Comparison of Microscopic and Bidomain Models of Anisotropic Conduction

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Abstract

The bidomain model is based on effective parameters to include the myocardial tissue properties into models of propagation of depolarization. In this study we examine whether these properties can be derived from histology by generating a geometrical model of cardiac tissue and computing the effective conductivity. We tested this hypothesis by generating a detailed model of cardiac tissue in which we simulated the propagation of depolarization directly, using the so-called microdomain approach. We compared both the the conduction across and along the fiber of the myocardium under both healthy and ischemic conditions. Under healthy conditions both the microdomain and bidomain approximation resulted in conduction velocities that were within 3% of each other. However under ischemic conditions the conduction velocity across the fiber approximated 20%, indicating that the effective conductivity tensors under those conditions are not a good approximation.

1. Introduction

As computer models of the heart are more frequently used to scrutinize the complexities of cardiac disease, there is an increased need for these models to describe both healthy and pathological conditions. Hence, a good understanding of the assumptions underlying the model's parameters is paramount in modifying these parameters to reflect real pathologies. In this paper we explore the parameters underlying the models for predicting the electrical activation sequence of cardiac tissue.

The most commonly used approach for simulating cardiac activation is the so-called bidomain model [1]. This model assumes that there are two major components in predicting the spread of action potentials: (1) an active component in the form of the cell membrane, that injects currents based on the state of the membrane into the second component of the model, (2) a passive electrical conductor, that diffuses and spreads the action potentials. As there is a huge amount of information on how to incorporate disease state into the membrane dynamics of cardiac myocytes, we focus in this paper on the second component of the model: the parameters of the model that describe the electrical properties of the tissue.

These properties are dominated by the fact that cardiac tissue is an anisotropic conductor. As cardiac myocytes have an elongated shape and are stacked end-to-end to form myocardial fibers, the electrical conductance along the fiber is higher than across the fiber. Hence in almost all of the bidomain approaches the electrical properties of cardiac tissue are summarized by means of tensor. Generally, the electrical properties of the bidomain model are summarized by three different parameters: the conductivity tensor for the intracellular space, the conductivity tensor for the extracellular space, and the surface-to-volume ratio for the active membrane surface. Moreover, these three parameters reflect the macroscopic tissue properties that incorporate structural parameters such as the distribution of gap-junctions within the tissue, and the distribution of extracellular space.

However the influence of pathological conditions on cardiac tissue is often described in terms of histology and not in terms of bidomain parameters. Hence an additional translation is needed to interpret the data. For example the structural difference between the tissue of a neonate and an adult is often described in terms of gap-junction distribution and myocyte shape differences [2].

However not every structural changes is described as histology, other sources of information for instance include the macroscopic electrical resistance, *i.e.* the electrical resistance measured between two distant electrodes. For example the collapse of the extracellular space at the onset of acute ischemia is often characterized this way [3].

Despite the abundance of information on changes within cardiac tissue due to different pathologies, the question remains **whether these macroscopic measurements of electrical resistance in fact reflect the resistance observed by the currents injected into tissue by the membranes at a microscopic level**, *i.e.* the resistance observed between two distant electrodes and the one from within the tissue at a microscopic level are not necessarily the same. Furthermore, it is not apparent **how the structural information can be translated into effective conductivity tensors that reflect these changes in the bidomain**

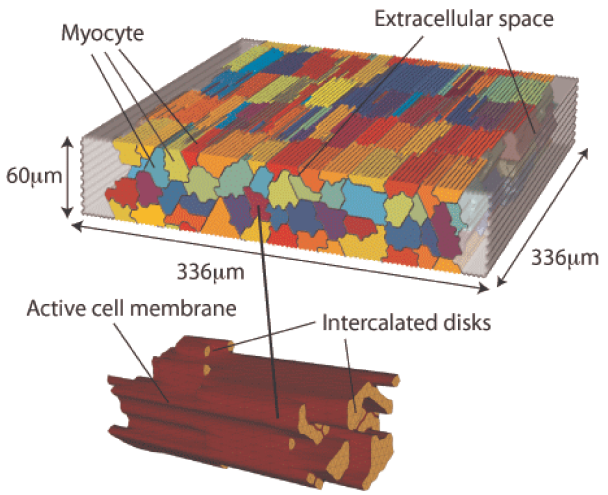

Figure 1. Histology based geometrical model of cardiac tissue

model.

In order to start answering these questions, we have created an 3D histological computer model of cardiac tissue, that can be used to simulate the spread of action potentials at a microscopic state as well as to evaluate the effective tissue resistances of the same piece of tissue. As the model explicitly includes geometrical details like the shape of individual myocytes, the distribution of gap-junctions, and the shape of the interstitial space, these histological determined features can be altered directly within the model and do need the translation into effective properties.

The 3D histological computer model we used in this study was based on a model generated by Stinstra *et al.* [4, 5]. This model was specifically developed to compute the effective bidomain conductivities of a small piece of tissue, typically about 64 myocytes. The results of this study showed that the electrical conductivities along the fibers of the cardiac muscle were in good agreement with the values typically used in bidomain models. However the value of intracellular conductivity across the fiber was substantially lower than values typically used in bidomain studies [4], but similar to the value found in other estimations of the intracellular conductivity across the fiber based on geometrical arguments of the size of the myocytes and the distribution of gap-junctions, see for example Neu *et al.* [6]. Hence, this discrepancy constituted the third question: **whether a model based on a geometrical/histological description would result in realistic propagation of action potentials**.

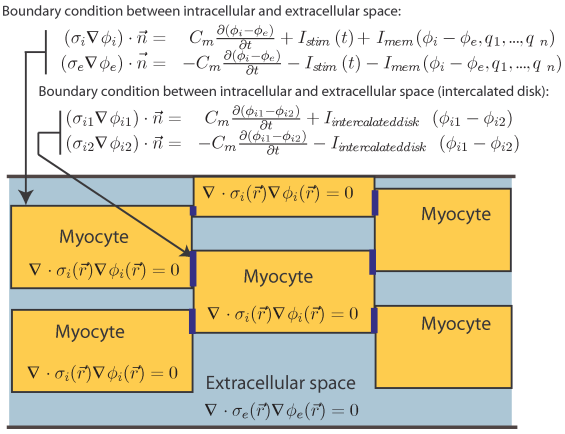

Figure 2. The microdomain method

2. Methods

In order to test the hypothesis whether the effective bulk conductivities can be used as parameters for the bidomain model, we conducted the following experiment *in silico*: we generated a surrogate geometry of cardiac tissue that consisted of geometrical description of each myocyte and its surrounding extracellular space based on histological data from the literature and used this geometrical model (1) to simulate the propagation of an action potential using the *microdomain approach* [7] and (2) to compute the effective resistance of the tissue and use these effective properties to simulate the propagation of an action potential using the *bidomain approach*.

An example of this geometrical detailed model of cardiac tissue that was generated for this comparison is depicted in Fig. 1. The upper panel of this figure depicts an example of a stack of cardiac myocytes, each colored domain is a separate myocyte that is embedded inside an extracellular matrix. The lower panel of Fig. 1 depicts an example of a single myocyte and the locations of the intercalated disks (surfaces infused with gap junctions) that lock the cells together. In order to render an accurate model of cardiac tissue the model was optimized using histological data such as extracellular volume fractions, gap-junction distributions, and metrics on the average size of typical myocytes. A detailed description of the algorithm and parameters used to generate this surrogate tissue model is given by Stinstra *et al.* [4].

In order to compute the conduction velocity, *i.e.* the speed at which the depolarization front travels through the tissue, we used the *microdomain approach*. An overview of this approach is given in Fig. 2. Unlike the bidomain model, this model incorporates the actual shapes of the myocytes and assumes that each cell is its own volume conductor embedded in a larger volume conductor that

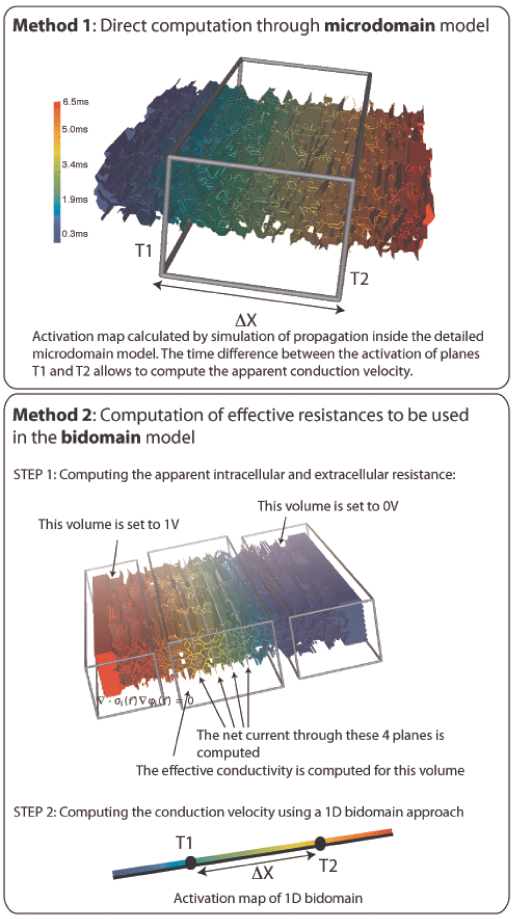

Figure 3. Comparison between two methods of computing the conduction velocity

consists of the interstitial space. In this approach the different volumes are connected by common boundary conditions that reflect a description of the active membrane behavior. In the model depicted these boundary conditions are divided into two groups, the membrane between intracellular and extracellular spaces that in this case follows the membrane dynamics are described by Luo and Rudy [8] and the membrane between two myocytes that is described as a passive resistor and models a membrane containing many gap-junctions. By solving the partial differential equations given in Fig 2 as a function of time, a propagating depolarization front can be simulated [7, 9].

The second approach to the computation of the conduction velocity, is to first compute the effective electrical conductivity and then use a *bidomain approach* with a far lower discretization to solve for the propagating depolarization front. Unlike the *microdomain approach*, the *bidomain approach* is far less computational intensive, as it requires only one solve for the full geometrical model and relies on effective properties to describe the tissue architecture well enough to ensure to simulate a realistically propagating depolarization front. In this case the geometrical model is used to compute the effective properties of the tissue by applying an external potential across the outer endings of the model and simulating the current that flows through the model. As the *bidomain approach* requires both an intracellular as well as an extracellular conductivity tensor, both are computed separately by assuming that there is no current flow across the membrane and by computing the net current through both the intracellular and extracellular spaces. By spatially rotating the applied potential difference from along the fiber to across the fiber, both components of the tensor can be computed. In this case we assume that the effective conductivity in the two directions perpendicular to the myocardial fiber are effectively the same. An overview of the difference between the two methods is given in Fig. 3.

Table 1. Comparison between microdomain and bidomain approaches.

Healthy Tissue Model		
parameters:		
interstitial space thickness		1.1 μm
Intercalated disk surface resistance		0.0015 $k\Omega cm^2$
Interstitial space fluid conductivity		2.0 S/m
Cytoplasm conductivity		0.3 S/m
Membrane capacitance		1.0 $\mu F/cm^2$
microdomain approach:		
conduction velocity	0.420 m/s	0.090 m/s
effective conductivity + domain approach:		
intracellular conductivity	1.58 mS/m	0.049 mS/m
extracellular conductivity	2.13 mS/m	0.996 mS/m
surface-to-volume ratio	2328 $1/cm$	
conduction velocity	0.415 m/s	0.096 m/s
Ischemic Tissue Model		
parameters:		
interstitial space thickness		0.22 μm
Intercalated disk surface resistance		0.0075 $k\Omega cm^2$
Interstitial space fluid conductivity		2.0 S/m
Cytoplasm conductivity		0.3 S/m
Membrane capacitance		1.0 $\mu F/cm^2$
microdomain approach:		
conduction velocity	0.227 m/s	0.058 m/s
effective conductivity + domain approach:		
intracellular conductivity	0.79 mS/m	0.019 mS/m
extracellular conductivity	0.43 mS/m	0.186 mS/m
surface-to-volume ratio	2381 $1/cm$	
conduction velocity	0.230 m/s	0.048 m/s

3. Results

We computed the conduction velocity for two sets of conditions: a model that reflects a healthy state of tissue and a model that reflects an ischemic state of tissue.

Table 1 lists both the parameters that were used to generate both models, as well as the conduction velocities that are predicted by the *microdomain approach* and the *bidomain approach*. The table lists as well the effective conductivities of intracellular and extracellular space that were used in the *bidomain approach*. The values in the left column are the resistances and conduction velocities along the fiber of the tissue and the ones on the right are the ones across the fiber direction.

4. Discussion and conclusions

The model for the healthy conditions shows that the predicted conduction velocities of the *bidomain approximation* and the *microdomain approximation* are within 3% and show a good agreement. However under ischemic conductions the conduction velocity across the fiber show a considerable difference of about 20%. Besides the correlation between the two approximation the values are also in reasonable agreement with experimentally observed value of 0.46 ± 0.03 m/s reported by Cascio *et al.* [10]

Hence under healthy conditions the histological approach by building a geometrical model of tissue and computing the effective properties based on this model is a good approximation for the bidomain. However under ischemic conditions with intracellular resistances becoming larger due to the closure of gap junctions, the method of approximating the bidomain tensors by computing the effective tensors is not the best approximation under those conditions.

The other thing that the model shows is that despite the effective intracellular conductivity being lower than normally used in simulations, the model results in conduction anisotropies that are not abnormally low. One of the factors that is often not taken into account in this respect is that the extracellular resistance is an important contributor to the resistance anisotropy. Whereas for the intracellular case the intracellular resistance is dominant, for the extracellular case the resistance is in fact distributed equally between both spaces. Hence the overall resistance anisotropy is a combination of the intracellular and extracellular anisotropy.

Acknowledgements

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