Modeling electrical activity of myocardial cells incorporating the effects of ephaptic coupling

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Existing models of electrical activity in myocardial tissue are unable to easily capture the effects of ephaptic coupling. Homogenized models do not account for cellular geometry, while detailed spatial models are too complicated to simulate in three dimensions. Here we propose a unique model that accurately captures the geometric effects while being computationally efficient. We use this model to provide an initial study of the effects of changes in extracellular geometry, gap junctional coupling, and sodium ion channel distribution on propagation velocity in a single 1D strand of cells. In agreement with previous studies, we find that ephaptic coupling increases propagation velocity at low gap junctional conductivity while it decreases propagation at higher conductivities. We also find that conduction velocity is relatively insensitive to gap junctional coupling when sodium ion channels are located entirely on the cell ends and cleft space is small. The numerical efficiency of this model, verified by comparison with more detailed simulations, allows a thorough study in parameter variation and shows that cellular structure and geometry has a nontrivial impact on propagation velocity. This model can be relatively easily extended to higher dimensions while maintaining numerical efficiency and incorporating ephaptic effects through modeling of complex, irregular cellular geometry.

cardiac electrophysiology | extracellular conductivity | microdomain effects

While gap junctional coupling is usually considered to be the primary mechanism for action potential propagation, there is evidence that other mechanisms are important. In particular, only a moderate reduction of cardiac propagation velocity was found in murine hearts with inactivated Connexin43 (Cx43) gene (1). In mice with heterozygous Cx43[±] down-regulation, either a 23–44% decrease in propagation velocity (2–4) or no discernible decrease in propagation velocity (5–8) was found. In Cx43^{−/−} mice with no expression of the protein, propagation was still found, although discontinuous and at much slower speeds (7). These experimental findings are in conflict with the classical understanding of how gap junctions determine propagation velocity.

One possible explanation for these intriguing observations is that ephaptic (i.e., field effect) coupling may be significant (1, 9–12). However, the study of ephaptic effects is made difficult by the fact that these effects are most important in microdomains such as junctional clefts.

Existing homogenized models, while computationally accessible, are not able to deal with the effects of microdomains and hence do not capture the effects of ephaptic coupling (13, 14). On the other hand, detailed spatial models have shown that geometry plays an important role in the conduction velocity but are too expensive to implement for a full 3D tissue (11, 12, 15–19).

Here we present a model that captures the effects of the intricate cellular geometry with simplifications that will allow the model to be extended more readily to three dimensions while maintaining computational efficiency. With this model we expect to be able to study the effects of changes in geometry (for example, due to hydration or dehydration) and pathology (such as ischemia) on propagation velocity.

In this paper, we present the model and show results of simulation for an idealized 1D strand of cardiac cells. We find that

ephaptic coupling increases propagation velocity at low gap junctional conductivity while it decreases propagation at higher conductivities. We also find that conduction velocity is relatively insensitive to gap junctional coupling when ionic channels are located entirely in the junctional clefts and junctional space is small. The consistency of these results with previous findings (11) and a comparative study with a more detailed model presented in *Discussion* validate the assumptions made in this model.

The Model

The complicated structure of cardiac myocytes cells can be described as intercalated, irregular bricks. These long cells are surrounded by a thin layer of extracellular space, of which the junctional cleft is particularly narrow and tortuous. The two domains, the intracellular and extracellular spaces, are separated by cell membranes. We expect that the complicated geometry can cause the electrical interactions to also be highly irregular.

The classical derivation of the equations for action potential propagation makes use of cable theory, in which the extracellular resistance is assumed to be isopotential zero and the intracellular space conductivity is taken to be proportional to the cross-sectional area of the cell (11, 20). While this is the appropriate approximation for axons in a bath, it may not be so for cardiac cells. In fact, the bidomain model allows for resistance in both the intracellular and extracellular spaces.

Ephaptic coupling occurs because the junctional space resistivity is high and therefore is not isopotential with the rest of extracellular domain. This is the result of the small cross-sectional area in the narrow gaps between the ends of cells. With this realization, it seems apparent that it is the resistivity of the extracellular space that is the most important determinant of propagation velocity, not the resistivity of intracellular space. Thus, in the model here, we make the assumption that the intracellular space of each cell is isopotential and the extracellular potential is spatially varying. Quantitatively, the resistance in the intracellular space is subdominant to that of the extracellular space. The intracellular conductivity of 6.7 mS/cm (21) with cell radius 0.001317 cm (cell diameter is approximately 1/6 of the cell length 0.0158 cm) (13) gives rise to an intracellular longitudinal conductance of $6.7(\pi 0.001317^2)/0.0158 \approx 2.3 \times 10^{-3}$ mS. The extracellular conductivity of 20 mS/cm with extracellular width 1.33×10^{-5} cm (see Table 1) gives rise to an approximate extracellular longitudinal conductance of $20(2\pi)(0.001317)(1.33 \times 10^{-5})/0.0158 \approx 1.39 \times 10^{-4}$ mS. Similar calculations can be done for the transverse conductances. Because the intracellular conductance is at least an order of magnitude larger than that of the extracellular space, we make the simplifying assumption that the intracellular space is represented by a single potential, whereas the potential in the extracellular space requires detailed

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Table 1. Parameter values

Parameter	Value	Reference
C_e	20 mS/cm	Neu and Krassowska (14)
C_m	1 μ F/cm ²	Weidmann (25)
$W(x)$ (cleft)	1.5×10^{-6} cm	Sperelakis (10)
$W(x)$ (membrane)	1.33×10^{-5} cm	Extracellular volume 2%
$\bar{g}_{jk}$	259 mS/cm ²	Total gap junctional and intracellular resistance (22)
$\bar{C}_{\text{eff}t}$	3×10^{-5} cm	
$\bar{\theta}_m$	1	

spatial resolution. The validity of this assumption is further corroborated by a comparison with a more detailed model (see *Discussion* section), in which the intracellular potential is allowed to vary in space. This assumption is also consistent with the results of ref. 16, in which a detailed 3D model shows isopotential cellular interiors with spatially varying extracellular potentials. Additionally, given the narrow gaps between cells, the extracellular potential is assumed to be uniform across the shortest distance between cells. This enables us to view the extracellular space as a 2D surface rather than a 3D volume. The width of the extracellular space is factored into the computation of the conductivity of the 2D surface at any given position.

The setup is as follows: The j th cell occupies the space Ω^j . The extracellular space is the complement of intracellular space; however, because this is generally quite thin, we view extracellular space as the 2D surface of 3D cells, hence the extracellular space is $\Omega_e = \cup_j \partial\Omega^j$. Notice that the junctional clefts are part of extracellular space. For each point x in the extracellular space there are $\kappa(x)$ adjoining cells specified by the index set $E(x)$. For x on the boundary of the tissue, $\kappa(x) = 1$, and otherwise $\kappa(x) = 2$ (with the exception of points at corners, which will not matter in what follows). Similarly, each cell has neighbors to which it is coupled by gap junctions, denoted by the indices I^j . We denote the gap junctional coupling strength between cell j and its neighbors by $g_{jk}(x)$ for $k \in I^j$ and g_{jk} can be nonzero only for x such that cells j and k are adjoining (i.e., $x \in \partial\Omega^j \cap \partial\Omega^k$). The membrane capacitance is denoted by C_m , extracellular conductivity by C_e , extracellular width by $W(x)$, ionic currents by I^j_{ion} , intracellular potential by ϕ^j_i , and extracellular potential ϕ_e . See Figs. 1 and 2 for the idealized geometrical and discretized electrical notations.

Current conservation in the extracellular space is

$$-\nabla \cdot (W(x)C_e \nabla \phi_e) = \sum_{j \in E(x)} \left(C_m \frac{\partial}{\partial t} (\phi^j_i - \phi_e) + I^j_{\text{ion}} (\phi^j_i - \phi_e x) \right), \quad [1]$$

and current conservation in the intracellular space is

$$\begin{aligned} \chi^j C_m \frac{\partial \phi^j_i}{\partial t} - C_m \frac{\partial}{\partial t} \int_{\partial\Omega^j} \phi_e dx + \int_{\partial\Omega^j} I^j_{\text{ion}} (\phi^j_i - \phi_e x) dx \\ = \sum_{k \in I^j} \int_{\partial\Omega^j} g_{jk}(x) (\phi^k_i - \phi^j_i) dx, \end{aligned} \quad [2]$$

Fig. 1. Notation for a cylindrical strand of cells.

where $\chi^j = \int_{\partial\Omega^j} dx$ is the total surface area of the j th cell. We rearrange these to put them into a somewhat familiar form,

$$\begin{aligned} \kappa(x) C_m \frac{\partial \phi_e}{\partial t} - C_m \frac{\partial}{\partial t} \sum_{j \in E(x)} \phi^j_i = \nabla \cdot (W(x) C_e \nabla \phi_e) \\ + \sum_{j \in E(x)} I^j_{\text{ion}} (\phi^j_i - \phi_e x), \end{aligned} \quad [3]$$

$$\begin{aligned} \chi^j C_m \frac{\partial \phi^j_i}{\partial t} - C_m \frac{\partial}{\partial t} \int_{\partial\Omega^j} \phi_e dx = \sum_{k \in I^j} \int_{\partial\Omega^j} g_{jk}(x) (\phi^k_i - \phi^j_i) dx \\ - \int_{\partial\Omega^j} I^j_{\text{ion}} (\phi^j_i - \phi_e x) dx. \end{aligned} \quad [4]$$

Methods

This system of differential equations can be written in the form

$$\frac{\partial}{\partial t} A \Phi = L \Phi + g(\Phi), \quad [5]$$

where A and L are linear operators, L being a Laplacian-like operator. For numerical simulations, A and L are spatially discretized (see Fig. 2) via a standard cell-centered finite difference scheme, with resultant operators $\tilde{A}$ and $\tilde{L}$. Because these equations resemble a parabolic system, we use the Crank–Nicholson scheme, where $\Phi^n = \Phi(t = t_n)$, for temporal discretization

$$\frac{\tilde{A} \Phi^{n+1} - \tilde{A} \Phi^n}{\Delta t} = \frac{\tilde{L} \Phi^{n+1} + \tilde{L} \Phi^n}{2} + g(\Phi^n), \quad [6]$$

providing a method to update the potentials of the system.

For an initial study of the effects of the geometry of extracellular space on conduction, we consider a single strand of cylindrically symmetric cardiac cells. The entire strand is surrounded by a layer of extracellular space, and neighboring cells are separated by narrow junctional clefts. Cells are also connected end-to-end by uniformly distributed gap junctions (see Fig. 1). Ionic currents are given by the simplified Beeler–Reuter equations,

$$I^j_{\text{ion}} (\phi^j_i - \phi_e x) = -i_K - \theta(x) i_{Na} - i_l \quad [7]$$

where i_K , i_{Na} , and i_l represent the currents from the potassium ions, sodium ions, and leakage component; details are given in *Appendix*. In Eq. 7, $\theta(x)$ represents the distribution of sodium ion channels at position x , with $\theta(x) = \theta_j$ if x is in the junctional space and $\theta(x) = \theta_m$ elsewhere on the membrane. We include this parameter due to experimental evidence of increased density of sodium channels on cell ends (10, 11, 22, 23). The total number of sodium ion channels is held constant, so that

Fig. 2. Discretized electrical circuit diagram for cells.

from the rest of the extracellular space. Fig. 4*B* shows the junctional-leading case, where the potentials in the cleft at the propagation front are higher than those of the extracellular space around the rest of the cell. We remark here that while junctional-lagging and junctional-leading effects can be elicited in different ways to varying degrees, for these simulations junctional-lagging clefts were created by removing all sodium ion channels in the clefts and reducing the conductivity in the extracellular clefts to 15% of the nominal value. Junctional-leading, on the other hand, was produced by distributing all the channels to the ends of cells and allowing the conductivity in the clefts to remain at its nominal value. Gap junctional conductivity in both these cases was kept at its nominal value.

For a complete study of the parameter variation, we change the conductivity of the gap junctions, the distribution of the sodium ion channels, and the width of the junctional cleft and find the resulting propagation speeds. In Fig. 5, we show conduction velocities for gap junctional conductivities g_{jk} that range from 0% to 100% of the nominal conductivity values. The distribution of nonjunctional sodium ion channels θ_m ranges from 0 to A_T/A_m , which is from 0% to 108.3% of its nominal value of 1. The width of the junctional cleft varied in such a way that the effective conductivity C_{eff} changed between 0% and 100% of its nominal value. At low gap junctional conductivities, ephaptic effects generally increase the conduction velocity, whereas at high gap junctional conductivities, the ephaptic effects are slightly deleterious. This is evident in the reversal of trends shown from left to right in the top panel of Fig. 5. Additionally, for small junctional cleft widths, as the ionic channels are distributed more heavily to the ends of the cells, the gap junctional conductivity plays a smaller and smaller role in determining the conduction velocity. The bottom panel of Fig. 5 shows the curves of conduction speeds appearing to collapse together at small cleft widths as the distribution of channels is increasingly placed on the ends of cells.

Discussion

We have presented a unique approach to modeling the electrical coupling of myocardial cells by assuming an isopotential cellular interior, along with a 2D extracellular space. This model, given by

Eqs. 3 and 4, can be simulated more efficiently than a full 3D model, yet is able to capture the effects of the details of cellular geometry. Our initial study of a 1D strand of cells shows that the fraction of extracellular space [in changing $W(x)C_e$ in the extracellular space at the ends of the cells] affects the propagation speed greatly, in agreement with ref. 19. We also find that with large gap junctional conductivity, the decreased conductivity in the junctional cleft leads to an increase in propagation speed, agreeing with previous numerical studies (11, 18). At low gap junctional conductivities, the ephaptic coupling increases action potential propagation speed and can even prevent conduction failure in the case of no gap junctional coupling, similar to findings by (11, 12).

The assumption of an isopotential intracellular space, based on relative conductances, can be further studied by a numerical comparison between our model and one in which the intracellular space has been discretized in the longitudinal direction. Fig. 6 shows the results of this comparison. The potential gradient at the moving front of the action potential in the intracellular space is subdominant to that of the extracellular space. When all parameters are taken at nominal values, the error in propagation velocity caused by smoothing out the intracellular potential is approximately 0.4%. Any reduction in the coupling from nominal value results in decreasing the steepness of intracellular potential gradients, amplifying the dominance of the extracellular potential gradient.

For large gap junctional conductivity, ephaptic effects are mostly deleterious. As the conductivity in the clefts decrease, the cell ends depolarize quickly and do not aid in the positive feedback loop of the ionic current that is necessary to enhance the propagation speed. Additionally, reduced conductivity in the clefts slows the diffusion into the rest of the extracellular space. These two effects lower the propagation speed from that of the nominal values.

As the gap junctional conductivity decreases, the baseline (shown in gray in the top panel of Fig. 5), in which none of the ionic channels are on the ends of the cell, decreases steadily. For small gap junctional coupling, cell-to-cell communication depends heavily on the cleft space. Small cleft width and sodium

Fig. 5. Propagation velocities as the gap junction conductivity changed between 0% and 100% of its nominal value. (Top) Trends are shown as the junctional cleft width varies from 0% to 100% of its nominal value, for differing ionic channel distributions. (Bottom) Trends are shown as the junctional cleft width varies from 0% to 100% of its nominal value, for differing gap junctional coupling.

Fig. 6. The potentials of the detailed and simplified models are closely matched at nominal values. The intracellular potential gradients at the front of the action potential are subdominant to those of the extracellular space. (Inset) The intracellular gradient seen in the detailed model is flattened in the simplified model.

channels that favor the ends of the cells will greatly enhance propagation speeds through ephaptic effects (see [Movies S3](#) and [S4](#)).

At small cleft conductivities and with ionic channel distributions that favor the ends of the cells, the coupling of the gap junctions has a less dramatic effect on the propagation velocity. Localization of ionic channels on the ends of cells has been shown in several studies (10, 11, 22, 23), and in conjunction with our findings, may provide an explanation for the slight reduction in conduction speeds with the down-regulation of Cx43 found in experiments (1).

The parameters taken in this study are values extracted from experimental data. However, there is a large variation in the literature as to the range of these values. Changing the parameters that we use here will have a quantitative, but not qualitative, difference in the results. The trends established here by parameter variation make it clear that the complex cellular structure has a nontrivial and significant impact on the propagation velocity of an action potential. Similarly, the qualitative nature of these trends is not affected significantly by the details of the ionic currents, such as *L*-type calcium or other fast inward sodium channel descriptions.

A fundamental difference between our model and that of ref. 11 is that we take cells to be isopotential, while in ref. 11 extracellular space is taken to be isopotential. This feature of our model, which we have shown to be quantitatively valid, not only makes it computationally more tractable for higher dimensional tissue while still providing accurate results, but also allows us to incorporate complex, irregular geometry of cells. By allowing var-

iations in the width of the extracellular microdomain (this cannot be done if the extracellular space is taken to be isopotential, which is a common assumption), we will additionally be able to investigate possible side-to-side, nonjunctional ephaptic effects. We have shown in this study that ephaptic effects have the potential to greatly modify propagation speed. Such modeling is critical for realistic simulation of myocardial tissue.

In the future, we will study the effect of parameter variation in higher dimensional tissue with other additions, such as additional ionic currents. With this model, we will be able to study different geometries of cells and explore the dependence of ephaptic effects on sodium ion channel distribution and extracellular width. The simplifications we have presented in this paper improve upon existing microscale models, which can be used in a multiscale model to fully simulate myocardial tissue. Furthermore, the results of our 1D study suggest that extracellular currents cannot be neglected, and the approach described here could have a significant impact on our understanding of cardiac excitation propagation.

Appendix

Ionic currents for the simplified Beeler–Reuter equations:

$$i_K = 0.35 \left(\frac{4(\exp(0.04(v + 15)) - 1)}{\exp(0.08(v - 17)) + \exp(0.04(v - 17))} + \frac{0.2(v - 47)}{1 - \exp(-0.04(v - 47))} \right), \quad [9]$$

$$i_{Na} = 2.384 \left(\frac{\alpha}{\alpha + 4 \exp(\frac{-v}{18})} \right)^3 (v - 115), \quad [10]$$

$$\alpha = \frac{2.5 - 0.1v}{\exp(2.5 - 0.1v) - 1}, \quad [11]$$

$$i_l = 0.3(v - 10.6), \quad [12]$$

where $v = \phi_i^j - \phi_e - V_{eq}$ is the transmembrane potential. Here V_{eq} represents the equilibrium potential of -70 mV.

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1. Yao J-A, Gutstein DE, Liu F, Fishman GI, Wit AL (2003) Cell coupling between ventricular myocyte pairs from connexin43-deficient murine hearts. *Circ Res* 93:736–743.
2. Guerrero P, et al. (1997) Slow ventricular conduction in mice heterozygous for a Connexin43 null mutation. *J Clin Invest* 99:1991–1998.
3. Thomas SA, et al. (1998) Disparate effects of deficient expression of connexin43 on atrial and ventricular conduction: Evidence for chamber-specific molecular determinants of conduction. *Circulation* 97:686–691.
4. Eloff BC, et al. (2001) High resolution optical mapping reveals conduction slowing in connexin43 deficient mice. *Cardiovasc Res* 51:681–690.
5. Morley GE, et al. (1999) Characterization of conduction in the ventricles of normal and heterozygous cx43 knockout mice using optical mapping. *J Cardiovasc Electr* 10:1361–1375.
6. Vaidya D, et al. (2001) Null mutation of connexin43 causes slow propagation of ventricular activation in the late stages of mouse embryonic development. *Circ Res* 88:1196–1202.
7. Beauchamp P, et al. (2004) Electrical propagation in synthetic ventricular myocyte strands from germline connexin43 knockout mice. *Circ Res* 95:170–178.
8. Thomas SP, et al. (2003) Impulse propagation in synthetic strands of neonatal cardiac myocytes with genetically reduced levels of connexin43. *Circ Res* 92:1209–1216.
9. Copene ED, Keener JP (2008) Ephaptic coupling of cardiac cells through the junctional electric potential. *J Math Biol* 57:265–284.

10. Sperelakis N, McConnell K (2002) Electric field interactions between closely abutting excitable cells. *IEEE Eng Med Biol Mag* 21:77–89.
11. Kucera JP, Rohr S, Rudy Y (2002) Localization of sodium channels in intercalated discs modulates cardiac conduction. *Circ Res* 91:1176–1182.
12. Mori Y, Fishman GI, Peskin CS (2008) Ephaptic conduction in a cardiac strand model with 3d electrodiffusion. *Proc Natl Acad Sci USA* 105:6463–6468.
13. Hand PE, Griffith BE, Peskin CS (2009) Deriving macroscopic myocardial conductivities by homogenization of microscopic models. *B Math Biol* 71:1707–1726.
14. Neu J, Krassowska W (1993) Homogenization of syncytial tissues. *Crit Rev Biomed Eng* 21:137–199.
15. Stinstra JG, Hopfenfeld B, MacLeod RS (2005) On the passive cardiac conductivity. *Ann Biomed Eng* 33:1743–1751.
16. Stinstra JG, MacLeod RS, Henriquez CS, A comparison between a 3D microscopic model of anisotropic conduction in cardiac tissue and the bidomain model., in press.
17. Mori Y, Jerome JW, Peskin CS (2007) A three-dimensional model of cellular electrical activity. *Bulletin of the Institute of Mathematics, Academia Sinica* 2:367–390.
18. Roberts SF, Stinstra JG, Henriquez CS (2008) Effect of nonuniform interstitial space properties on impulse propagation: A discrete multidomain model. *Biophys J* 95:3724–3737.
19. Stinstra JG, Roberts SF, Pormann JB, MacLeod RS, Henriquez CS (2006) A model of 3D propagation in discrete cardiac tissue. *Comput Cardiol* 33:41–44.