Directional Characteristics of Action Potential Propagation in Cardiac Muscle

A Model Study

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Propagation of an elliptic excitation wave front was studied in a two-dimensional model of a thin sheet of cardiac muscle. The sheet model of $2.5 \times 10$ mm consisted of a set of 100 parallel cables coupled through a regular array of identical transverse resistors. The membrane dynamics was represented by a modified Beeler-Reuter model. We defined the charging factor (CF) to represent by a single number the proportion of input current used to charge the membrane locally below threshold and showed that CF is inversely correlated with the time constant of the foot of the action potential ($\tau_{\text{foot}}$) during propagation on a cable. A safety factor of propagation (SF) was also defined for the upstroke of the action potential, with SF directly correlated with the maximum rate of depolarization ($V_{\text{max}}$) and, for cablelike propagation, with propagation velocity. Propagation along the principal longitudinal axis of the elliptic wave front is cablelike but, in comparison with a flat wave front, transverse current flow provides a drag effect that somewhat reduces the propagation velocity, $V_{\text{max}}$, SF, and CF. With a longitudinal-to-transverse velocity ratio of 3:1 or more, the wave front propagating along the principal transverse axis is essentially flat and is characterized by multiple collisions between successive pairs of input junctions on a given cable; $V_{\text{max}}$, SF, and CF are larger than for longitudinal propagation, but CF is no longer correlated with $\tau_{\text{foot}}$. There are transient increases in propagation velocity and $V_{\text{max}}$ with distance from the stimulation site along both principal axes until stabilized values are achieved, and a similar transient decrease in $\tau_{\text{foot}}$. Away from the principal axes, the action potential characteristics change progressively along the elliptic wave front. When the isochrone curvature is relatively low, collisions take place and propagation is predominantly transverse. Beyond a certain degree of curvature, collisions are absent and propagation is predominantly longitudinal. Good correlations are found between our simulations and published experimental observations on strips of heart muscle, except for the behavior of $\tau_{\text{foot}}$. Based on the indications provided by the model, it is argued that the short recording distance used in experimental measurements may have led to an overestimation of $\tau_{\text{foot}}$ in the longitudinal direction because of transient changes in the foot of the action potential and possible distortions caused by the stimulus. (*Circulation Research* 1991;69:378–395)

The hypothesis that a circulating wave of excitation could occur in a region of intact myocardium was first documented by Allessie et al., who described a type of reentry in which a wave front traveled around a functional obstacle such as a region of blocked or prolonged action potentials. In that case a central vortex of activity is out of phase with the rest of the tissue, and its features may change somewhat with each passage of the reentrant wave front. In a similar vein Spach et al. have demonstrated that reentrant activity can be initiated in two-dimensional tissue with uniform membrane properties. Then the functional obstacle arises when a properly timed premature impulse is blocked in the direction of the long axis of the fiber, while steady propagation occurs in the transverse direction. As reentrant propagation developed, these authors also observed directionally dependent differences in the shape of the action potentials. These observations are inconsistent with a two-dimensional extension of cable theory, which predicts that action potential shape is not dependent on the direction of propagation.

This led Spach et al. to assert that cardiac tissue cannot be modeled as a functional syncytium and
that the propagated action potential is strongly influenced by the microscopic structural properties of the tissue. It is thus important to examine how the directionally dependent differences in propagation may arise from the interplay between changes in membrane conductance during propagation and the electrical loading at a given point arising from the passive properties of myocardium and the pattern of cellular interconnections. The basic premise is that the passive anisotropic properties of cardiac muscle have an independent role in determining excitability and the safety factor of propagation (SF) and that such properties can produce many of the conduction disturbances leading to reentry without the presence of spatial differences in refractory periods.4,5

This question is addressed in the present study by using a two-dimensional model of a thin sheet of cardiac muscle in the form of an assembly of interconnected parallel cables. We assumed uniform membrane properties throughout the sheet and neglected the possible effects of active ionic transport and ion accumulation. A regular pattern of interconnections was chosen, similar to that described by Kootsey and Wu.7 The regular spacing of the transverse connections (Δ), the fixed transverse resistance (R_y), and the constant intercable distance were chosen to yield a suitable ratio of transverse to longitudinal conduction velocity. This simplified model of anisotropic myocardium improves on previous models of this type and displays interesting effects of structural organization on the dynamic features of two-dimensional propagation. Starting from a set of passive tissue properties, we devoted particular attention to the changes in membrane capacitance charging factor (CF) and SF with respect to the shape of the propagating activation wave front and the direction of propagation.

Methods

Sheet Model

Our two-dimensional model is intended to represent a thin strip of cardiac muscle. Each cell element is a small uniform cylinder (radius a) with a constant surface-to-volume ratio (S_s=2/a). The cell membrane is represented by a modified Beeler-Reuter model that has served in many of our previous propagation studies. One of its main features is a more rapid Na⁺ current (I_{Na,t})⁸; it is given by I_{Na,t}=g_{Na,m}h(V-E_{Na}), where g_{Na,m} is the maximum conductance, m and h are activation and inactivation variables, respectively, E_{Na} is the Na⁺ equilibrium potential, and V is the transmembrane potential. The secondary inward current (I_o), the delayed K⁺ current (I_{K,t}), and the time-independent K⁺ current (I_{K,i}) are unchanged from the original Beeler-Reuter formulation.

The extracellular space is assumed to be isotropic and unbounded, with negligible resistivity compared with the intracellular space. In the direction of the long cell axis the cytoplasmic and junctional resistances are combined into an average intracellular resistivity (r_s), leading to the representation of a chain of cells as a discretized continuous uniform cable. The cable is discretized into segments of length δ, with an intracellular resistance R_s and a modified Beeler-Reuter membrane patch (Figure 1). The sheet model is developed as an arrangement of a large number of parallel cables with a specific pattern of transverse connections.10 Transverse current flow is then governed by a transverse resistance that can be chosen arbitrarily as to its location and value. In the present sheet model we use a regular network of fixed resistors (R_y) with a constant Δ (Figure 1).

Because extracellular resistivity is assumed to be small, we can approximate the intracellular potential with V. Propagation on any given cable is given by the cable equation

$$\frac{1}{r_s} \frac{d^2V}{dx^2} = C_m \frac{dV}{dt} + I_{ion}$$

(1)

except at the points of interconnection. C_m is the membrane capacitance, I_{ion} is the total ionic current, and x and t are distance and time, respectively. This equation can be discretized in time and solved at each of a set of time instants \{t_1, \ldots, t_n\}. Thus we have

$$\frac{1}{r_s} \frac{d^2}{dx^2} V(x,t_{i+1}) - V(x,t_i) = \frac{V(x,t_i) - V(x,t_{i-1})}{t_{i+1} - t_i} + I_{ion}(x,t_{i+1})$$

(2)

which is of the form

$$\frac{1}{K} \frac{d^2}{dx^2} V(x,t_{i+1}) - V(x,t_i) = F(x,t_i)$$

(3)

where K is a constant and F is a function of x. To model the two-dimensional network we consider m cables with potential on cable j denoted by V_j(x). Cable j is connected to two adjacent cables (except at the two borders of the sheet where connections are on one side only) by resistors R_y at points \hat{x}^i. The equation governing V_j(x) is the same as Equation 3, with the added condition that a current of strength S_s is injected at a discrete set of points, X={\hat{x}_1, \ldots, \hat{x}_n}. Its solution is the sum of the particular and homogeneous solutions to Equation 3,

$$\hat{V}(x) = V(x) + b_1 e^{Kx} + b_2 e^{-Kx}$$

(4)

where V(x) is the particular solution for each interval x_i<x<x_{i+1}, and K, b_1, and b_2 are constants that can be calculated by recognizing that the size of the discontinuity in dV/dx (i.e., jump|dV/dx|) is proportional to S_s and hence these constants can be calculated from R_y and the potential drop across it.10

A fast, accurate algorithm was described to solve this system.10 At each instant in time the potential distribution on each cable is calculated assuming that the cables are isolated from one another, and this distrib-
**Figure 1.** Electrical equivalent circuit of the anisotropic sheet model of myocardium. Individual cables run parallel to the longitudinal edge of the sheet, and their equidistant planar layout (four cables with a spacing $d$ are shown here) constitutes the transverse edge. Membrane patches obeying modified Beeler-Reuter (BRM) kinetics (generating current $I_m$) are coupled via axial resistors ($R_x$) to constitute a uniform cable. Each membrane patch corresponds to a cable segment of radius $a$ and length $\delta$. Transverse resistors ($R_y$) linking any two adjacent cables are located $2\Delta$ apart. Except for the first and last cables, which have only one neighbor, the transverse connections with the next neighbor are shifted by a distance of $\Delta$ relative to those with the preceding neighbor, thus generating a spacing of $\Delta$ between successive transverse connections on any given cable. An enlargement of a section of cable is shown on the right, illustrating the main features associated with a flat transverse wave front. Current $I_x$ from the preceding neighbor enters at input junctions (namely, nodes 1 and 5) and exits at output junctions (node 3). Because of the symmetry, an equal amount of axial current flows away from the input junction in both directions along the cable (i.e., $I_{x1}=I_{x5}$) and the propagating electrotonic and action potentials collide at the output junction. Consequently one finds a maximum voltage threshold at the input junction and a minimum at the output junction. Because of the collision at the output junction, the maximum rate of depolarization ($V_{\text{max}}$) during the action potential is maximum at that point.$^{10}$ $I_{\text{ion}}$, total ionic current; $C_m$, membrane capacitance.
tion is subsequently adjusted to account for the cable interactions. The algorithm may be summarized as follows: 1) calculate $I_{on}$ along each cable, 2) use $I_{on}$ and potential distribution at $t_i$ to calculate the right-hand side of Equation 2, 3) solve Equation 2 at $t_{i+1}$ assuming that the cables are isolated from one another to yield the potential distribution on each cable, 4) calculate coefficients $b_1$ and $b_2$ of Equation 4 to obtain the homogeneous solution of Equation 3, 5) add particular and homogeneous solutions to yield the new potential distribution on each cable in the presence of transverse connections, and 6) recalculate $I_{on}$ along each cable (step 1).

Simulations

Simulations were performed in three types of structures, all implemented using FORTRAN on a Silicon Graphics 4D-25S computer (Silicon Graphics, Mountain View, Calif.). One was a uniform cable discretized into 200 segments of 25 µm for a total length of 5 mm with nominal parameter values as given in Table 1. A single transverse resistance, $R_y$, was inserted at its midpoint (see the bottom panel in Figure 2), with the other end of $R_y$ maintained at a fixed potential of −87 mV. A pulse stimulus (1 msec in duration and approximately 1.5 times threshold intensity) was applied across the membrane at the proximal end of the cable to induce propagation.

Another structure was a rectangular sheet model consisting of 100 parallel cables discretized into 400 segments 25 µm in length for a total length of 10 mm. The center-to-center spacing between adjacent cables was fixed at 25 µm for a total sheet width of 2.5 mm. As with the single cable, a propagating wave front (elliptic shape as in Figure 6) was elicited by means of a pulse stimulus applied this time to a pair of neighboring cables at the center of the sheet and close to its proximal end. Whenever it was desired to generate a longitudinal or transverse flat wave front, a set of pulse stimuli was applied to either the transverse or longitudinal edge of the sheet, respectively.

The general features of a flat transverse wave front in the sheet model are depicted in the enlargement on the right of Figure 1. Because of the flat wave front, the same current ($I_1$) arrives through all input junctions and divides equally between $I_{y1}$ and $I_{y2}$. Below threshold, $I_1$ and $I_2$ flow decrementally toward the output junction located midway between any two input junctions. Because of the leak resistance $R_y$ at the output junction and despite the summation of $I_{y1}$ and $I_{y2}$, there is a lower membrane potential at that point compared with the value at the input junction. Consequently action potentials will be elicited first at input junctions, and the two propagating wave fronts will meet. The point on a cable at which two wave fronts come together is characterized by a local minimum and will be referred to as a collision site. In this case, because of the symmetrical arrangement of the transverse resistors, the collision occurs at output junctions, thus causing a larger maximum rate of depolarization ($V_{max}$) at the collision site despite the current leakage through $R_y$. Complete details of the propagation of a flat transverse wave front in the sheet model can be found in Reference 10.

Simulations were also performed in a truncated rectangular sheet to examine the effects of loading on propagation and the initiation of unidirectional block. The structure was a sheet of three parallel cables, 2.5 mm in length, abutted to a sheet of 100 parallel cables, also 2.5 mm in length (see bottom right panel of Figure 4). Stimulation was applied as a point source to either end of the sheet.

It was verified that the spatial mesh was fine enough to ensure that no numerical distortions occurred during propagation when nominal parameter values (Table 1) were used. The most sensitive quantity is $V_{max}$, and as shown in one-dimensional studies, its value remains unchanged when the discretization factor (segment length/length constant) is lower than 0.11.12 In the present case, the cable segment length (25 µm) and length constant (838 µm) of Table 1 give a discretization factor of 0.03, which is well below the critical limit.

The time step used in all simulations was constant at 2 µsec. The activation time was defined as the zero crossing of the action potential upstroke. Propagation velocity was measured by taking the difference in activation times over a distance of 50 µm in either the longitudinal or transverse direction. The time constant of the foot of the action potential ($τ_{foot}$) was calculated from the slope of the linear part of the $V(V)$ curve (see Figure 7).

We studied propagation of excitation through changes in $V_{max}$, $τ_{foot}$, and conduction velocity under various conditions determined by the choice of $R_y$ and $Δ$ values. We also calculated CF corresponding to the subthreshold portion of the upstroke and SF corresponding to the suprathreshold portion (see bottom panel of Figure 2). The voltage threshold is

<table>
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<th>TABLE 1. Nominal Model Parameters</th>
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<tr>
<td>Parameter</td>
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<tr>
<td>Membrane capacitance, $C_m$ (µF/cm²)</td>
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<td>Resting membrane resistance, $R_m$ (kΩ·cm²)</td>
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<td>Cable radius, $a$ (µm)</td>
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<td>Length of cable segment, $δ$ (µm)</td>
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<td>Cable intracellular resistivity, $τ_i$ (Ω·cm)</td>
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<td>Length constant of isolated cable, $λ$ (µm)</td>
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Sheet model

| Parameter                        | Value |
|-----------------------------------|
| Distance between adjacent cables, $d$ (µm) | 25    |
| Transverse resistance, $R_y$ (MΩ) | 2     |
| Distance between transverse connections on a given cable, $A$ (µm) | 100   |
| Transverse velocity of flat wave front, $θ_{rr}$ (m/sec) | 0.11  |
| Longitudinal velocity of flat wave front, $θ_{rl}$ (m/sec) | 0.71  |
the point at which the rapid rise in voltage begins and is defined as the membrane potential at which $I_{ion}$ begins to flow inward (see Figure 7). Both CF and SF are defined for any cable segment in terms of the input current $I_{in}$ and the membrane current $I_{ion}$, where $I_{in} = I_c + I_{ion}$ ($I_c$ is the capacitive current). CF is the ratio of $I_{ion}/I_{in}$, but since $I_{ion} = 0$ below threshold we have $CF = I_c/I_{in}$ (i.e., the fraction of input current used to charge the membrane at a given point). It can be verified that CF is essentially constant over the duration of the foot of the action potential, thereby allowing us to express it as a single number. It may be expected that CF will be correlated with $\tau_{foot}$ and we show in "Results" that it is indeed the case.

The definition of SF arises from the consideration that the action potential upstroke is the major determinant of propagation. On a given cable segment we have $I_{in} = I_{in} - I_{out}$, where $I_{in}$ is the input current and $I_{out}$ is the current flowing downstream. $I_{in}$ is outward and $I_{ion}$ is inward during the upstroke (Figure 7), and $I_{ion}$ represents the charge supplied by $I_{in}$ and $I_{ion}$. When the charge generated by $I_{ion}$ is larger than the local requirements of $I_c$, it makes some contribution to $I_{out}$.

**Figure 2.** Correlation between charging factor (CF) and time constant of the foot of the action potential ($\tau_{foot}$) in a cable with a single transverse resistance. Bottom panel: A 5-mm cable with a transverse resistance ($R_z$) junction at its midpoint. The other end of $R_z$ is maintained at a fixed potential of $-87$ mV. Observations are made in the central region of the cable over a distance of 1.4 mm. The sketch of the action potential upstroke on the left indicates that the threshold level separates the regions corresponding to the CF and safety factor of propagation (SF). The vertical broken line (JCN) on each graph represents the location of $R_z$. Panels A and C: CF and $\tau_{foot}$ with maximum conductance ($g_{Na}$) = 100% for $R_z$ values of 50, 20, and 9 M$\Omega$. Panels B and D: CF and $\tau_{foot}$ with $g_{Na}$ = 25% for $R_z$ values of 50, 20, 10, and 9 M$\Omega$. $\tau_{foot}$ was not calculated with $R_z$ of 9 and 10 M$\Omega$, because the foot of the action potential did not show a sufficiently well-defined exponential time course. Note that propagation was blocked for $R_z = 9$ M$\Omega$ (see also Figure 3B). Nominal conditions of Table 1 apply unless otherwise indicated.
and continued propagation is assured. A useful definition of SF is then one that expresses the excess of charge available to contribute to charging the downstream membrane. We can write

$$SF=\frac{\int_A I_{\text{ion}}dt}{\int_B I_mdt} \frac{\int_A I_{\text{ion}}dt}{\int_B (I_{\text{ion}}+I_m)dt}$$

$$A=\{t|I_{\text{ion}}<0\}$$

$$B=\{t|I_m<0\}$$

The numerator is the total charge generated by $I_{\text{ion}}$ during the upstroke, and the denominator is the total charge left once $I_m$ has been taken into account. The limits of integration ensure that only inward parts of $I_{\text{ion}}$ and $I_m$ are considered. When $SF\leq 1$, there is no contribution of $I_{\text{ion}}$ to $I_{\text{out}}$ and propagation is decremental and eventually fails. Under nominal conditions (Table 1), stable propagation on a uniform cable corresponds to $SF=2.17$. There is then a substantial excess of charge generated by the membrane patch and it serves to charge the membrane locally and maintain the axial downstream current required for propagation.

In comparison, Delgado et al. defined SF as the total charge of $I_{\text{out}}$ during the upstroke divided by the threshold charge that was sufficient for continued propagation. The threshold charge was found by setting $I_{\text{out}}$ to zero after a predetermined cutoff time, with the cutoff time established by trial and error until the amount of charge generated by $I_{\text{out}}$ was just sufficient to maintain propagation. This measure is extremely time-consuming to calculate and unfeasible for the large-scale simulations described in this paper.

**Results**

Propagation of excitation is studied first in a uniform cable with a transverse resistance $R_y$ to clarify the significance of CF and SF in relation to changes in $V_{\text{max}}$, $T_{\text{foot}}$, and conduction velocity. Next we consider two types of sheet structures with different combinations of $R_y$ and $\Delta$ values.

**Uniform Cable With a Transverse Resistance**

The cable has characteristics similar to those of a constitutive cable of the sheet model, except for the number of transverse connection points, which is limited to only one in this case (see bottom panel of Figure 2). Reducing the value of $R_y$ allows more current to flow out of the cable, and the propagation velocity is reduced. Propagation fails when $R_y$ is sufficiently low.

Events proximal to the junction. CF is expressed as a single number and applies to the entire foot of the action potential (below threshold where $I_{\text{ion}}=0$, see bottom panel of Figure 2 and Figure 7). Results presented in Figure 2 correspond to $g_{N_s}=100\%$ or $g_{N_s}=25\%$ and to $R_y$ ranging from 9 to 50 MΩ. CF decreases gradually as the action potential wave front approaches the junction. The magnitude of the decrease at the junction is larger for lower values of $R_y$ (Figure 2A), but propagation is maintained even with $R_y=9$ MΩ. Just beyond the junction CF jumps back up to the base value of 0.158. With $g_{N_s}=25\%$ of its nominal value (Figure 2B) the base value of CF decreases to about 0.09 (about a 40% reduction), and its minimum reaches 0.04, a level that is sufficient to produce propagation failure with $R_y=9$ MΩ.

The decrease in CF reflects a proportional decrease in the charging of the capacitance (see “Methods”) and is closely correlated with an increase in $\tau_{\text{foot}}$. With $g_{N_s}=100\%$ the base value of $\tau_{\text{foot}}$ is 0.25 msec (Figure 2C), and it increases to 0.75 msec with $g_{N_s}=25\%$ (Figure 2D). Therefore, a 40% reduction in CF corresponds to a 300% increase in $\tau_{\text{foot}}$. Similarly, with a given value of $R_y$, the decreased CF value at the junction is also paralleled by a proportionally more pronounced increase in $\tau_{\text{foot}}$ (compare Figures 2C and 2D). With $g_{N_s}=25\%$ there was some distortion of the foot of the action potential with $R_y=10$ MΩ, so $\tau_{\text{foot}}$ could not be calculated.

SF is a single number that applies to the action potential upstroke (see bottom panel of Figure 2 and “Methods”). Like CF, SF decreases gradually as the wave front approaches the junction and shows a larger reduction as $R_y$ is decreased (Figure 3). One may note, however, that SF begins to change at a distance from the junction that is about twice the corresponding distance for CF. Changes in SF are closely correlated with changes in $V_{\text{max}}$ and conduction velocity (Figure 3). For example, with $g_{N_s}=100\%$ the baseline $V_{\text{max}}$ is 235 V/sec, and it is reduced to 156 V/sec at the junction with $R_y=9$ MΩ (Figure 3C); correspondingly, the baseline velocity of 0.71 m/sec is reduced to a minimum of 0.5 m/sec (not shown). With $g_{N_s}=25\%$, SF is lowered somewhat, and the corresponding baseline velocity is 0.4 m/sec (Figure 3D). It may be noted that the minimum velocity occurs slightly before the junction in Figure 3D (some 50 μm), but since velocity is calculated over a distance of 50 μm, this particular location is not entirely meaningful and the minimum may be taken to occur at the junction. As indicated above, propagation fails with $g_{N_s}=25\%$ and $R_y=9$ MΩ since SF is decreased below unity at some point preceding the junction (Figure 3B).

The changes in conduction velocity and $V_{\text{max}}$ are positively correlated (Figure 3), and both quantities are inversely correlated with changes in $\tau_{\text{foot}}$ (Figure 2). The simulated changes in $V_{\text{max}}$ and $\tau_{\text{foot}}$ are in the same direction as published observations for Purkinje fibers and the atrium.

Events distal to the junction. As Figure 3 indicates, SF increases progressively toward its base level as the action potential propagates beyond the junction. Changes in $V_{\text{max}}$ and conduction velocity occur in a similar manner and, taking into account the artifact regarding the occurrence of the minimum conduction velocity noted above, they are essentially symmetrical with respect to the junction. One may conclude, therefore, that the capacity of the action potential upstroke
(which is reflected by SF) to maintain propagation is reduced progressively as the excitation wave front approaches the junction (which acts as a current sink) and that it is reestablished equally progressively as the wave front moves away from it.

Although CF resumes its baseline value just beyond the junction (Figure 2), \( \tau_{\text{foot}} \) continues to increase and reaches its peak slightly further down the cable (some 50–100 \( \mu \text{m} \), depending on \( g_{\text{Na}} \) and \( R_s \)). As \( \tau_{\text{foot}} \) decreases toward its baseline value beyond the junction, there is a parallel transient decrease in CF over a similar distance. As was the case before the junction, the magnitude of the changes in \( \tau_{\text{foot}} \) and CF follow the value of \( R_s \). One can then interpret these events as a transient reduction in the charge sustained by the membrane capacitance over some distance beyond the junction, paralleled by a return of \( \tau_{\text{foot}} \) to its baseline value.

For example, with \( g_{\text{Na}}=25\% \) and \( R_s=10 \, \text{M} \Omega \) in Figure 2B, the large transient decrease in CF beyond the junction suggests that propagation was nearly extinguished, as is also indicated by the fact that SF reached a value of 1.0 in Figure 3B (with a minimum conduction velocity of 0.1 m/sec [Figure 3D]). It follows then, in the continuous cable, that CF and SF express in a complementary way the conditions reflecting the potential failure of propagation.

**Truncated Sheet Model**

Using the truncated sheet model depicted in the bottom right panel of Figure 4, we analyzed the propagation of a wave front passing through a region characterized by a large increase in loading. This situation is similar in many ways to the branching fiber or equivalent expanding cylinder model of an axon described previously by Goldstein and Rall.\(^{16} \)

They showed that increasing the downstream loading affected the propagated action potential and if branching (or the fiber radius) increased sufficiently that propagation would fail.

When stimulation was applied at the proximal end, a flat wave front traveled along the narrow section of the sheet (width of three cables, 75 \( \mu \text{m} \)) and was transformed into an elliptic shape as it entered the large portion just beyond the junction.

With \( g_{\text{Na}}=100\% \) and \( R_s=2 \, \text{M} \Omega \) (curve 1 in Figure 4), SF starts to decrease about 400 \( \mu \text{m} \) proximal to the junction and reaches its minimum about 100 \( \mu \text{m} \) distal to it. The minimum value of SF=1.4 indicates that propagation is secure at the entrance to the large portion of the sheet, corresponding to a \( V_{\text{max}} \) of 150 V/sec and a conduction velocity of 0.42 m/sec. One also notes a parallel decrease in CF as well as a substantial increase in \( \tau_{\text{foot}} \). All these events occur over a distance of 0.5 mm or less beyond the junction, and further away from it the various quantities return to a baseline corresponding to stable propagation over the large section of the sheet model.

Reducing \( g_{\text{Na}} \) to 25\% of its nominal value and increasing \( R_s \) to 6 M\( \Omega \) to reduce the leak current at output junctions allows current to be maintained through the junction, as indicated by curve 2 in

**Figure 3.** Correlation between safety factor of propagation (SF), maximum rate of depolarization (\( V_{\text{max}} \)), and propagation velocity for the cable of Figure 2. Panels A and C: SF and \( V_{\text{max}} \) with maximum conductance (\( g_{\text{Na}}=100\% \)) and transverse resistance (\( R_s \)) values of 50, 20, and 9 M\( \Omega \) as indicated. Panels B and D: SF and propagation velocity with \( g_{\text{Na}}=25\% \) for \( R_s \) values of 50, 20, 10, and 9 M\( \Omega \) as indicated. Note that propagation was blocked for \( R_s=9 \, \text{M} \Omega \). The vertical broken line (JCN) on each graph represents the location of \( R_s \).
Figure 4. \( \tau_{foot} \) cannot be measured when propagation becomes critical, however, since the foot of the action potential is no longer exponential. In this simulation, the baseline value of the various quantities over the narrow section of the sheet is shifted down from the nominal situation, particularly \( V_{max} \), which is reduced from 240 to 70 V/sec (Figure 4B). The conditions for sustained propagation are obviously more critical since SF is down to a minimum of 1.15, CF to 0.04, \( V_{max} \) to 20 V/sec, and conduction velocity to 0.17 m/sec (curve 2 in Figures 4A–4D).

Failure of propagation occurs with \( g_{Na}=25\% \) and \( R_y=4 \, \text{M}\Omega \) (curve 3 in Figure 4), as SF crosses the 1.0 line at the junction, signaling that the other quantities will reach a zero value a short distance away.

Because the wave front propagating on the narrow portion of the sheet is essentially flat, the effects of the load on the events proximal to the junction are qualitatively similar to those described above for the uniform cable. Differences are due solely to the nature of the load, which is spatially diffuse in the present situation. Although conduction block was observed when propagation was initiated at the proximal end of the sheet for simulations in which \( g_{Na}=25\% \) and \( R_y \) was 4 M\( \Omega \) or less, this was not the case for impulses initiated by a point source applied...
at the distal end of the sheet. In this case an elliptic wave front was initiated, the characteristics of which were not affected by its passage through the junction.

Two-dimensional Sheet Model

Flat wave propagation. Stimulation of the sheet model along its longitudinal edge activates the first cable simultaneously over its whole length and initiates a flat transverse wave front. As described elsewhere,\textsuperscript{10} such a wave front is strongly influenced by $R_s$, $R_c$, $\Delta$, and membrane properties. With the particular pattern of transverse connections chosen here, an action potential is first initiated at an input junction and propagates toward an output junction on the cable. Because any output junction is positioned equidistantly between two input junctions (Figure 1), the two action potentials collide at the output junction. From there on, each output junction supplies current to an input junction for the next cable and the same process is repeated.

The consequence of this mode of flat transverse propagation is a spatial diversity of potential levels and action potential characteristics over the surface of the sheet. Because the transverse resistance at the output junction provides a current leak for the active cable, the membrane potential at the output junction is slightly lower than at the input junction. On the other hand, despite the lack at the output junction the action potential collision at the output junction generates a higher $V_{\text{max}}$ than at the input junction (Figure 1). As a consequence, on any given active cable there is a cyclic fluctuation of membrane potential and $V_{\text{max}}$ with distance, with a period of $2\Delta$ (see Figure 9 of Reference 10).

Elliptic wave fronts. Suprathereshold stimulation at a given point on the sheet gives rise to excitation in both the longitudinal and transverse directions, which yield the expected elliptic isochrones of an anisotropic medium. This situation is diagrammed in Figure 5, where stimulation on the center cable generates elliptic contours with a higher velocity in the longitudinal direction than in the transverse direction. In the transverse direction at a sufficient distance from the center cable, the isochrone is nearly equivalent to a flat transverse wave front (point A in Figure 5), and propagation in this region occurs as described above: the time delay $\Delta_t$ between the activation of two neighboring input junctions is negligible, and collision occurs at the output junction (see upper diagram A on the right-hand side of Figure 5).

Closer to the center cable the curvature of the isochrone is slightly more pronounced and there is a small time delay, $\Delta_t$, between the activation of two neighboring input junctions. As a result the collision does not occur exactly at the output junction but slightly closer to the input junction that is activated last. Still closer to the center cable (events at C in Figure 5), the time delay $\Delta_t$ is larger and the collision site is shifted further. Depending on the exact value of $\Delta_t$ and the proximity of the second input junction, only a partial collision may occur.

Finally, near the center cable, the curvature is such that the activation time between two neighboring input junctions is larger than the propagation time between two output junctions, and no collision occurs (events at D in Figure 5). Instead, there is a summation of the axial current on the cable with the current at the input junction.

Elliptic activation isochrones obtained with the model are shown in Figure 6. There are transient changes in propagation velocity and action potential characteristics as the activation wave front moves away from the stimulation site, and these events reach a relatively stable value a few length constants away in either the longitudinal or transverse direction. For example, under nominal conditions, the final velocity of the flat longitudinal wave front is reached 2 msec after the stimulus onset, while the velocity along the principal longitudinal axis of the ellipse $(\theta_1)$ reaches a value of 0.64 msec at 3 msec after the stimulus onset and its final value of 0.67 msec at 6 msec.

It should be noted that $\theta_1$ is consistently lower than the velocity of the flat longitudinal wave front $(\theta_1)$ because of the presence of a transverse current during elliptic propagation. Changing $R_s$ affects $\theta_1$ but has little effect on $\theta_t$, while a change in $r_i$ produces important effects in both quantities (Table 2). The effect of changing $\Delta$ on propagation is qualitatively the same as changing $r_i$.\textsuperscript{10}

Spatial diversity of action potential characteristics. Differences in the membrane current components along an isochrone corresponding to stable propagation are depicted in Figure 7. Because threshold is defined as the point at which $I_{\text{th}}$ begins to move inward on the diagram, only the capacitive current is present below threshold. Thus the linearity of the subthreshold portion of the current–voltage curve reflects the exponential nature of the foot of the action potential, and the slope of the linear segment gives the value of $\tau_{\text{foot}}$. As illustrated in Figure 7, $\tau_{\text{foot}}$ has essentially the same value on the principal longitudinal and transverse axes of a given isochrone.

The curvature of the elliptic isochrone segment on the principal transverse axis is very small at some distance from the stimulation site (e.g., isochrone 12 in Figure 6), and one has a nearly flat wave front. Then the situation depicted on the right of Figure 1 for a flat transverse wave front applies, and the voltage threshold is lower at the output junction than at the input junction. This situation is reflected in Figure 7 by the relative positions of vertical arrows 1 and 3. An intermediate value of the threshold potential (arrow 2) occurs along the principal longitudinal axis.

The spatial diversity of action potential characteristics in the anisotropic sheet is best illustrated through variations in $V_{\text{max}}$ (or its equivalent, peak I). One can see in Figure 7 that peak I, is lowest in the principal longitudinal direction (point 2 of inset). It is
**Figure 5.** Diagram of elliptic propagation in the two-dimensional sheet model of Figure 1. Cable 1 (on the longitudinal edge of the sheet) to cable 50 (center cable) and beyond are shown on the left, with a schematic representation of resistors $R_z$. Events corresponding to various degrees of isochrone curvature are shown as points A–D along the vertical broken line. The isochrone segment at A involves negligible delay of activation ($\Delta t$) between two neighboring input junctions (JCN), a situation that is equivalent to the flat transverse wavefront characterized by a collision at the output junction. The isochrone at B, C, and D involves increasingly larger curvature and delay between the two neighboring input junctions, resulting in the rightward displacement of the collision site and, finally, its partial or complete disappearance. $I_x$, transverse current; $I_{x1}$ and $I_{x2}$, axial currents.
also higher at an output junction than at an input junction in the principal transverse direction (points 1 and 3 of inset).

Variations in $V_{\text{max}}$ across the sheet at points away from the principal transverse axis are shown in Figures 8 and 9. We have chosen to describe the events along the transverse broken line shown in the upper panel of Figure 8 at 3.75 mm from the stimulation site. Because of the pattern of transverse connections used in the present study (Figure 1), there is an alternation between input and output junctions on successive cables along the broken line of the upper panel of Figure 8, starting with an output junction on cable 1 on the longitudinal edge of the sheet. As illustrated in Figure 5, such a transverse line perpendicular to the longitudinal direction of the sheet allows the full range of isochrone curvatures to be encountered. Simulation results with $\Delta=100$ $\mu$m and $R_y=4$ M$\Omega$ gives a range of average $V_{\text{max}}$ of $220-280$ V/sec (Figure 9B), where the average $V_{\text{max}}$ is the mean between values at neighboring input and output junctions on each cable. As depicted in Figure 8, however, there are substantial variations in $V_{\text{max}}$ values between input and output junctions, particularly when the curvature of the wave front is low near the border of the sheet (difference of about 25 V/sec). Both the average $V_{\text{max}}$ value and the difference between input and output junctions decrease

![Figure 6](image)

**Figure 6.** Isochrone patterns of action potential upstroke (activation) obtained with the sheet model of Figure 1 and the nominal parameter values of Table 1. Isochrone numbers correspond to the time elapsed from the onset of the stimulus in milliseconds. The sheet dimensions are $2.5 \times 10$ mm, comprising 100 identical parallel cables spaced 25 $\mu$m apart and 10 mm in length. The stimulation site is at the center of the smallest elliptic contour.

![Figure 7](image)

**Figure 7.** Changes in membrane currents as a function of potential during the action potential upstroke in the sheet model of Figure 1, with nominal parameter values of Table 1. The upstroke for longitudinal propagation (dotted curves) corresponds to a location on the central cable (point 2 in the inset) and to the threshold marked by vertical arrow 2. The upstroke for transverse propagation corresponds to locations on the transverse axis passing through the stimulation site; point 1 is at an input junction (broken curves), and point 3 is at an output junction on the same cable (solid curves); the corresponding threshold potentials are indicated by vertical arrows 1 and 3, respectively. $I_m$ is the total membrane current representing the sum of the capacitive current ($I_c=C_dV/dt$) and ionic current ($I_{\text{ion}}$).
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FIGURE 8. Spatial variations in maximum rate of depolarization (\(\dot{V}_{\text{max}}\)) associated with the propagation of an elliptic excitation wave front as in Figure 6, with the distance between transverse connections on a given cable fixed at 100 \(\mu\)m and transverse resistance of 4 M\(\Omega\). Upper panel: Observation points are in the transverse direction (heavy vertical broken line), 3.75 mm ahead of the stimulation site. \(\dot{V}_{\text{max}}\) values correspond to an input junction on even-numbered cables and to an output junction on odd-numbered cables, thus giving a lower \(\dot{V}_{\text{max}}\) at input junctions during transverse propagation (as indicated in Figure 1). This pattern is lost at cable 35 where, over a small region extending over five cables, a different mode of variation in \(\dot{V}_{\text{max}}\) occurs (situation C in Figure 5). Still closer to the central cable, starting at cable 40, a longitudinal pattern of propagation prevails (summation of longitudinally propagating wave front and input current; situation D in Figure 5) where changes in \(\dot{V}_{\text{max}}\) are reversed compared with transverse propagation, the highest \(\dot{V}_{\text{max}}\) now occurring at the input junctions.

when approaching the center of the sheet, that is, as the curvature of the isochrone increases (Figures 8 and 9).

We define propagation as “predominantly transverse” when a collision occurs on the cable (namely, situations A and B in Figure 5). Then \(\dot{V}_{\text{max}}\) at the output junction on a given cable is always larger than at input junctions on the two adjacent cables. In other words, because of the alternation between input and output junctions on successive parallel cables along a transverse direction, there is an alternation between high and low \(\dot{V}_{\text{max}}\) values as a function of distance during transverse propagation. This condition is responsible for the sawtooth pattern of \(\dot{V}_{\text{max}}\) variations on the left-hand side of Figure 8. This particular result shows that predominantly transverse propagation persists until cable 35 is reached, corresponding to an average \(\dot{V}_{\text{max}}\) of 240 V/sec.

Closer to the center cable the isochrone curvature is still more pronounced and the pattern of transverse alternation between \(\dot{V}_{\text{max}}\) values is lost. In this intermediate zone (cables 25–40 in Figure 8) one can
suspect that only partial collisions occur (situation C in Figure 5).

Still closer to the center cable (namely, cables 25–40 in Figure 8) there is summation of axial and transverse currents on a given cable (situation D in Figure 5) and we have “predominantly longitudinal” propagation. This situation corresponds to the lowest average $V_{\text{max}}$ values along the isochrone, as indicated in Figures 7 and 9B. There are then only small $V_{\text{max}}$ variations between input and output junctions on adjacent cables (longitudinal zone in Figure 8), and one can note that the sawtooth pattern is now reversed with the higher $V_{\text{max}}$ occurring at the input junctions (even-numbered cables).

The magnitude of $V_{\text{max}}$ variations with the curvature of the isochrone is reduced with a stronger transverse coupling, as indicated by the simulation results of Figure 9B with $R_y$ values of 2 and 1 MΩ. As expected, the average $V_{\text{max}}$ of longitudinal propagation is not affected appreciably by a change in $R_y$ since no action potential collisions are involved. The decrease of $V_{\text{max}}$ occurs in the zone of predominantly transverse propagation and, with $R_y=1$ MΩ, $V_{\text{max}}$ changes very little except in the vicinity of the center cable (cables 35–50). Therefore, with the particular pattern of transverse connections chosen here, it is clear that the spatial diversity of $V_{\text{max}}$ becomes noticeable only when the anisotropy ratio of the sheet is sufficiently large. Under nominal conditions and $R_y=1$ MΩ we have $\theta_L/\theta_T=5.4$ (Table 2), and a range of $V_{\text{max}}$ variations of only 10 V/sec is detectable in the small zone of high curvature of the elliptic wave front. Based on the results of Figures 3 and 4, one expects a positive correlation between $V_{\text{max}}$ and SF in the rectangular sheet model. This is verified in Figure 9, and one notes that SF increases as the curvature of the isochrone becomes lower. The range of SF variations is very small, however. With $R_y=4$ MΩ, a maximum increase in $V_{\text{max}}$ of 27% corresponds to only a 3% increase in SF.

The sensitivity of SF to changes in a variety of parameters is described by the results shown in Table 3. As expected, the SF of a flat wave front (SF$_{\text{LF}}$) is

**Figure 9.** Correlation between safety factor of propagation (SF, panel A) and maximum rate of depolarization ($V_{\text{max}}$, panel B) for elliptic excitation wave fronts as in Figure 6. The distance between transverse connections on a given cable is fixed at 100 μm, and transverse resistance values of 1, 2, and 4 MΩ were used. Measurements were obtained along the transverse axis as indicated in the upper panel of Figure 8, and the values plotted represent an average for each cable over a distance of eight cable segments (200 μm). Dotted curve at 4 MΩ in panel B is the average of the jagged curve of Figure 8. Nominal conditions of Table 1 apply unless otherwise indicated.

### Table 2. Longitudinal and Transverse Conduction Velocities Along the Principal Axes of Elliptic Isochrones (See Inset of Figure 7)

<table>
<thead>
<tr>
<th>$\Delta$ (μm)</th>
<th>$R_y$ (MΩ)</th>
<th>$r_i$ (Ω·cm)</th>
<th>$\theta_L$ (m/sec)</th>
<th>$\theta_T$ (m/sec)</th>
<th>$\theta_L/\theta_T$ (m/sec)</th>
<th>$\theta_T$ (m/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>1</td>
<td>200</td>
<td>0.67</td>
<td>0.124</td>
<td>5.4</td>
<td>0.71</td>
</tr>
<tr>
<td>100</td>
<td>2</td>
<td>200</td>
<td>0.67</td>
<td>0.11</td>
<td>6.1</td>
<td>0.71</td>
</tr>
<tr>
<td>100</td>
<td>4</td>
<td>200</td>
<td>0.65</td>
<td>0.074</td>
<td>8.9</td>
<td>0.71</td>
</tr>
<tr>
<td>100</td>
<td>2</td>
<td>400</td>
<td>0.48</td>
<td>0.069</td>
<td>6.9</td>
<td>0.502</td>
</tr>
<tr>
<td>100</td>
<td>4</td>
<td>400</td>
<td>0.47</td>
<td>0.05</td>
<td>9.0</td>
<td>0.502</td>
</tr>
</tbody>
</table>

$\theta_L$ and $\theta_T$, longitudinal and transverse conduction velocities, respectively; $\theta_L/\theta_T$, velocities of flat longitudinal and transverse wave fronts, respectively. For other definitions, see Table 1.

### Table 3. Safety Factor of Propagation in the Longitudinal and Transverse Directions Along the Principal Axes of Elliptic Isochrones (See Inset of Figure 7) and for a Flat Longitudinal Wave Front

<table>
<thead>
<tr>
<th>$\Delta$ (μm)</th>
<th>$R_y$ (MΩ)</th>
<th>$S_{\text{iso}}$ (%)</th>
<th>SF$_{\text{L}}$</th>
<th>SF$_{\text{T}}$</th>
<th>SF$_{\text{LF}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>1</td>
<td>100</td>
<td>1.94</td>
<td>2.0–2.07</td>
<td>2.17</td>
</tr>
<tr>
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<td>2</td>
<td>100</td>
<td>1.95</td>
<td>2.0–2.10</td>
<td>2.17</td>
</tr>
<tr>
<td>100</td>
<td>4</td>
<td>100</td>
<td>1.98</td>
<td>2.09–2.27</td>
<td>2.17</td>
</tr>
<tr>
<td>150</td>
<td>2</td>
<td>100</td>
<td>1.95</td>
<td>1.9–2.16</td>
<td>2.17</td>
</tr>
<tr>
<td>150</td>
<td>4</td>
<td>100</td>
<td>1.98</td>
<td>1.98–2.32</td>
<td>2.17</td>
</tr>
<tr>
<td>100</td>
<td>2</td>
<td>50</td>
<td>1.79</td>
<td>1.79–1.98</td>
<td>1.98</td>
</tr>
<tr>
<td>100</td>
<td>4</td>
<td>50</td>
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<td>1.85–2.0</td>
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</tr>
<tr>
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<td>2</td>
<td>25</td>
<td>1.56</td>
<td>1.60–1.67</td>
<td>1.67</td>
</tr>
<tr>
<td>100</td>
<td>4</td>
<td>25</td>
<td>1.56</td>
<td>1.60–1.68</td>
<td>1.67</td>
</tr>
</tbody>
</table>

$S_{\text{iso}}$, Maximum conductance; SF$_{\text{L}}$ and SF$_{\text{T}}$, safety factor of propagation in the longitudinal and transverse directions, respectively; SF$_{\text{LF}}$, safety factor of propagation for a flat longitudinal wave front. For other definitions, see Table 1.
not affected by the changes in $\Delta$ and $R_s$ because each cable behaves as if it were isolated. It is reduced by a decrease in $\delta_{Na}$, however, since the axial current available to depolarize the downstream current is decreased accordingly. While the SF along the principal longitudinal axis of an elliptic wave front (SF_L) is somewhat lower than SF_{FL}, the results of Table 3 show that it behaves in the same way as SF_{FL}. There is, then, for longitudinal propagation, a clear parallel between relative changes in conduction velocity (Table 2) and SF. On the other hand, while the SF along the principal transverse axis (SF_T) is about equal to SF_L at input junctions (smaller number in SF_T column of Table 3), it is substantially larger at output junctions (larger number in SF_T column of Table 3) where collisions occur and $V_{max}$ is largest. Both SF_L and SF_T are reduced as $\delta_{Na}$ is lowered.

The value of $\tau_{foot}$ is largest in the vicinity of the stimulation site, and it decreases nearly exponentially with distance in both the longitudinal and transverse directions. For the example given in Figure 10 with $R_s=1 \, \text{M}\Omega$ and $\Delta=100 \, \mu\text{m}$, longitudinal and transverse length constants of decrease in $\tau_{foot}$ are 0.55 and 0.15 mm, respectively. When relatively stable propagation has been established (approximately 6 msec in this example), longitudinal and transverse $\tau_{foot}$ values are about equal. The situation was not studied at very low transverse coupling (e.g., $R_s=4 \, \text{M}\Omega$ and $\Delta=200 \, \mu\text{m}$) because the foot of the action potential can no longer be described by a single exponential (a waveform similar to so-called foot potentials is observed).

As shown in Table 4, the CF along the principal longitudinal axis of an elliptic wave front (CF_{L}) is consistently lower than that of a flat longitudinal wave front (CF_{FL}). This situation parallels similar relations for conduction velocity (Table 2) and SF (Table 3). The difference between CF_{L} and CF_{FL} is reduced with a large $R_s$ because a lower transverse current is involved, and both quantities become about equal with $R_s=8 \, \text{M}\Omega$.

The inverse correlation between CF and $\tau_{foot}$ is valid only for cablelike propagation and does not hold for CF_{T} because of the different mode of propagation. Instead of the persistent traveling activation wave front of longitudinal propagation, an action potential is triggered de novo by the transverse current (I_y in Figure 1) at each input junction on a given cable. The higher CF_{T} indicates that a relatively larger proportion of I_y is used to charge the membrane locally (Table 4). In addition, as $R_s$ is increased, there is less current leakage at output junctions and, although I_y is then smaller, CF_{T} is increased substantially because a greater proportion of it serves to charge the membrane locally. Although $\tau_{foot}$ could decrease with distance as the action potential propagates away from the input junction, this did not occur because the collision took place only a short distance away ($\Delta$). Therefore, $\tau_{foot}$ is determined largely by the conditions for action potential triggering at input junctions, and it tends to have roughly the same value as $R_s$ is changed, approximately equal to the stabilized $\tau_{foot}$ of longitudinal propagation at a sufficient distance from the center cable (e.g., 0.5 mm or more) (Figures 7 and 10). Substantially lower $\tau_{foot}$ values could arise during transverse propagation only if $\Delta$ were large enough to allow a sufficient distance for the transient reduction in $\tau_{foot}$ to occur before collision.

**Discussion**

In this theoretical study we examined the role of microstructure on propagation of impulses in cardiac tissue.
tissue. Our simulation results are consistent with several published experimental observations showing deviations of cardiac propagation from the principles of continuous cable theory, thereby highlighting the importance of structural organization in determining the fine details of propagation. The two major aspects emphasized in this paper are the directionally dependent differences in action potential upstroke and the preferential direction for conduction block.

Propagation along the principal longitudinal axis of an elliptic wave front in the model is essentially cablerike. We then find close correlations between the propagation velocity, $V_{\text{max}}$, SF, and CF. Along the principal transverse axis, propagation is in the form of a nearly flat wave front characterized by multiple collisions and substantial variations in $V_{\text{max}}$. There are then no correlations between the various parameters of propagation. Away from the principal axis, the characteristics of propagation are intermediate between these two extreme situations, and the events are more and more cablerike as the degree of curvature of the elliptic wave front increases. In accord with published experimental results, $V_{\text{max}}$ is substantially higher in the oblique and transverse directions than in the longitudinal direction, and our simulations show that SF is directly correlated with $V_{\text{max}}$. On the other hand, contrary to published experimental findings, the stabilized value of $\tau_{\text{foot}}$ is roughly the same at all points along the wave front.

Given the structural complexity of cardiac muscle,\textsuperscript{18,19} the sheet model used in the present theoretical study is a highly oversimplified representation of "microscopic" anisotropic propagation. Nevertheless, taking into account the success achieved in simulating the essential features of propagation of activation wave fronts, we believe that the organizational features adopted are reasonable. First, because anisotropic properties of cardiac muscle reflect a tight electrical coupling of cardiac cells in the longitudinal direction (despite a preliminary report that challenges this hypothesis\textsuperscript{20}), it appears acceptable to view a sheet of myocardium as a set of parallel uniform cables. Each cable may be taken to represent a string of cells, abutted end to end, forming an intracellular continuum of resistivity $r_i$ enveloped by a uniform excitabile membrane. Second, because the tissue is far less well coupled transversely, a regular network of sparsely distributed transverse resistors seems to be a reasonable choice. From the geometry of isolated myocytes and the distribution of intercalated disks and accompanying nexus membrane, one might expect the distribution of cell-to-cell connections to be spatially variable to some extent in all directions. Here, for simplicity, we assume a simple symmetric arrangement with uniform center-to-center spacing of 25 $\mu$m between any two adjacent cables. Given a radius of 5 $\mu$m, a transverse spacing of 11 or 12 $\mu$m instead of 25 $\mu$m would have been more realistic; on the other hand, this is mathematically equivalent to the slightly more realistic case of a fiber diameter of 15 $\mu$m and $r_i=0.30$ k$\Omega$-cm. Other choices for the value of the center-to-center spacing or intracellular resistivity can easily be made to reduce the size of the extracellular space without changing the results. It is only with respect to the calculation of the extracellular field that these parameter values become important. Third, by assuming that the sheet of parallel cables is bathing in an unbounded volume conductor of negligible resistivity, we neglect the concentration-dependent active transport of ions across the membrane and the accumulation of ions in the cytoplasm and in the restricted interstitial space of myocardial tissue. This appears to be acceptable also because these factors are expected to give rise to second-order effects compared with the passive conductance properties of the membrane.

The sheet model is capable of reproducing the essential features of electric propagation in cardiac tissue. A suprathreshold pulse stimulus applied to a small area of the sheet gives rise to the familiar pattern of elliptic isochrones. While there are transient changes in propagation velocity and action potential characteristics as the activation wave front moves away from the stimulation site, stable values under nominal conditions are attained within 6 msec after stimulus onset. In a previous paper,\textsuperscript{10} we showed that the structural organization of the sheet model induces multiple collisions during flat transverse propagation, thus causing a diversity of microscopic behaviors in terms of voltage threshold and action potential characteristics. The results of the present study describe the peculiarities of this spatial diversity of microscopic behaviors along an elliptic activation wave front. Overall, because the model membrane properties are uniform throughout the sheet, variations in action potential upstroke and propagation characteristics are due to the structural organization, passive properties, and dynamic behavior of the sheet model.

In this respect, it must be emphasized that propagation of excitation along the principal longitudinal axis of the elliptic isochrone is not very different from propagation along a cable. The situation is quite different along the principal transverse axis, however, where the nearly flat isochrone segment has the essential features of flat transverse propagation. Because propagation in the usual sense of progressive displacement of a membrane depolarization wave front can occur only along longitudinally oriented cables in the sheet model, the concept of a transversely propagating wave front differs fundamentally from that of cable theory.

In fact, the transverse activation wave front is an undulating potential surface (see Figure 9 of Reference 10), which has the general shape and amplitude of the action potential upstroke. Under nominal conditions ($\Theta=0.11$ m/sec), the rising phase of the wave front extends roughly over 125 $\mu$m (six equally spaced cables with center-to-center spacing of 25 $\mu$m), and its duration is about 1.1 msec. Intermediate situations arise between the two principal axes, giving
rise to progressive quantitative changes in the upstroke and propagation characteristics.

The basic events governing the behavior of the model are associated with either the presence or absence of action potential collisions on individual cables. When propagation is predominantly transverse, the timing is such that a collision occurs between a pair of successive input junctions and $V_{max}$ is large. Otherwise, as the curvature of the isochrone increases, the collision occurs nearer to the downstream input junction, it is less complete, and $V_{max}$ is lower. As the degree of curvature becomes larger, the collision is absent and propagation is predominantly longitudinal. Because of some loss of current in the transverse direction, $V_{max}$ is then actually lower than for longitudinal flat wave front propagation.

**Propagation Velocity, $V_{max}$ and $r_{foot}$**

The ratio of experimentally determined longitudinal to transverse propagation velocity in two-dimensional myocardium may vary from 10:1 in crista terminalis to about 3:1 in ventricular myocardium. In the present model $\theta_t$ is determined solely by $r_t$. On the other hand, $\theta_r$ is governed by a combination of three factors: $R_{m}$, $\Delta$, and $r_t$. It is not possible to modify $\theta_r$ without affecting $\theta_t$. In fact, as shown in Table 2, increasing $r_t$ while keeping $R_{m}$ and $\Delta$ unchanged yields a substantially larger decrease in $\theta_t$ than in $\theta_r$. This is in accord with published experimental results of steady-state variations of $\theta_t$ and $\theta_r$ with stimulus frequency (see Figure 4 of Reference 22).

It has also been observed that $\theta_t$ along the principal longitudinal axis of an elliptic wave front in a strip of dog myocardium is somewhat lower than $\theta_{li}$, $0.35 \pm 0.42$ m/sec compared with $0.29 \pm 0.35$ m/sec. This result occurs in the present model with $\theta_t=0.67$ m/sec under nominal conditions (Table 2) compared with $\theta_{li}=0.71$ m/sec (Table 1). Therefore, as suggested by Levine et al., transverse current flow along the elliptic wave front provides a drag effect and leads to a lower velocity along the principal longitudinal axis.

The spatial variation of $V_{max}$ along a flat transverse wave front is about 10% higher at output junctions than at input junctions when $\Delta=100 \mu m$ and may be 30% or more when $\Delta$ is larger. The situation along an elliptic wave front depends on the degree of curvature (Figures 8 and 9). Over the flat portion of the ellipse in the vicinity of the principal transverse axis, the average $V_{max}$ is large and small displacements of the recording electrodes may yield substantial variations, depending on the proximity of the electrode tip to an input or output junction. Near the tip of the ellipse, in the proximity of the principal longitudinal axis, the average $V_{max}$ values decrease monotonically as the degree of curvature of the isochrone increases. These simulation experiments are in good qualitative agreement with published experimental observations. In a strip of canine ventricle, $V_{max}$ and conduction velocity were shown to change monotonically in an inverse manner: $V_{max}=24 V/sec$ at 0.5 m/sec and $V_{max}=171 V/sec$ at 0.19 m/sec. Comparable results were obtained in the atrium along the principal longitudinal axis ($V_{max}=161 V/sec$ at 1.0 m/sec) and the principal transverse axis ($V_{max}=200 V/sec$ at 0.1 m/sec). To our knowledge, there are no experimental data available to test the hypothesis of possible variations in $V_{max}$ at neighboring points (corresponding to input and output junctions) along a flat transverse wave front. The present results suggest that substantial variations in $V_{max}$ would reflect a relatively large spacing between successive transverse junctions.

With a medium anisotropy ratio, corresponding for example to a velocity ratio of 5.4 ($\theta_t/\theta_r$ in Table 2), there is a negligible difference between the stabilized values of $r_{foot}$ along the longitudinal and transverse axes (Figure 10). A similar result is obtained with higher anisotropy ratios, and when $r_{foot}$ can be reasonably estimated, we find only small directionally dependent differences in $r_{foot}$. Although this is consistent with some published results, it is at variance with others, which show a substantial difference between longitudinal $r_{foot}$ during high-velocity propagation and transverse $r_{foot}$ during low-velocity propagation.

A possible explanation for this discrepancy could be related to the transient changes in $r_{foot}$ as the wave front moves away from the stimulation site along the principal axes of the isochrone (Figure 10). The transient disappears over a short distance in the transverse direction, and even if measurements are made close to the stimulation site, $r_{foot}$ has nearly reached its stabilized value. In the longitudinal direction, however, the transient persists over a much greater distance and $r_{foot}$ is still far above its stabilized value at a distance of 1.0 mm. This suggests that experimental measurements in cardiac tissue may involve an overestimation of $r_{foot}$ along the long axis because of the short distance between the stimulus and recording sites, which would not allow $r_{foot}$ to decrease to its final stabilized value. Another possible contributing factor would be the decremental electrotonic spread of the local response produced by the stimulus. One-dimensional simulation studies have suggested that the propagated local response may produce a distortion of the foot of the action potential extending three or four length constants away from the stimulus site. The nature of the distortion is a flattening of the foot and thus an artificial increase in $r_{foot}$. Its magnitude is a function of the shape and amplitude of the stimulus that may or may not favor the generation of a fully developed local response.

The data in Table 5 were obtained from strips of canine hearts. Assuming that the transverse $r_{foot}$ of 0.29 m/sec is the reference value in atrial tissue, the above argument would have to account for an overestimation of 0.09 m/sec (30%) in the longitudinal direction when the propagation velocity increases from 0 to 1.0 m/sec over a distance of 4.5 mm. In the case of the ventricular muscle, an overestimation of 0.25 m/sec (40%) would occur as the propagation velocity increases from 0 to 0.5 m/sec over a distance...
of 1.7 mm. It seems possible, as argued above, that the incomplete transient decrease in $\tau_{foot}$ associated with a sharp rise in propagation velocity and the electrotonus caused by the extracellular stimulation could account for such differences in $\tau_{foot}$ values. This conclusion is supported qualitatively by our simulations, but the quantitative agreement is not quite satisfactory. For example, taking 0.29 msec as the correct $\tau_{foot}$ measured 0.5 mm away in the transverse direction in Figure 10, a 30% larger longitudinal $\tau_{foot}$ of 0.38 msec would correspond to a longitudinal recording distance of only 0.6 mm. This quantitative discrepancy may be due to a number of factors such as fiber diameter, transverse coupling, and membrane properties.

**Charging and Safety Factors**

The CF is the proportion of input current used to charge the membrane capacitance at a given point. During stable propagation, CF is constant. When a larger amount of current is drawn downstream (e.g., because of a transverse resistance in the case of a uniform cable in Figure 2), less current is available to charge the membrane and CF is decreased. The value of CF is also inversely correlated with $\tau_{foot}$. Thus a lower CF corresponds to a higher $\tau_{foot}$, indicating that less of the axial current is available to charge the membrane capacitance and that the charging process is slower.

With a complex load, as during elliptic propagation in the two-dimensional sheet, CF$_L$ is lower than the CF for a flat longitudinal wave front. Thus less of the current is available to charge the membrane because of the presence of the transverse current, a situation that does not occur during flat longitudinal propagation when the transverse current is zero. As with the difference between $\theta_1$ and $\theta_L$ noted above, the drag effect causing the lower $\theta_L$ also yields a slightly lower CF. In this situation the inverse correlation between CF and $\tau_{foot}$ found in the uniform cable is applicable and the $\tau_{foot}$ of elliptic longitudinal propagation is slightly larger than $\tau_{foot}$ of flat longitudinal propagation.

One notes also in Table 4 that CF$_T$ (CF along the principal transverse axis of the elliptic wave front) is much larger than CF$_L$ as $R_e$ is increased (higher anisotropy ratio, or higher $\theta_1/\theta_L$ in Table 2). It follows that a larger proportion of the input current is used to charge the membrane locally, in comparison with the situation occurring during longitudinal propagation. However, because of the noncablelike transverse propagation (see “Results”), the larger CF$_T$ does not reflect a lower transverse $\tau_{foot}$. Because $C_m$ is uniform all over the sheet and because CF is directionally different, one may conclude that $C_m$ is charged more efficiently in the transverse direction because of the lower loading current.

There is a very close correlation between SF, $V_{max}$ and propagation velocity in the continuous cable (Figure 3). A similar but less precise correlation is found in the truncated sheet (Figure 4). Here the complex loading resulting from the increased sheet area leads to a large decrease in $V_{max}$ and velocity, but the minimum value is shifted away from the junction in the distal direction. In general our simulation results indicate that changes in $V_{max}$ and conduction velocity are good indicators of changes in SF, but in a two-dimensional setting, these changes do not coincide exactly with the site of the disturbance.

We found that the largest SF value was associated with a flat longitudinal wave front (Table 3). With an elliptic wave front, however, there is a lower SF$_T$ than SF$_L$, where flat transverse propagation occurs. This is in agreement with results in strips of normal cardiac tissue. Based on one-dimensional simulations and their own definition of SF, Delgado et al found a contrary result, that is, a higher SF in a continuous cable simulating longitudinal propagation than in a discontinuous cable simulating transverse propagation. As with Equation 5, their own SF leads to SF=1 as the critical condition for continued propagation. However, because the axial downstream current (which they use to calculate the total charge available) depends directly on the downstream load, it is not always a reliable indicator of the excess charge available to sustain propagation. For instance, an increased axial downstream current caused by a lower load may yield a large SF (according to their definition) if the threshold charge does not increase as much as the total charge. This could be a mistake because the capacity of the axial downstream current to sustain propagation depends not only on the total charge available but also on its spatial concentration. In other words, part of the axial downstream current may not be concentrated enough to depolarize the downstream membrane sufficiently to sustain propagation.

The ratio of $\theta/\theta_L$ has also been proposed as an indicator of SF in a one-dimensional cable, where $\theta$ is the actual propagation velocity and $\theta_L$ is the theoretical value of $2A/r$. Under nominal conditions (Table 1) we have $\lambda$=838 mm and $\tau$=5.6 msec for $\theta_L$=0.3 msec. Using a polynomial representation of the membrane current–voltage relation, Jack et al.
have suggested that a large SF could be represented by $(\theta \theta^\gamma)$. Experimental estimations of the SF on that basis point to a value of about 5.27–29 Because $\theta_0$ is a constant, this suggestion is equivalent to using the change in propagation velocity as an indicator of change in SF. Our present simulation results suggest that this estimation is good when the propagation is predominantly longitudinal. It may not apply to transverse propagation.

References

KEY WORDS • cardiac muscle model • action potential propagation • safety factor of propagation • directionally dependent effects of anisotropic tissue
Directional characteristics of action potential propagation in cardiac muscle. A model study.
L J Leon and F A Roberge

doi: 10.1161/01.RES.69.2.378

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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