were run for 230 ms of the cardiac cycle since only the onset of depolarization was of interest. In the model the CCS was coupled to the bulk myocardium through Purkinje-Myocyte Junctions (PMJ) which are represented as fix resistances. At the structure endpoints, current can flow from or to the PMJs, and initiates a depolarization wavefront on the endocardium [7]. The possibility of having a bidirectional flow is important when modeling retrograde activation observed in paced hearts.

For phenomenological wave propagation modeling we use the simple Eikonal equation to model the wave-front propagation [8]. It is based on the Hamilton-Jacobi Equations (HJE), a first-order non-linear partial differential equation (PDE). Coupling CCS terminals and bulk myocytes was performed with a junction element that interchanges the information between myocyte domain and CCS terminals with a conduction velocity that is equal to that of the Purkinje system. Each junction element connects the Purkinje terminal node to the nearest node on the myocardium domain. Since the junction element transfers information in both directions, the coupling provided between the CCS elements and myocyte elements is tight and will be able to simulate the retrograde impulse from myocardium tissue to the CCS. The implementation of the phenomenological model and its numerics was performed in the OpenCMISS (Open Continuum Mechanics, Imaging, Signal processing and System identification) mathematical modeling environment.

3. Results

We considered three experiment setups; i) simulations with biophysical and phenomenological models including CCS and in normal sinus rhythm activation; ii) simulations with phenomenological model with and without CCS to study the mesh resolution effects; and iii) simulations with both biophysical and phenomenological models coupled with CCS and activation initiated from 2 pacing leads at the myocardium.

First experiment set: Isochronal maps of local activation times (LAT) were calculated to analyze the activation patterns (Fig. 2). These simulations were run in sinus rhythm, therefore the electric impulse was transmitted from the His bundle to the right and left bundle branches, and propagated from there to the Purkinje fibers. The delay from the initial stimulus at the AV node to the first depolarized endocardial cell was of 30 ms that only depends on the electrophysiological properties of the CCS. The Total Activation Time (TAT), was computed using the first

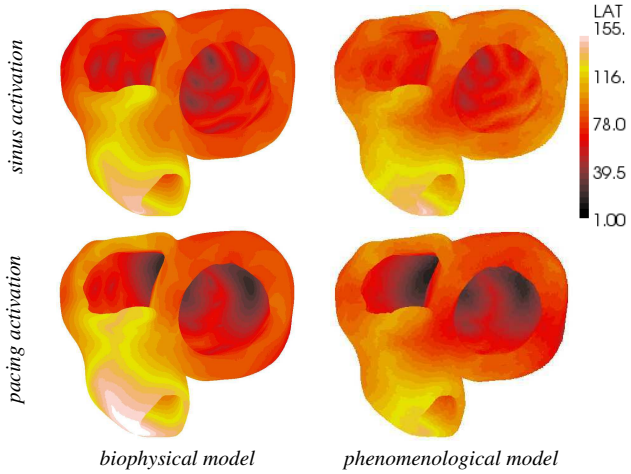


Figure 2. Local activation time (LAT) in the presence of CCS for biophysical (first column) and phenomenological (second column) models during sinus rhythm (first row) and CRT pacing (second row).

endocardial breakthrough as a starting time, and was 116 ms for this set. Since we need the corresponding parameters of biophysical equations in the phenomenological one, and there is not relation between these parameters, we used the activation times observed from biophysical results in the biophysical model to calculate the conduction velocities in the phenomenological model. Since there is not a direct relation between the parameters and the models we used an iterative procedure to reduce that difference. The conduction velocity normal to the fiber direction was set to one third of the one measured along fibers. Given this procedure we set in the phenomenological model the conduction velocity for Purkinje system to 2.56 m/sec and for myocardium tissue equal to 1.16 and 0.38 m/sec along and normal plane respectively. In the phenomenological model the TAT was 117 ms after fitting the free parameters. The CCS homogenizes the pattern of activation and propagation at endocardium and epicardium at both models (see Fig. 2). In order to have a numerical comparison, the cumulative frequency histogram in Fig. 3(a) shows the percentage of activated tissues at different times. The difference between the histogram curves show that although the TAT and activation pattern are very similar, there are significant differences in the activation process over time.

Second experiment set: In the second set of simulations the models were tested with different mesh resolutions on the phenomenological model. We did not check this with the biophysical model, since there are strong constraints derived from the cellular models that only allow high resolution meshes. We applied the same activation setup as in the first experiments, but varying mesh size. The change in TAT was considered as a measure of the sensitivity of the models to the numerical method. Our

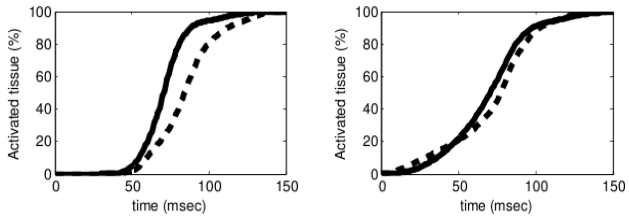


Figure 3. Cumulative frequency histograms of the normalized percentage of activated tissue for biophysical (solid line) and phenomenological (dashed line) models in the presence of CCS during (a) sinus rhythm and (b) CRT pacing.

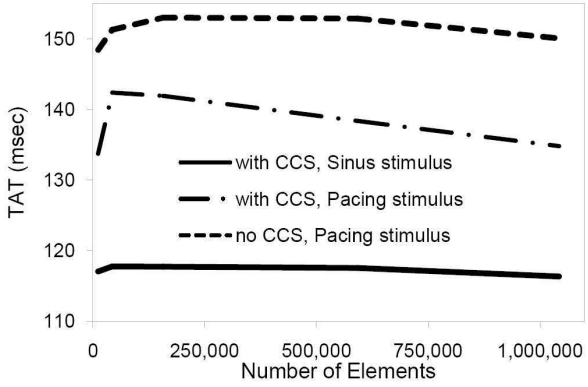


Figure 4. The effect of mesh size with a model coupled to the CCS which is stimulated at sinus node (solid line) and pacing points (dash-dot line) and without CCS that is stimulated at pacing points (dashed line). Due to the presence of CCS there is 30 ms delay in initializing the activation in sinus-activated with-CCS case.

experiments with phenomenological models and different mesh sizes confirmed the independency of model results from the mesh sizes as it is shown in Fig. 4.

We repeated this study with and without CCS in computational domain and including two pacing leads positioned similar to the CRT cases on the RV endocardium apex and on the LV epicardium free lateral wall. Interestingly we found out that the variations are more less in the model that included a CCS and stimulus starts from sinus (see Fig. 4). For a wide range of mesh sizes (between $1mm$ and $5mm$ of average internodal distances) the change of the TAT when the CCS model is included is about 1% with stimulus started from Sinus node and about 6% with stimulus from pacing. The same experiments without CCS with pacing stimulus clearly showed the effect of the mesh size, where there were variations of about 3% regarding TAT between different mesh sizes.

Third experiment set: A third set of simulations was carried out including an external stimulus from a biventric-

ular pacemaker in presence of CCS. The lead positions of the CRT device were modeled as in the second experiment. In this scenario it is important the effect of the retrograde conduction into the CCS produced by the pacing points at the myocardium. TAT from the biophysical model and phenomenological models were 155 ms and 134 ms, respectively (see Fig. 2). Despite the activation from phenomenological model being faster, the histogram in Fig. 3(b) shows that the activation sequence follows a similar pattern in both models. It should be mentioned that in all the models the outflow tract of RV was the latest activated due to the activation from pacing at the apical part of heart.

4. Conclusions

Our simulations with and without CCS show the importance of heterogeneous structures on the distribution of LAT in a computational domain. Moreover, experiments on meshes with different resolutions show that when CCS is included and stimulation starts from sinus node, the errors due to the myocardium mesh size are smoothed. This means that with stimulation from Sinus node, the inclusion of CCS reduces the sensitivity of the numerical results to the myocardium mesh size (with CCS of 1% change in TAT). We can expect that with the stimulation starting from the distributed terminals of the CCS, a limited number of vortex and filament will be formed in the continuous myocardium domains as it is discussed in [9]. A well distributed CCS in the domain (without CCS-block) using a combined biophysical CCS model with a phenomenological myocardium model will improve the computational performance.

Given a proper conduction velocity, the phenomenological model can simulate a pattern of activation that can visually resemble the one of the biophysical model and be used as an input for a mechanics solver.

The comparison of the computational time between the phenomenological model (about 1h on a one core PC with a mesh resolution of 1mm) and the biophysical model (about 4h on a 32 core cluster with a mesh resolution of 0.5mm) shows the advantage of the phenomenological over the biophysical, specially for intraoperative decision making. The decision of choosing one over the other should also be based on the specific target pathologies.

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