The Evolution of Cardiac Tissue Models

Craig S. Henriquez
Department of Biomedical Engineering
Duke University
Durham, NC, 27708, USA
ch@duke.edu

Marjorie Letitia Hubbard
Department of Biomedical Engineering
Duke University
Durham, NC, 27708, USA
letitia.holden@duke.edu

***Abstract*—In 1970, Heppner and Plonsey formulated the first model of cardiac tissue that was coupled to a description of the membrane currents to study impulse propagation. The model was consisted of two cardiac cells separated by a gap junction. Their model predicted a gap specific resistance of 4 Ohm- cm2 was needed for successful transmission, a value similar to the value obtained experimentally. In 1984, Barr and Plonsey presented the first model of propagation in two-dimensional cardiac tissue that incorporated both the intracellular and interstitial spaces. This model recapitulated the theoretical predictions of Muler and Markin, and demonstrated that the conductivities of both spaces impact the flow of membrane currents. These two important contributions have led to the rapid development of tissue models to assist in uncovering the mechanisms of arrhythmia and defibrillation. Here we present models of cardiac tissue that combines details of cell shape and gap junction distributions with a representation of the extracellular space. Such models may be useful to understand how disease induced changes in the tissue microstructure impact propagation and arrhythmogenesis.**

Keywords—Bidomain, Tissue Models, Impulse Propagation

I. INTRODUCTION

The first model of cardiac tissue that included a biophysically inspired model of the membrane was developed by Heppner and Plonsey in 1970 to elucidate the magnitude of the gap junction conductance needed to support propagation [1]. The model consisted of two "cells" connected by a resistive gap junction region and incorporated a simple model of the membrane currents as given by Noble [2]. The model predicted changes in the action potential upstroke, such as the presence or pre-potentials, resulting from transmission across the gap that would be shown experimentally by Spach and colleagues almost a decade later [3].

The effect of the gap junction on both normal and abnormal impulse propagation became an important focus of cardiac electrophysiology for the next 40 years. Experimental evidence emerged showing a relationship between cardiac structure and arrhythmogenesis in the heart [4]. These experiments also drove the development of computer models to become increasingly realistic. Unfortunately, computational constraints forced certain choices about how best to represent the tissue mathematically [5]. The early two and three-dimensional models ignored the details of cellular architecture and considered the tissue as a continuum. One advantage of this description was the ability to apply traditional numerical methods like finite differences and finite elements. One feature of tissue structure that was challenging to incorporate in multi-dimensional tissue models was the interstitial space. In 1969, Otto Schmidt presented a conceptual model of cardiac tissue where the intracellular and interstitial spaces could be described as "interpenetrating domains'' that occupied the same physical space and were coupled through the membrane [6]. To enable this representation, the electrical properties of each domain would need to be scaled appropriately to the new volume. Muler and Markin formalized this model of a bi-syncytium and predicted the effect of different degrees of anisotropy in both spaces on the shape of a wavefront of propagation in two dimensions [7]. In 1984, Barr and Plonsey [8] developed a computer model of a sheet of bi-syncytial tissue (termed by Tung for cardiac muscle as the bidomain [9]) in which the intracellular and interstitial spaces were connected by an excitable membrane represented by a Hodgkin Huxley model [10]. The model showed that properties of the interstitial space not only affected the wavefront as predicted by Muler and Markin but also affected the time course of the action potential. The active bidomain model has allowed the ability to study the effects of extracellular stimuli or fields on wavefront initiation and dynamics as well as understand the basis of clinically recorded extracellular waveforms on the heart surface,

The majority of cardiac tissue models have assumed mostly normal or idealized cardiac structure. There is growing evidence, however, that a number of arrhythmias like atrial fibrillation (AF) are a consequence of changes in tissue structure, primarily fibrosis, due to aging or disease [11]. The disease process leads to changes in the extracellular/interstitial environment, such as the deposition of collagen and changes in the distribution and the magnitude of the gap junction conductances connecting cells. The increased heterogeneity in both spaces affect the speed and direction of wavefront propagation and enhance the likelihood of the formation of small zones of localized conduction failure or anchors for reentry, producing a substrate that is prone to arrhythmia. To capture the diseased induced changes in structure, the next generation of tissue models will need to be formulated to incorporate the heterogeneity of properties of both spaces. In this work, we briefly explore some of the approaches that could be used to model the microstructural changes associated with disease.

II. MODELS

The bidomain model was formally developed under the assumption that the intracellular and interstitial spaces are continuous [12]. Specifically, the bidomain model consists of the equations for the intra- and interstitial/extracellular potentials, Φ_i and Φ_e, coupled through the transmembrane potential, $V_m = \Phi_i - \Phi_e$, for

$$\begin{aligned} \nabla \cdot D_i \nabla \Phi_i &= \beta \left\{ C_m \frac{\partial V_m}{\partial t} + I_{ion}(V_m, q) \right\}, \\ \nabla \cdot D_e \nabla \Phi_e &= -\beta \left\{ C_m \frac{\partial V_m}{\partial t} + I_{ion}(V_m, q) \right\}, \qquad (1) \\ \frac{\partial q}{\partial t} &= \mathsf{M}(V_m, q), \end{aligned}$$

$x \in \Omega$ and $t > 0$:

where $\Omega \subset \mathsf{R}^d$ ($d > 0$) is the bounded physical domain occupied by the cardiac tissue; q is a set of state variables such as ionic concentrations which define the physiological state of the cellular structures; β is a surface-to-volume ratio of cardiac cells, C_m is the membrane capacitance per unit area and D_i, D_e are *specific* conductivity tensors in intra- and extracellular spaces respectively; $I_{ion}(V_m, q)$ and $\mathsf{M}(V_m, q)$ are functions approximating the cellular membrane dynamics.

A. 1D and 2D Discontinuous Bidomain

While the bidomain usually represents a continuum, the concept can be extended to discrete or heterogeneous tissue. Spach, et al. developed a "2-domain" model of cardiac tissue in which a monolayer of myocytes connected via gap junctions was linked to passive capillaries through an interstitial space [13]. The model showed that the resistance of the capillary wall and the physical separation of the active and passive layers both affected the shape of the rising phase of the action potential. These results suggested for the first time that the loading effects of passive elements such as capillaries and fibroblasts in the interstitial region could affect the propagating impulse.

Simulations have also revealed that extracellular properties can modulate the effects of the intracellular heterogeneities. For example, Hubbard et al. showed in a 1D bidomain that uniformly increasing the interstitial resistivity causes an increase in intracellular delay, but a decrease in gap junction delay [14]. In poorly-coupled fibers, this translates to a flattening of conduction velocity that is not observed in continuum models with increased interstitial resistivity, suggesting a need for discrete models in diseased regions of tissue with high source-load mismatch.

B. 3D Discontinuous Bidomain

Hooks et. al. simulated wavefront propagation in a three-dimensional discontinuous bidomain representing a slab of tissue that was reconstructed from confocal data [15]. Anisotropy in the intracellular and extracellular architecture was defined with spatially varying conductivity tensors that incorporated fiber rotation and intracellular discontinuity across interlaminar clefts in the extracellular space. The model represented disruption of cellular connections across cleavage planes by removing elements of the trilinear mesh from the intracellular domain and applying no-flux boundary conditions along the resulting internal intracellular domain boundaries. The model suggested that clefts between layers of myocytes can alter the flow of current provide and much like intracellular discontinuities like gap junctions, could provide an additional mechanism for bulk activation of tissue during defibrillation

C. 3D Bundle Model

One of the key assumptions of the bidomain model is that two spaces are be defined to occupy the same physical space. In tissue, the interstitial spaces are typically 10-20% of the total volume fraction [16]. By allowing both spaces to occupy the total volume, it is possible to use the same spatial discretization. However, one approach to incorporating interstitial and intracellular heterogeneity is to represent each domain a spatially distinct.

Wang et al. developed a model of a bundle of coupled and uncoupled cardiac fibers embedded in a uniform extracellular space [17]. Instead of using a bidomain model, they applied the boundary element method where only the surface membrane of each fiber was discretized. They assumed one active fiber surrounded by passive fibers and found that when the when the fibers were uncoupled with an inter-fiber spacing of 1 nm, the conduction velocity was 15% slower for a fiber inside the bundle compared to a fiber near the surface. When the fibers were coupled, however, conduction velocity was the same for internal and surface fibers and the velocity was slightly larger than the conduction velocity of the uncoupled inner fiber. Although conduction velocity was the same, the wavefront was concaved and waveshape characteristics varied with depth into the bundle core. Wang et al. showed that an unequal distribution of extracellular space created a interstitial gradient transverse to the bundle, increasing the load felt by the outer fibers. While these results were consistent with those obtained using a bidomain with an adjoining bath [18], the method provides a framework for representing each space as spatially distinct.

D. 3D Microdomain

One disadvantage of the BEM approach is that it requires that the interstitial domain have homogenous properties. The incorporation of heterogeneous properties in the interstitial space in 3D requires a different method such as finite elements. Stinstra et al. [19] used an FEM approach to extend the model of Spach et al. into three dimensions. In the model, 64 or 132 myocytes were stacked inside an extracellular matrix such that, at some locations, the myocytes adjoined neighboring cells while in other regions there were small laminar sheets of extracellular space separating myocytes. The model can be viewed as multiple non-overlapping compartments: a single compartment for the extracellular space and separate compartments for each myocyte in the model. Here Laplace's equation holds for the intracellular and extracellular spaces, namely

$$\begin{aligned} \nabla \cdot \sigma_i \nabla \Phi_i &= 0, \\ \nabla \cdot \sigma_e \nabla \Phi_e &= 0 \end{aligned} \tag{2}$$

where σ_i and σ_e are the intracellular and interstitial conductivities, respectively. For the surfaces separating the intracellular and extracellular spaces, the following set of boundary conditions apply.

$$\begin{aligned} (\sigma_i \nabla \Phi_i) \cdot \hat{n} &= -(\sigma_e \nabla \Phi_e) \cdot \hat{n} = I_m \\ &= C_m \frac{d(\Phi_i - \Phi_e)}{dt} + I_{ion}(V_m, q) \end{aligned} \tag{3}$$

where I_m is the membrane current, and $\hat{n}$ is the normal vector at the boundary. For boundaries separating two myocytes, a surface resistance and capacitance associated with the gap junction current I_{gap} gives rise to the following conditions connecting cell 1 to cell 2, namely

$$\begin{aligned} (\sigma_{i2} \nabla \Phi_{i2}) \cdot \hat{n} &= I_{gap} = \\ & C_{gap} \frac{d(\Phi_{i1} - \Phi_{i2})}{dt} + g_{12}(\Phi_{i1} - \Phi_{i2}) \end{aligned} \tag{4}$$

$$\begin{aligned} (\sigma_{i2} \nabla \Phi_{i2}) \cdot \hat{n} &= -I_{gap} = \\ & -C_{gap} \frac{d(\Phi_{i1} - \Phi_{i2})}{dt} - g_{12}(\Phi_{i1} - \Phi_{i2}) \end{aligned} \tag{5}$$

where g_{12} and C_{gap} are the gap conductance between the two cells and the gap specific capacitance, respectively.

The model was shown to give rise to experimentally measured propagation velocities using only parameters from histology and allows the ability to compute both intracellular and extracellular potentials. This histologically realistic model allows for the inclusion of specific variations in myocyte size and coupling, and other cell types and compartments (e.g. fibroblasts and capillaries) that may be affected by disease.

III. Discussion

Models of cardiac tissue have exhibited rapid growth over the past four decades. The bidomain approach has been used to represent realistic heart geometries and fiber orientations. The membrane models describing the ion fluxes have grown in sophistication including Markov state descriptions of channel mutations [20]. These bidomain models are being used in combination with experiments to elucidate mechanisms of arrhythmia and to design or optimize new therapeutic interventions [21]. Despite the sophistication, however, there is no consensus as to how best to incorporate the microstructural changes that accompany ischemia, infarction or disease. Because both simulation and experiments have shown conclusively that propagation is profoundly affected by the tissue properties, the 3D microdomain model represents an important step in the evolution of cardiac tissue models. Although not computationally tractable to extend to a whole heart, the 3D microdomain can be used to determine how microstructural changes of shape, structure, or cellular composition are best converted into the associated bidomain parameters. Alternatively, the microdomain model may need to be embedded into the bidomain in scenarios that involve critical regimes of conduction failure due to the discrete structure. Regardless of the approach, the use of the microdomain model will require better information as to how disease affects the intracellular and interstitial spaces at a microscopic level. Advances in optical imaging and immunohistochemistry offer hope that this information can be obtained in a relatively straightforward manner. But until then, tissue models will make use of incomplete knowledge of critical parameters affecting conduction and as a consequence may limit the predictive power. It is important that structural models of the heart evolve in manner analogous to models of the membrane so that they can serve as a better tool in understanding the mechanisms of arrhythmia.

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