Action Potential Propagation in a Thick Strand of Cardiac Muscle

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A theoretical model of action potential propagation in a thick strand of cardiac muscle is presented. The calculation takes into account the anisotropic and syncytial properties of the tissue, the presence of the interstitial space, the effect of the surrounding tissue bath, and the variation of the potential both along the strand length and across the strand cross section. The bidomain model is used to represent the electrical properties of the tissue, and the Ebihara-Johnson model is used to represent the properties of the active sodium channels. The calculated wave front is curved, with the action potential at the surface of the strand leading that at the center. The rate of rise of the action potential and the time constant of the action potential foot vary with depth into the tissue. The velocity of the wave front is nearly independent of strand radius for radii greater than 0.5 mm. The conduction velocity decreases as the volume fraction of the interstitial space decreases. In the limit of tightly packed cells, an action potential propagates quickly over the surface of the strand; the bulk of the tissue is then excited by a slow inward wave front initiated on the surface. This model does not predict an increase in conduction velocity when cells are tightly packed, a hypothesis that has been proposed previously to explain the fast conduction velocity in Purkinje fibers of some species. (Circulation Research 1991;68:162–173)

Since the early experiments of Fozzard and Weidmann, many issues in cardiac electrophysiology have been analyzed using the one-dimensional cable model. However, recent theoretical and experimental studies question the applicability of this model to thick strands of cardiac muscle. The cable model is based on the assumption that the radius of the strand is small compared with the spatial extent of the depolarization wave front, which can be 0.5 mm or less. When considering a papillary muscle with a radius of 0.5 mm or larger, we expect significant deviations from one-dimensional behavior. Furthermore, the cable model is appropriate for single fibers, but cardiac muscle is a multicellular tissue, with each cell surrounded by interstitial space and coupled to its neighbors through intercellular channels. Voltage gradients that significantly affect propagation can develop in the interstitial space.

Much evidence suggests that the one-dimensional cable model is not adequate. Sperelakis and Picone have shown that measurements of the passive length constant in a thick strand are influenced by the anisotropy. Fozzard determined a different membrane capacitance when he used subthreshold cable theory than when he calculated capacitance from the time constant of the foot of the action potential, a difference that may be due to the restricted interstitial space. Fundamental questions such as the dependence of conduction velocity on strand radius are presently unanswered. Suenson has presented evidence that the shape of the wave front across a strand of cardiac muscle is curved, with the action potential on the surface propagating ahead of that deeper in the strand. He suggests that this curvature may lead to an alternative explanation of the data presented by Spach et al, who used measurements of conduction velocity, rate of rise of the action potential, and the time constant of the action potential foot to conclude that propagation in cardiac muscle is discontinuous. Kleber and Rieger have shown that the interstitial space can have a dramatic impact on the electrical behavior of cardiac muscle. Several models have been developed to explain these observations, but few have adequately described the effect of strand thickness, anisotropy, and the interstitial space on wave front propagation.

In this paper we present a three-dimensional model of propagation along a thick strand of cardiac muscle. Henriquez and colleagues recently presented a model similar to ours. Using several approx-
We describe the electrical properties of cardiac tissue with the bidomain model, which is a continuum model that accounts for variations of the electrical potential averaged over many cells.\textsuperscript{21} The bidomain model was first derived in the late 1970s\textsuperscript{22-24} and has since been applied extensively in cardiac electrophysiology. It has been used to compute the intracellular and interstitial potentials when the transmembrane action potential is known\textsuperscript{4,5,25-28} and to calculate the transmembrane potential induced in passive tissue in response to applied currents.\textsuperscript{29,30} In this paper we solve the more complex problem of calculating the transmembrane potential produced by active cardiac muscle. This computation is closely related to one-dimensional calculations of propagating action potentials,\textsuperscript{31-33} except that we take into account the variations of the potential with depth into the strand, the presence of anisotropy, and the effect of the interstitial space. Previous calculations similar in spirit to this one describe propagation in a strand using a two-dimensional cable model\textsuperscript{20} and in a two-dimensional sheet of cardiac tissue.\textsuperscript{34-36} Henriques and colleagues\textsuperscript{7-10} used the bidomain model to simulate propagation in a cylindrical strand of cardiac muscle, but they assumed equal anisotropy ratios for the tissue conductivities, used a Hodgkin-Huxley membrane model instead of one appropriate for cardiac muscle, and considered only steadily propagating wave fronts. Our calculations eliminate these restrictions.

Consider a cylindrical strand of cardiac tissue, such as a papillary muscle, of radius \( a \) and immersed in a saline bath (\( e \)) of conductivity \( \sigma_e \) (Figure 1). We use a cylindrical coordinate system to describe position, with the direction along the strand denoted by \( z \) and the distance from the center of the strand by \( \rho \). Throughout our discussion we assume axial symmetry, so the azimuthal angle \( \theta \) plays no role in our calculation. The tissue itself consists of two volumes (or domains), intracellular (\( i \)) and interstitial (\( o \)), separated by the cell membrane. Our goal is to calculate the potentials in the two domains (\( \Phi_i \) and \( \Phi_o \)) as well as the potential in the bath (\( \Phi_e \)).

The electrical properties of the two domains are assumed to be homogeneous and can be described by the conductivity tensors \( \sigma_i \) and \( \sigma_o \). We assume that the individual cardiac cells are oriented parallel to

![Figure 1. Schematic representation of a cylindrical strand of cardiac muscle of radius \( a \) lying in a tissue bath of conductivity \( \sigma_e \). A cylindrical coordinate system (\( \rho, \theta, \) and \( z \)) specifies position in the tissue. The strand is stimulated by two ring electrodes, an anode to the left and cathode to the right.](image-url)

The interstitial conductivity in the direction perpendicular to the strand can be modeled as\textsuperscript{5}

\[
\sigma_{io} = \frac{1-f}{1+f} \sigma_o
\]  

This model implies an anisotropy ratio of the interstitial space \( \sigma_{io}/\sigma_o \) of \( 1+f \). It is less clear how the intracellular radial conductivity relates to the microscopic parameters, but both theoretical\textsuperscript{35,37} and experimental\textsuperscript{38-40} considerations indicate that the anisotropy ratio of the intracellular space is about 10:

\[
\sigma_{ii} = 0.1 \sigma_{iz}
\]  

These relations would be more complicated if we used a more complex microscopic model of the tissue structure, in which case factors such as tortuosity might become important.\textsuperscript{41} Note that we are not...
restricted to tissues having equal anisotropy ratios ($\sigma_{1f}/\sigma_{2f}=\sigma_{3f}/\sigma_{op}$).

Current flows in the intracellular and interstitial domains and passes from one domain to the other by crossing the cell membrane. The total membrane current per unit volume ($I_m$) (outward current is positive) is related to the membrane current density by the surface-to-volume ratio ($\beta$). If the radius of the individual cardiac cells is $b$, then $\beta$ can be expressed in terms of the microscopic tissue parameters as

$$\beta = \frac{2f}{b}$$  

where we ignore contributions to $\beta$ from membrane folding or subcellular membranes such as transverse tubules.

The membrane current density contains one component due to the membrane capacitance per unit area ($C_m$) and another due to several different ionic channels ($I_{ion}$). We represent the active membrane properties using a model consisting of a passive (or leak) term and a fast sodium channel:

$$I_{ion} = g_L(\Phi_m - V_L) + g_{Na}m^3h(\Phi_m - V_{Na})$$  

where $\Phi_m$ is the transmembrane potential ($\Phi_m = \Phi_e - \Phi_i$), $g_L$ is the leak conductance per unit area, $V_L$ is the leak reversal potential (in this model, $V_L$ is equal to the rest potential), $g_{Na}$ is the maximum sodium conductance per unit area, $V_{Na}$ is the sodium Nernst potential, and $m$ and $h$ are gating parameters obeying Ebihara-Johnson kinetics. We restrict our attention to the depolarization phase of the action potential.

The influence of the saline bath on the electrical behavior of the tissue is of central importance in our model. At the interface between the tissue (a bidomain) and the bath (a monodomain), three boundary conditions must be met. The interstitial and bath potentials are equal because we assume that the interstitial space is contiguous with the bath. To ensure continuity of current, the component of the current density normal to the tissue surface is continuous when passing from the tissue to the bath. Finally, the intracellular current density normal to the tissue surface vanishes.

We can summarize the above considerations mathematically by the following equations:

**Tissue:**

$$J_i = -\sigma_i \nabla \Phi_i$$  

$$J_o = -\sigma_o \nabla \Phi_o$$  

$$\nabla J_i = -I_m$$  

$$\nabla J_o = I_m$$

**Membrane:**

$$I_m = \beta \left( C_m \frac{\partial \Phi_m}{\partial t} + J_{ion} \right)$$  

$$\Phi_m = \Phi_i - \Phi_o$$

**Bath:**

$$J_c = -\sigma_c \nabla \Phi_c$$  

$$\nabla J_c = 0$$

**Boundary conditions:**

$$\Phi_e = \Phi_o$$  

$$J_e \cdot n = J_c \cdot n$$  

$$J_e \cdot n = 0$$

where $J_i$, $J_o$, and $J_e$ are the current densities in the intracellular and interstitial domains and the bath, respectively, $t$ is time, $\nabla$ and $\nabla \cdot$ are the gradient and divergence operators, respectively, and $n$ is a unit vector normal to the tissue surface, pointing outward from the tissue into the bath.

We stimulate the tissue using two electrodes, an anode and cathode, which are located in the saline bath. In keeping with our assumption of axial symmetry, these are ring electrodes placed around the strand, not point electrodes as often used in experiments. The tissue bath is large but not unbounded; we assume that the strand lies centered in a cylindrical bath. A ground electrode in the bath provides a reference potential.

The values of the parameters in this model are listed in Table 1. Unless otherwise stated, we assume that the intracellular volume fraction is 0.75, the cell radius is 5 $\mu$m, and the strand radius is 0.5 mm. The membrane properties and cell radius are the same as those used by Spach, and the electrical properties of the intracellular and interstitial spaces are typical of the measurements by Kleber and Riegger.

The numerical implementation of the model is described in detail in the “Appendix.” Briefly, the equations reduce to a nonlinear ordinary differential equation for the transmembrane potential and a boundary value problem for the interstitial and bath potentials. At each time step the transmembrane potential is solved using the interstitial potential from the previous time step as its source. Then $\Phi_e$ and $\Phi_c$ are calculated at the new time step using the new transmembrane potential as their source. We use finite difference equations to approximate the differential equations, and the resulting system of difference equations is solved using a systematic overrelaxation algorithm. When comparing our results with one-dimensional cable theory, we solve the one-dimensional cable equation using an explicit algorithm (space step of 25 $\mu$m, time step of 0.25
Results

For our first simulation we consider a 0.5-mm-radius strand lying in a 4.0-mm-radius, 12.8-mm-long bath. The stimulating electrodes are 0.5 mm apart (cathode to the right) and 0.2 mm from the surface of the tissue; they pass a current of 2.5 mA for 0.5 msec, starting at \( t=0 \). A contour plot of the extracellular potential produced by this stimulus, as a function of \( \rho \) and \( z \), is shown in Figure 2. The position \( \rho=0 \) corresponds to the center of the strand, and the three-dimensional voltage distribution is obtained by rotating the plot about the \( z \) axis. The positions of the anode and cathode are denoted by dots. The electrodes have negligible width, so the potential at the position of the electrode goes to infinity. There is a

\[ \mu \text{sec} \], obtaining results consistent with those calculated by Spach.\textsuperscript{32}

**FIGURE 2.** The extracellular potential at \( t=0 \) as a function of cylindrical coordinates \( \rho \) and \( z \), produced by a 2.5 mA current in the stimulating ring electrodes (shown by dots). The isopotential lines are labeled in millivolts.

**FIGURE 3.** The transmembrane potential as a function of cylindrical coordinates \( \rho \) and \( z \) for several different times \((t=0.5, 1.0, 1.5, 2.0, 3.0, \text{ and } 4.0 \text{ msec})\). The isopotential lines are labeled in millivolts.
the transmembrane potential is primarily a passive response restricted to the surface of the strand. By \( t=1.0 \) msec, the passive hyperpolarization decays to a small value, but the depolarization gives rise to an action potential. This action potential is restricted to the strand surface, with the transmembrane potential at the strand center deviating by less than 10 mV from its resting value. For the next 2 msec, the wave front propagates both slowly inward and rapidly along the strand length. By \( t=3.0 \) msec, the inwardly propagating wave front reaches the center of the strand, after which the propagation becomes primarily longitudinal. There is a significant curvature to the wave front at this time, with the action potential along the surface fibers propagating nearly 0.6 mm ahead of that along the inner fibers. By \( t=4.0 \) msec, the curvature of the wave front is reduced, with a 0.3-mm separation between propagation at the surface and the center of the strand.

At \( t=8 \) msec, the wave front reaches a steady-state shape, as shown in Figure 4a. The action potential at the surface leads that at the center by about 0.2 mm at the point where the action potential rises most rapidly. The spatial extent of the rising phase of the action potential is different at the surface than at the center of the strand and is similar to that predicted by Henriquez and Plonsey. The intracellular and extracellular potentials are presented in Figures 4b and 4c. The isopotential lines for the intracellular potential are shaped quite differently than those for the transmembrane potential, particularly in the region of the action potential foot and the onset of the plateau. The extracellular potential shows a rapid drop near the surface of the strand and has a peak-to-peak magnitude of about 20 mV. The steady-state conduction velocity is 0.549 m/sec, typical for ventricular muscle. Besides stimulating the tissue with electrodes in the bath, we have initiated the action potential in several other ways, including launching a planar wave front. The steady-state shape of the wave front is the same in every case tested.

The transmembrane potential as a function of time is shown in Figure 5 at four locations: directly under the cathode \((z=1.7 \text{ mm})\) and at \( z=7.0 \text{ mm}\), both at the center and surface of the strand. The shape of the action potential at the surface of the strand under the cathode (Figure 5, position a) is determined in part by stimulus artifact. The action potential in Figure 5, position b, is created by the cylindrical wave front collapsing into the center of the strand (Figure 3) and therefore has a high (26.3 mV) peak potential \((V_{pk})\) and a fast \((409 \text{ V/sec})\) rate of rise \((V_{max})\). At \( z=7 \text{ mm}\), where the wave front has reached its steady state, \( V_{pk} \) and \( V_{max} \) are larger at the center of the strand \((16.7 \text{ mV}, 220 \text{ V/sec})\) than at the surface \((10.3 \text{ mV}, 159 \text{ V/sec})\). Figure 6 shows a phase-plane plot of the steady-state action potentials at the surface and center of the strand, compared with that calculated using the one-dimensional cable model. In one dimension, the action potential has a peak voltage of 15.5 mV, a maximum rate of rise of 192 V/sec, and an exponential foot (straight line in a phase plot) with a time constant \((\tau_{foot})\) of 291 \text{ \mu sec}\. Using the bidomain
model, we predict that the initial rise of the action potential is not exponential. If we arbitrarily define \( \tau_{foot} \) using the best-fit straight line in the phase-plane plot between \( \Phi_m \) of \(-75\) and \(-70\) mV, then at the center of the strand \( \tau_{foot} \) is 263 \( \mu\)sec, while at the surface it is 490 \( \mu\)sec.

We further compare the bidomain model with the one-dimensional cable model by considering the conduction velocity. Using the one-dimensional model, we calculated that an action potential has a conduction velocity of 0.655 m/sec when propagating along a single fiber that has a radius of 5 \( \mu \)m and an intracellular conductivity of 0.5 S/m and lies in a low resistance bath. If this fiber is surrounded by tissue with an intracellular volume fraction of 0.75 and an interstitial fluid conductivity of 1.5 S/m, so the ratio of intracellular to extracellular resistance is 1, then from one-dimensional theory we predict that the conduction velocity is 0.463 m/sec. Our value of 0.549 m/sec, found using the bidomain model, lies between these two limiting cases.

We have performed calculations for strands with radii ranging from 0.05 to 2.0 mm to determine how the curvature of the wave front and the propagation velocity depend on the strand radius. Computed steady-state wave fronts are shown in Figure 7 for \( a = 0.1, 0.2, 0.5, \) and 1.0 mm. The shape of the wave front becomes more curved at larger strand radii, with the action potential at the strand surface leading the center by approximately 0.6 mm for a 1-mm-radius strand. The conduction velocity as a function of strand radius is shown in Figure 8.

There are several limiting cases of the bidomain model that are of interest. For instance, we can set the bath conductivity equal to a low value (1.5 \( \times \) 10\(^{-6}\) S/m), simulating a strand of cardiac muscle in oil\(^{10,11}\) or air.\(^{12,44}\) In this case, we calculate a planar wave front propagating with a conduction velocity of 0.463 m/sec, consistent with the one-dimensional calculation for a restricted extracellular space. Similarly, we can set both the bath conductivity and the conductivity of the interstitial fluid to a high value (1.5 \( \times \) 10\(^{6}\) S/m), in which case we again obtain a planar wave front but with a conduction velocity of 0.665 m/sec, almost the same as for the one-dimensional calculation for a single fiber in a low resistance bath. If we set the bath conductivity to a high value (1.5 \( \times \) 10\(^{6}\) S/m) but keep the conductivity of the interstitial fluid at its typical value of 1.5 S/m, we get results qualitatively similar to but not quantitatively identical to

![Figure 6](http://circres.ahajournals.org/)

**Figure 6.** Phase-plane plots (transmembrane potential \( \Phi_m \) versus \( d\Phi_m/dt \)) for a steadily propagating wave front, calculated using a one-dimensional model (position a), the bidomain model at the surface of the strand (cylindrical coordinate \( p = 0.5 \) mm) (position b), and the bidomain model at the center of the strand (\( p = 0 \)) (position c). The inset shows in more detail the initial foot of the action potential.

![Figure 7](http://circres.ahajournals.org/)

**Figure 7.** The transmembrane potential as a function of position for a steady wave front propagating in a strand with a radius of 0.1 mm (panel a), 0.2 mm (panel b), 0.5 mm (panel c), and 1.0 mm (panel d). \( p \) and \( z \) are cylindrical coordinates. The isopotential lines are labeled in millivolts.

![Figure 8](http://circres.ahajournals.org/)

**Figure 8.** The steady-state conduction velocity \( u \) versus strand radius \( a \). The horizontal lines at 0.655 and 0.463 m/sec indicate the velocity of an action potential propagating along a one-dimensional fiber in a low resistance bath and a tissue of infinite extent, respectively.
FIGURE 9. The transmembrane potential (panel a), intracellular potential (panel b), and extracellular potential (panel c) as functions of position for a steady wave front propagating in a strand with a radius of 0.5 mm and an intracellular volume fraction of 0.98. ρ and z are cylindrical coordinates. The isopotential lines are labeled in millivolts.

those presented in Figure 4 (conduction velocity equal to 0.565 m/sec). The simulations presented above were for a large but bounded bath of radius 4 mm. If this radius is reduced to 2 mm, there is less than a 0.1% change in the rate of rise of the calculated action potential, indicating that a 0.5-mm-radius strand lying in a 4-mm-radius bath behaves identically to one in an unbounded volume conductor.

A limiting case that deserves particular attention is when the cells are very tightly packed, so that the interstitial conductivity is small relative to the bath conductivity. In this case, the electrical behavior of the cells is quite different in the tissue bulk than in the “boundary layer” on the strand surface. For tight packing, the width of this boundary layer is proportional to $\sqrt{\sigma_{\text{opt}}}$ so that in the limit when the interstitial conductivity goes to zero the transition from surface to bulk behavior occurs in an infinitely thin layer on the strand surface. To demonstrate this effect, Figure 9 shows the transmembrane, intracellular, and interstitial potentials of a stably propagating wave front in a strand with $f=0.98$, so that the interstitial space occupies only 2% of the tissue volume. Note that the transmembrane potential gradient is much smaller at the surface of the strand than in the bulk tissue and that the boundary layer has a width of approximately 50 μm. The wave front throughout the bulk is almost conical. The extracellular potential has a large gradient near the strand surface and along the wave front, and its peak-to-peak amplitude at the center of the strand is over 80 mV. The intracellular potential varies smoothly throughout the tissue, without any large gradients. The conduction velocity of this wave front is 0.419 m/sec.

Figure 10 shows the conduction velocity as a function of the intracellular volume fraction, $f$ (the cell radius is held constant, and $f$ is changed by varying the number of cells in the strand). As $f$ approaches zero (loosely packed cells), the conduction velocity approaches the one-dimensional limit for a low resistance bath (upper line). As $f$ approaches one (tightly packed cells), the conduction velocity decreases, but not as quickly as predicted by the one-dimensional model with a restricted extracellular space (lower curve).

For a 0.5-mm-radius strand, calculation of the propagation velocity at values of $f$ above 0.98 becomes numerically difficult because of the small space step required for accuracy and the large spatial extent of the wave front. However, the calculation is practical for thin strands with tight packing (e.g., Purkinje fibers). Using a strand radius of 50 μm, the wave front velocity for $f=0.95$, 0.98, 0.99, and 0.995 is 0.579, 0.520, 0.465, and 0.402 m/sec, respectively. It is not clear from these results whether the conduction velocity vanishes or approaches a constant in the limit as the interstitial conductivity goes to zero.

We performed one simulation to demonstrate how propagation depends on the radius of the individual cardiac cells. When the cell radius, $b$, was doubled, from 5 to 10 μm, the wave front flattened, and the conduction velocity increased approximately by a factor of $\sqrt{2}$ (from 0.549 to 0.792 m/sec), implying that the conduction velocity is proportional to $\sqrt{b}$, as expected for one-dimensional behavior. Another simulation was performed to study how sensitive the model is to the active membrane properties. When the maximum sodium conductance, $g_{\text{Na}}$, was de-
creased from 350 to 175 S/m², the rate of rise of the action potential at the strand surface fell from 159 to 92 V/sec, and the conduction velocity decreased from 0.594 to 0.434 m/sec. However, the spatial extent and curvature of the wave front were qualitatively similar to those in Figure 4.

Plonsey suggested that the boundary condition in Equation 11 should be replaced by the condition that the intracellular radial current density equals the membrane current at the surface of the strand. We incorporated Plonsey’s boundary condition into our model and found small changes in the predicted transmembrane potential under normal conditions (a=0.5 mm, f=0.75, b=5 µm). In the steady state, the rate of rise of the action potential is nearly the same (within 0.25%) at the center of the strand (220 V/sec) regardless of the boundary condition used, but with Plonsey’s boundary condition, the rate of rise is 181 V/sec at the surface; with our boundary condition, it is 159 V/sec, a difference of 12%. Similarly, using Plonsey’s condition, the action potential amplitude increases 0.5% and $\tau_{\text{foot}}$ decreases 1.5% compared with our calculation at the surface of the strand.

**Discussion**

These results resolve several open questions in cardiac electrophysiology and introduce new questions for future research. Consider the shape and velocity of the propagating wave front as the strand radius increases. Plonsey et al. predicted that in a thick strand of cardiac muscle the wave front speed should be intermediate between that of an action potential propagating along a one-dimensional fiber in a low resistance bath and in tissue of infinite extent (oil bath). Furthermore, they hypothesized that, as the radius of the strand increases, the propagation velocity should approach the one-dimensional limit of a strand in an oil bath. Our results indicate that the conduction velocity is indeed between the two one-dimensional limits but that, as the strand thickness increases, the velocity approaches a constant value that is different from the velocity predicted for a strand in an oil bath (Figure 8). Moreover, the transmembrane potential wave front is not planar at any depth but instead takes on a conical shape for thick strands (Figure 7d). These results indicate that at all depths into the tissue the presence of the low resistance bath influences propagation. For strands with radii larger than about 0.5 nm, the conduction velocity is nearly independent of strand radius (0.540 m/sec). *We were not able to test these predictions for strands with radii larger than 2 mm because the computations became too time consuming. However, there is no length scale in the system that should modify the behavior at even larger strand radii. Therefore, we believe, but have not proven, that our conclusions hold for arbitrarily thick strands.*

*The nonplanar shape of the wave front is exaggerated when the cardiac cells are tightly packed (when $f$ approaches 1). When $f=0.98$, the transmembrane potential wave front is so curved that it can best be described as a fast, longitudinal wave front propagating on the strand surface that initiates a slow, radial wave into the tissue bulk. In previous calculations of the extracellular potential produced by a strand of cardiac muscle, the wave front was assumed to be independent of the depth into the tissue. Clearly, for tightly packed cells this assumption is incorrect, and the results of calculations using this assumption are not reliable. The true behavior can better be described as a boundary layer on the strand surface in which the electrical behavior is quite different from that in the tissue bulk. We add, however, that for small interstitial conductivities the width of the boundary layer becomes similar to or smaller than the radius of a single cell. In that case the bidomain model must be used with caution, since a continuum model is not necessarily applicable.

We can illustrate much of the behavior predicted in our simulations with a simple model. Propagation occurs by two rules: during each time step ($\Delta t$), the wave front propagates radially inward a distance $d$, and at the strand surface it also propagates longitudinally a distance $D$, where $D>d$ (in the bulk tissue, we ignore longitudinal propagation). Figure 11 shows transmembrane potential wave fronts at several times that were predicted by using these rules. Surface velocity is assumed to be three times the inward velocity ($D=3d$), and $D$ is set equal to the strand radius. Three time increments are required for the steady-state wave front to be created, after which the
wave front propagates longitudinally at the speed of the surface propagation (D/Δt). This simple model reproduces many of our results. For instance, in a thicker strand, more time is required before a steady-state profile is reached, the steady-state conduction velocity is independent of radius, and the wave front is conical. The angle the wave front makes with the axis of the strand is determined by the ratio of D to d. These results hold for arbitrarily thick strands. When the surface and bulk propagation velocities are similar (D≈d), we cannot neglect longitudinal propagation in the bulk, and this simple model breaks down. However, based on the results for thick strands in Figures 3 and 7, the model appears to be applicable even for physiologically normal cardiac muscle.

In large mammals and birds, Purkinje fibers have an interstitial space that is quite restricted (for sheep, f=0.998). Sommer suggested that the tight packing allows the strand to behave like a single large cell and thereby increases its conduction velocity. We also have previously presented the hypothesis that, in the limit of a small interstitial conductivity, a bidomain strand acts like a single cell. Our new results indicate that the conduction velocity always decreases as the interstitial space is made more restricted. Thus, to the extent that the bidomain model is applicable, it does not support the hypothesis that tight packing increases conduction velocity. However, because of the limitations of a continuum model for tightly packed cells, a microscopic model of propagation along a Purkinje fiber is required to conclusively determine the relation between conduction velocity and the volume fraction of the interstitial space.

Our calculations allow us to analyze two recent experiments on thick strands of cardiac tissue. Suenson found that the ratio of uSF : uT increased with increasing strand diameter and observed indirectly that the wave front is curved with a curvature of 430 μm. In each case our model correctly predicts the qualitative change in the strand behavior when the Tyrode’s bath is replaced by silicone fluid but does not accurately determine the magnitude of the change. This latter discrepancy could, in part, arise because the model parameters, such as the intracellular volume fraction or the cell radius, are not appropriate to ferret cardiac muscle.

Kleber and Rieger have observed increases in the interstitial resistance of ventricular muscle strands when arterial perfusion was interrupted. In these experiments, the strand was surrounded by air, which in our model corresponds to a low bath conductivity. Their results can be accurately analyzed using the one-dimensional cable model, but the validity of their results for the case of a low resistance bath is not clear. Our model can provide some insight into the effect of interstitial conductivity changes in strands bathed in a low resistance bath. Before perfusion is interrupted, we assume that the interstitial volume fraction is 0.250 in a 0.5-mm-radius strand. Arresting perfusion causes the interstitial volume fraction to decrease to 0.163, a 35% drop, and the conduction velocity to decrease by 13%.

Our model predicts that if the same change in interstitial volume fraction occurred with the strand lying in a low resistance bath, only a 5% change in conduction velocity would be observed (Figure 10). Thus, when the tissue is bathed in a relatively low resistance fluid, smaller changes than those observed by Kleber and Rieger should be expected upon the immediate interruption of perfusion.

Our results provide two notes of caution for the experimentalist. First, the shape of the transmembrane potential wave front cannot be determined by using a microelectrode to measure the intracellular potential with respect to a distant ground. Such a measurement yields an incorrect value for the rate of rise of the action potential and the time constant of the action potential foot. Both intracellular and extracellular potential must be measured, and the two electrodes must be positioned very accurately to avoid introducing errors. Furthermore, for the 0.5-mm-radius strand, the wave front does not reach steady state until more than 8 msec after the stimulus, at which point the action potential has propagated nearly 7 mm. More time is required for thicker strands (in a 2-mm-radius strand, 40 msec is required to reach steady state) or, if the strand is stimulated with a point electrode, breaking the cylindrical symmetry assumed here. These results imply that experimentalists must be careful to use long strands if they wish to create a stable wave front in a thick strand of cardiac muscle.

Our boundary conditions are identical to those proposed by Henriquez and Colli Franzone but are different from those suggested by Plonsey, who assumed that the intracellular current normal to the tissue surface is equal to the membrane current.
In normal tissue, the only significant difference between the results using the two boundary conditions is the 12% difference in the maximum rate of rise of the action potential at the surface of the strand. This difference is small enough that verifying one boundary condition over the other by comparing experimental results to model predictions may be difficult. Larger differences between results using the two conditions were observed in abnormal tissue states. One disadvantage of Plonesy’s boundary condition is that it produces a radial current density in situations such as a strand surrounded by oil or air, where symmetry requires that no radial current density exists.

Although our results provide much insight into propagation in a thick strand, there are several limitations of this model that should be kept in mind. First, the parameters describing the tissue and membrane properties may not be applicable for most species. The conductivities used in our simulations are based on the measurements by Kleber and Riegger on rabbit ventricular muscle. These values may differ among species. In fact, Clerc found a significantly lower interstitial axial conductivity using calf ventricular muscle. An obstacle to testing our model results quantitatively is the lack of complete electrophysiological and histological data from any single experiment. Other difficulties arise when attempting to verify these results experimentally. For example, in a strand superfused by a bath, oxygen and other nutrients can only diffuse several hundred microns into the strand, implying that deeper cells may not be as healthy as surface cells. This difficulty could be surmounted using Kleber and Riegger’s arterial perfusion.

The bidomain model breaks down at large frequencies, specifically at frequencies greater than the β frequency of the tissue. When the current is changing with time too quickly, the membrane capacitance shunts current across the membrane, resulting in variations of the transmembrane potential over distances on the order of the cell radius, thereby violating our assumption of macroscopic behavior. Thus, we do not expect our model to predict correctly the initial response (for the first few tens of microseconds) to the stimulus.

We choose to use the Ebihara-Johnson model to represent the sodium channel kinetics because it is the simplest model appropriate for depolarization in ventricular tissue that is based on experimental data. Other membrane models for ventricular muscle and Purkinje fibers are available that better account for repolarization. Our simulation using a reduced maximum sodium conductance indicates that the qualitative prediction of wave front curvature is not unique to the membrane model we used, although quantitative results are model dependent.

The bidomain model is a macroscopic description of cardiac tissue and therefore cannot correctly predict behavior that depends on the discrete nature of the individual cells. Spach et al have presented experimental evidence indicating that in the direction transverse to the strand propagation may be discontinuous. This behavior may be due to uncoupling of transverse connections between fibers, or bundles of fibers, which increases with age.53 This hypothesis has been studied theoretically by several authors, and one of these studies concluded that in healthy tissue the effects of cell junctions are not important. It is likely, but not certain, that the bidomain model is applicable when the tissue has “uniform anisotropic properties” associated with smooth, biphasic extracellular potentials. Tissues producing very complex extracellular wave forms certainly must be represented with a different model that can take into account microscopic discontinuities in the tissue structure. Possibly the bidomain model can be extended to incorporate the intercellular junctions in a way analogous to the model by Krassowska et al, in which a two-scale analysis was used to account for the periodic structure of the cells. It is also possible that a bidomain model such as ours could explain the data of Spach et al, which they interpret as evidence for discontinuous propagation. To test this possibility would require using a planar instead of cylindrical tissue geometry.

**Appendix**

**Numerical Implementation of the Model**

In this appendix we discuss the numerical implementation of the model. Starting from Equations 6–16 in the text we eliminate \( \Phi_i \) in favor of \( \Phi_m \), resulting in the three equations

\[
-\nabla \cdot \sigma_o \nabla \Phi_o = \beta \left( C_m \frac{\partial \Phi_m}{\partial t} + J_{ion} \right) \tag{A1}
\]

\[
\nabla \cdot (\sigma + \sigma_o) \nabla \Phi_o = -\nabla \cdot \sigma \nabla \Phi_m \tag{A2}
\]

\[
\nabla^2 \Phi_e = 0 \tag{A3}
\]

for the three unknown potentials \( \Phi_m, \Phi_o, \) and \( \Phi_e \). The gradient, \( \nabla \), and divergence, \( \nabla \cdot \), operators are expressed in cylindrical coordinates. Equation A1 is a nonlinear ordinary differential equation for \( \Phi_m \) with a source term that depends on \( \Phi_o \), Equation A2 is a linear partial differential equation for \( \Phi_e \) with a source term that depends on \( \Phi_m \), and Equation A3 is Laplace’s equation for \( \Phi_e \). The boundary conditions at the tissue-bath surface, \( r = a \), are

\[
\Phi_e = \Phi_o \tag{A4}
\]

\[
\sigma_{op} \frac{\partial \Phi_o}{\partial r} = \sigma_e \frac{\partial \Phi_e}{\partial r} \tag{A5}
\]

\[
\frac{\partial \Phi_m}{\partial r} + \frac{\partial \Phi_o}{\partial r} = 0 \tag{A6}
\]
The spatial derivatives are approximated as finite differences on a square grid. Each point is separated from its neighbor by 25 μm in the p and z directions (a grid spacing of 15.6 μm produces a 1% difference in the V_{max} of the steady wave front). At large radial distances in the bath (ρ>1 mm), a courser grid is used (grid spacing of 50 or 100 μm), and when the volume fraction of the intracellular space, f, is greater than 0.8, a finer grid is used in the tissue (a minimum grid spacing of 12.5 μm). At the boundaries, three-point difference formulas are used for the first derivative, preserving the second-order accuracy of the finite difference approximation in space^{59} (in contrast to Henriquez's use of "fictitious nodes" above the surface of the tissue). The time derivatives in Equation A1, as well as those appearing in the equations for the membrane gates, are replaced by forward difference formulas, with a constant increment, Δt, between time steps of 1 μsec (a time step of 0.5 μsec produces less than a 0.05% change in V_{max}).

Solution of these equations proceeds as follows. Given the value of the variables at time t, the transmembrane potential and gates are stepped forward to time t+Δt using an explicit, first-order accurate algorithm (Euler's method). Next, the interstitial and bath potentials are calculated at time t+Δt by solving the boundary value problem represented by Equations A2−A6, using the new transmembrane potential as the source. This procedure is then repeated for the next time step, t+2Δt.

The boundary value problem is solved using a systematic overrelaxation algorithm^{59} an iterative technique. This algorithm is attractive because at each time step an excellent initial guess for the potential is obtained from the previous time step. We terminate the iteration when the largest residual over the ρ, z plane is less than 5 μV (terminating for a residual of 2 μV produces less than a 0.01% change in V_{max}). When the stimulus is on, we write Φ_i as the sum of two terms: one due to the electrodes in an unbounded homogeneous bath and another that enforces the boundary conditions at the bath walls and tissue surface. The first term is calculated from an integral expression for the potential due to a pair of ring electrodes, and the second term is determined using the systematic overrelaxation algorithm.

The membrane is initially at rest: Φ_{m} = -80 mV, m=m_{c1}(-80), h=h_{c1}(-80). At the ends of the strand, the derivatives of both the transmembrane and interstitial potentials with respect to z vanish. Also, at the walls of the bath, the normal derivative of the interstitial and bath potentials are set to zero. For the simulation presented in Figure 2, the grid consists of 513 points in the axial direction and 142 in the radial direction (21 in the tissue, 121 in the bath), for a total of 72,846 points. The computer program is written in FORTRAN and runs on an XMP-24 supercomputer (Cray Research, Inc., Minneapolis, Minn.) at the Advanced Scientific Computing Laboratory, National Cancer Institute, Frederick, Md. A simulation of 10 msec takes typically 25 minutes of computer time.

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