The Impact of Adjacent Isotropic Fluids on Electrograms from Anisotropic Cardiac Muscle

A Modeling Study

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SUMMARY. Recent studies have reported good agreement between extracellular potentials recorded at the surface of a tissue bath preparation and calculated potentials derived from intracellular action potentials assuming interstitial space is unbounded, homogeneous, and isotropic. In fact, heart muscle is electrically anisotropic. To investigate the effect of interstitial anisotropy, we developed a computer model in which the heart muscle and the perfusate are represented by a three-dimensional grid of resistors. Electric sources are related to transmembrane cardiac action potentials through a bisyncytial model of the heart which considers intracellular space and interstitial space to be interpenetrating domains or syncytia. The sources are affected by intracellular anisotropy. The model study gave the following results: there is good agreement between the model and potentials reported by others for a tissue bath preparation and for epicardial potentials on an insulated heart; to a good approximation, interstitial anisotropy can be ignored in calculating extracellular potentials at the surface of the tissue when it is immersed in perfusate, although there are differences between calculated and experimental values consistent with those observed; interstitial anisotropy becomes important when the electrode penetrates the tissue or when the fluid level drops below 1 mm; potentials are significantly affected by the presence of a very thin layer of fluid; the scale factor for potential amplitude is consistent with a theoretical model previously derived. (Circ Res 51:602-613, 1982)

RECENT studies by Spach et al. (1979) have shown good agreement between extracellular potentials recorded at the surface of a tissue bath preparation and calculated potentials derived from intracellular action potentials. The model used for calculating the potentials assumes that the sources are immersed in an unbounded homogeneous isotropic volume conductor. In fact, the tissue sample is electrically anisotropic and is placed in a fluid which is a bounded isotropic conductor.

In this paper we will show why it is reasonable to neglect extracellular (interstitial) anisotropy in the tissue bath preparation. The problem is approached using a digital computer model in which interstitial space is characterized by a finite element model comprising a resistor grid. Calculations from this model, which incorporates anisotropy and finite extent of the volume conductor, are compared with calculations assuming an unbounded homogeneous isotropic volume conductor. In fact, the tissue sample is electrically anisotropic and is placed in a fluid which is a bounded isotropic conductor.

In this paper, we will first sketch the theory that relates bioelectric sources to action potentials. We will then develop the theory based on reciprocity for relating potentials in the volume conductor to these sources.

Bisyncytial Model

Consider that heart muscle consists of two interpenetrating domains: an intracellular space and an extracellular or interstitial space (Miller and Geselowitz, 1978; Geselowitz, 1980). These spaces will be designated by subscripts i and e, respectively. Both of these domains behave as syncytia so that the current density, J, is given by

\[ \mathbf{J} = \mathbf{J}_i + \mathbf{J}_e = -\frac{1}{\rho_i} \nabla \phi_i - \frac{1}{\rho_e} \nabla \phi_e \]  

where \( \phi \) is the electric potential in either domain and \( \rho \) is the resistivity. Heart muscle is anisotropic, so the \( \rho \) has one value along the fiber axis and a different...
value transverse to it. Hence, in Equation 1, \( \rho_i \) and \( \rho_e \) are to be interpreted as tensors.

The two domains are separated by the cell membrane. Current entering interstitial space at any point is thus the membrane current at that point and is identical to the current leaving intracellular space. In mathematical form, this statement is

\[
I_m = \nabla \cdot j_e = -\nabla \cdot j_i = -\nabla \cdot \frac{1}{\rho_i} \nabla \phi_i = \nabla \cdot \frac{1}{\rho_e} \nabla \phi_e
\]  

(2)

where \( I_m \) is the membrane current per unit volume.

If interstitial space is unbounded, homogeneous, and isotropic, then from Equation 2 it is apparent that \( \phi_e \) is related to \( I_m \) through Poisson's equation. The membrane current, in turn, is related to the second spatial derivative of the intracellular potential. From Poisson's equation, for the unbounded case

\[
\nabla^2 \phi_e = \frac{1}{\rho_e} \nabla \cdot j_e = \frac{1}{\rho_e} \nabla \cdot j_i
\]  

(2)

where \( \phi_e \) is the extracellular potential field, \( j_e \), and \( j_i \) are the current densities entering and leaving the intracellular space, respectively. In point of fact, heart muscle is not isotropic and the volume conductor is bounded. In the general case \( \phi_e \) can be written in terms of a transfer function, \( Z \), as follows

\[
\phi_e(x', y', z') = \int Z I_m(x, y, z) \, dv
\]  

(3)

where \( r \) is the distance from the element of volume, \( dv \), to the observation point. In point of fact, heart muscle is not isotropic and the volume conductor is bounded. In the general case \( \phi_e \) can be written in terms of a transfer function, \( Z \), as follows

\[
\phi_e(x', y', z') = \int Z I_m(x, y, z) \, dv
\]  

(4)

where \( (x', y', z') \) is the observation point and \( (x, y, z) \) is a point in the source region. \( Z \) is a scalar point function which, for a given observation point, depends on \( (x, y, z) \).

\( I_m \) and \( j \) can be related to the transmembrane potential, \( V_m \), by considering propagation at the microscopic level (Geselowitz, 1980). Provided extracellular resistivity can be neglected in comparison with intracellular resistivity,

\[
I_m = \frac{1}{K} \left( \theta_x^2 \frac{\partial V_m}{\partial x^2} + \theta_y^2 \frac{\partial^2 V_m}{\partial y^2} + \theta_z^2 \frac{\partial^2 V_m}{\partial z^2} \right) \]  

(5)

\[
\nabla \cdot j_i = -\frac{1}{K} \left( i \theta_x^2 \frac{\partial V_m}{\partial x} + \theta_y \frac{\partial V_m}{\partial y} + \theta_z \frac{\partial V_m}{\partial z} \right)
\]  

(6)

where \( \theta_x, \theta_y, \theta_z \) are the velocities in the \( x, y, z \) directions respectively, and where \( K \) is given by

\[
K = (\rho_{ct} + \rho_{et}) \theta_x^2 = (\rho_{ct} + \rho_{et}) \theta_y^2
\]  

(7)

where subscripts \( ct \) and \( et \) refer to the longitudinal and transverse directions, respectively, \( K \) can be related to the membrane capacitance, \( C_m \), fiber radius, \( a \), and time constant of the foot of the action potential, \( \tau_{foot} \), as follows

\[
K = \frac{a}{2 C_m \tau_{foot}}
\]  

(8)

Note that the sources depend on \( K \) and the conduction velocity, whereas the volume conductor in which the sources are immersed is characterized by the interstitial resistivities.

In the present simulation, \( \theta_x = 0.4 \text{ mm}/\text{msec}, \theta_y = 0.2 \text{ mm/msec}, K = 132 \text{ \Omega cm-mm}^2/\text{msec}^2, \rho_{ct} = 150 \text{ \Omega cm, \rho}_{et} = 450 \text{ \Omega cm}. \) These values were used in all calculations presented in the figures below except where noted otherwise.

Our primary objective in this study was to examine the effects of changes in the conducting medium near muscle undergoing excitation. In the context of Equation 4, our objective was to examine the effects of changes in \( Z \) rather than effects of changes in \( I_m \). In real muscle, or in experimental preparations, it is difficult to examine the effects of changes in \( Z \) alone, since changes in \( Z \) produce changes in \( I_m \). For example, sufficiently high extracellular resistivity stops excitation altogether. One of the opportunities afforded by having a mathematical-numerical model was to avoid this linkage; that is, we chose the nominal values for \( K, \theta_x, \) and \( \theta_y \) given above and left them unchanged despite changes in extracellular resistivity or anisotropy. As a consequence, the results below show the changes in extracellular waveforms that would result from changes in degree of anisotropy or level of adjacent isotropic fluid assuming that the time course of membrane currents remained constant.

Reciprocity

To obtain \( Z \), we will use the reciprocity theorem. A point current source \( I \) at \( (x, y, z) \) gives rise to a potential \( \phi \) at \( (x', y', z') \). Conversely, a current source \( I' \) at \( (x', y', z') \) gives rise to a potential \( \phi' \) at \( (x, y, z) \).

\[
\phi = Z I \]  

(9)

\[
\phi' = Z' I'
\]  

(10)

The reciprocity theorem states that

\[
Z = Z' = \phi' / \phi
\]  

(11)

If \( I = I_m \), \( dv \), then

\[
\phi_e = \int Z I_m \, dv = \int Z (-\nabla \cdot j_i) \, dv
\]  

(12)

where \( I_m \) and \( j_i \) are given by Equations 5 and 6. Hence, \( \phi_e \) can be calculated from a knowledge of cellular action potentials and the transfer function. In the present analysis, the transfer function will be obtained using reciprocity. Note that the reference for the potential \( \phi \) corresponds to the location of the sink for the current \( I' \).

Equation 12 may be cast in another form with use of the vector identity

\[
\nabla \cdot Z \hat{j}_i = Z \nabla \cdot \hat{j}_i + \hat{j}_i \cdot \nabla Z
\]  

(13)

Then

\[
\int \nabla \cdot Z \hat{j}_i \, dv = \int Z \hat{j}_i \cdot dS
\]  

\[
= \int Z \nabla \cdot \hat{j}_i \, dv + \int \hat{j}_i \cdot \nabla Z \, dv
\]  

(14)

If the surface \( S \) encloses the entire source region, \( j_i \)
= 0 on S, and from Equation 12

$$\phi_e = \int \vec{J}_r \cdot \nabla Z \, dv$$  \hspace{1cm} (15)

From reciprocity and Equation 10, $\nabla Z$ is the electric field arising from a unit current $I'$. This field is called the lead field (McFee and Johnston, 1953).

In the case of an unbounded homogeneous isotropic volume conductor of resistivity $\rho$

$$Z = \frac{\rho}{4\pi}$$  \hspace{1cm} (16)

and (compare with Equation 3),

$$\phi_e = \frac{\rho}{4\pi} \int \frac{1}{r} \, dv = - \frac{\rho}{4\pi} \int \vec{J}_r \cdot \nabla \left( \frac{1}{r} \right) \, dv.$$  \hspace{1cm} (17)

It is apparent from this equation that $\vec{J}_r$ may be interpreted as a current dipole moment per unit volume.

Equations for calculating extracellular potentials in terms of cellular action potentials may be obtained either by substituting Equation 5 into Equation 4 or by substituting Equation 6 into Equation 15. Hence,

$$\phi_e = \int \left[ \theta_x \frac{\partial^2 V_m}{\partial x^2} + \theta_y \frac{\partial^2 V_m}{\partial y^2} + \theta_z \frac{\partial^2 V_m}{\partial z^2} \right] \, dx \, dy \, dz$$  \hspace{1cm} (18)

and

$$\phi_e = -\frac{1}{K} \int \left[ \theta_x \frac{\partial Z}{\partial x} \frac{\partial V_m}{\partial x} + \theta_y \frac{\partial Z}{\partial y} \frac{\partial V_m}{\partial y} + \theta_z \frac{\partial Z}{\partial z} \frac{\partial V_m}{\partial z} \right] \, dx \, dy \, dz.$$  \hspace{1cm} (19)

Note that Miller and Geselowitz (1978) based their calculations on Equation 19, taking $\theta_x = \theta_y = \theta_z$, whereas Spach et al. used a two-dimensional version of Equation 18, taking $Z$ to be approximated by Equation 16. A major purpose of the present paper is to compare calculations using Equation 16 with those based on $Z$ determined with consideration of anisotropy and boundary effects for a tissue bath preparation.

Methods

Computation Sequence

In making use of the theory above to simulate waveforms, we used a finite element model and proceeded in the following sequence: (1) a block of "tissue" within a "tissue bath" was represented by a carefully chosen three-dimensional grid of resistors and the position of a single "electrode" on the surface of the "tissue" was identified; (2) the value of each resistor in the grid was computed, taking into account the varying resistivities of tissue and fluid, anisotropy, and the boundaries; (3) transfer coefficients between the electrode and the nodes throughout the portion of the grid that represented the tissue were determined, using reciprocity, by numerically injecting current at the electrode site, computing the resulting voltages everywhere in the tissue, and using Equation 11; (4) an "excitation time" was determined for each node in the grid representing the tissue, based on a postulated site of origin of excitation and form of spread (planar, elliptical, or ellipsoidal); (5) for a sequence of time values extending from before the earliest "excitation time" to after the latest one, the extracellular potential at the "electrode" was computed from the postulated intracellular potentials at all the nodes in the grid using the integral relationship of Equation 18 or 19. Since these equations give the extracellular potential at a single time instant, repeated evaluation of the integral was required to compute the entire extracellular waveform. The paragraphs below give the particular details of each of these steps.

Geometry

The geometry of the basic configuration that we studied was patterned after an experimental tissue bath preparation used by Spach. As shown in Figure 1, this geometry consisted of a block of "tissue" 28 mm on a side, and 10 mm in depth, immersed in a "perfusate" 100 mm on a side and 40 mm in depth.

The $z$ axis is directed vertically upward through the center of the block of tissue with $z=0$ at the lower surface. The $x$ and $y$ axes, respectively, are parallel to and transverse to the fiber axis. The $x$ axis is also designated the fast axis since the velocity of propagation is greatest along the fiber axis, i.e., in the longitudinal direction. Conversely, the $y$ axis is the slow axis. Coordinates will be given in millimeters.

For convenience, we calculated the extracellular potential waveform at the point at the top center of the tissue at the solution interface, i.e., at $(0, 0, 10)$. The calculations require a knowledge of the transfer impedance, $Z$, throughout the tissue. From reciprocity, $Z$ can be determined by injecting unit current at the observation point and calculating potentials in the tissue. To calculate potentials, the heart muscle and the perfusate were represented by a three-dimensional grid of resistors.

At first, we used a grid of resistors that had nodes evenly spaced 1 mm along each coordinate axis. We determined the value of each resistor in the grid by manual calculation prior to program execution. This procedure failed to produce accurate results for several reasons. Even spacing produced grossly inaccurate calculation of current flow within 2 mm of the current injection point. We found...
obvious inaccuracies, by comparing analytic and computed values for full isotropic examples, or by noting the large changes when we compared results for 1-mm spacing with results for 0.5-mm spacing. Accurate calculation near the injection point is essential, since the largest amplitude of \( \phi \) occurs when the excitation wave is very close to the observation point. The waveform of \( \phi \) is therefore dominated by the transfer coefficients near the injection point. Furthermore, with 1-mm spacing, we had \( 37 \times 37 \times 19 = 26,011 \) nodes in a restricted grid, a number large enough that we could not substantially decrease node spacing and still compute the voltages at each node within a practical amount of time with available computer facilities.

Therefore we revised the grid pattern to incorporate uneven spacing. Along the x or the y axis, the node coordinates in millimeters were as follows: 0, 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.40, 0.60, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, 25, 30, 40, 50, whereas along the z axis, nodes were located at 0, 2, 4, 6, 8, 9.5, 9.7, 9.80, 9.85, 9.90, 9.95, 10.00, 10.05, 10.1, 10.2, 10.5, 11, 12, 14, 16, 20, 30, 40. In the vicinity of the injection point, nodes were spaced quite close together, i.e., every 50 \( \mu \text{m} \), whereas near the periphery of the solution, node spacing increased to as much as 10 mm. Nodes were always placed at any boundary between regions of different conductivity. The value of the resistance between adjacent nodes then was computed in a straightforward and consistent way to be described below.

Resistor Calculations

A computer program was developed to calculate resistances for all resistors in the grid. An example of this calculation is given in Figure 2. Consider, for example, the value of the resistor connecting the node with coordinates \((x, y, z)\) to the adjacent node \((x, y + \Delta y, z)\), or in particular connecting \((0.05, 0, 10)\) with \((0.05, 0.05, 10)\). On Figure 2, this resistor connects the node in the center of the box with the corresponding node underneath the plane of the figure (i.e., in the \(y\) direction). Let the adjacent nodes in the \(x\) and \(z\) directions lie in the planes \(x + \Delta x\), \(x - \Delta x\), \(z + \Delta z\), and \(z - \Delta z\), or in particular, the planes \(x = 0, x = 0.1, z = 9.95, \) and \(z = 10.05\). Superscripts of +, — are used to indicate positive and negative directions for increments \(\Delta x, \Delta y, \Delta z\), since the node spacings are unequal in some cases.

The resistance connecting the nodes under consideration is the resistance along the \(y\) axis of the rectangular parallelepiped bounded by planes crossing the \(x\) axis at \(x + \Delta x/2\) and \(x - \Delta x/2\) \((x = 0.075, 0.025)\), crossing the \(z\) axis at \(z + \Delta z/2\) and \(z - \Delta z/2\) \((z = 10.025, 9.975)\), and bounded at the ends by \(y\) and \(y + \Delta y\) \((y = 0, 0.05)\). The \(x\) and \(z\) boundaries of the parallelepiped are indicated by the box in Figure 2 centered on \(x = 0.05\). The parallelepiped was divided into four quadrants, I through IV. The resistance of each quadrant \((R_i, R_m)\) was computed separately. Figure 2 shows the particular calculation for \(R_i\) and \(R_m\). In computing the resistance of each quadrant, we determined the length of each side of the quadrant \((e.g., \Delta x/2)\) by using a table that showed all node coordinates. The side lengths were designated \(\Delta x_i, \Delta y_i, \Delta z_i\) (as listed in Fig. 2) for quadrant I (and similarly for the other quadrants). Since nodes always were placed on boundaries separating regions of different resistivity, a particular quadrant always had uniform resistivity throughout. Therefore, it was necessary to determine whether a quadrant was located in tissue or in solution to find its resistivity, but once this was achieved, a single resistivity value characterized the entire quadrant with no further geometric subdivision necessary. In Figure 2, note that \(\rho_i = 50\) for quadrants I and II, but \(\rho_m = 450\), as does \(\rho_m\), since \(z = 10\) is a boundary.

The resistance \(R\) between adjacent nodes finally was computed as the parallel combination of the resistances of the four quadrants. Since the geometry is symmetric around the current injection point in the \(x\) and \(y\) directions, it was necessary to calculate resistances for only one quarter of the entire grid.

Calculation of Transfer Coefficients

With the use of the principle of reciprocity, transfer coefficients were determined by calculating the voltages produced at each node in the network as a result of unit current injected at the observation point (program AGQ). The standard observation (injection) point was \((0, 0, 10)\).

Three classes of anisotropy were considered: Z1—both the tissue and the fluid isotropic; Z2—both the tissue and the fluid anisotropic; and Z3—the tissue anistropic but the fluid isotropic. Cases Z1 and Z2 were used for checking the numerical solutions. The third case, Z3, was the one we believed most closely approximated real cardiac tissue in a tissue bath. For Z3, resistivities used in the tissue were 150 \(\mu\text{S}cm\) and 450 \(\mu\text{S}cm\), while the fluid resistivity was 50 \(\mu\text{S}cm\).

For the computation, the voltage at the current injection point was arbitrarily set to 1000. The voltages on the \(x\) and \(y\) periphery were held at 0. Hence, these peripheral points act as a current sink for the injected current. To reach a solution sooner, voltages at all other nodes were initialized according to the equation:

\[
\phi = \frac{C_n}{(C_{xx}x^2 + C_{yy}y^2 + C_{zz}z^2)^{3/2}}
\]

In this equation, values of the constants depended on whether the initialization was “isotropic” or “anisotropic.” In the former case, \(C_n = 162\), and \(C_x, C_y, C_z\) were all 1. In the latter case, \(C_n = 240\), \(C_x = 1\), and \(C_y, C_z = 3\).

An interactive calculation was executed, with a new voltage at each node, \(\phi\), found from the previously determined voltages at the six adjacent nodes, \(\phi\), using the condition
that the sum of currents into the node through the six
connecting resistors, \( R_{0i} \), was zero. That is, the new voltage,
\( \phi_n \), was computed according to the following equation:

\[
\phi_n = \left[ \sum_{i=1}^{6} V_i/R_{0i} \right] / \sum_{i=1}^{6} (1/R_{0i}).
\] (21)

In most calculations, 400 iterations were performed. Each
iteration consisted of computing a new value of the 12,696
(23 \( \times \) 23 \( \times \) 24) nodes. This calculation required just under
7 minutes on an IBM 370/165 computer. To obtain \( Z \), the
voltages at each node were normalized by dividing by the
current calculated to enter the injection point. See Equation
11.

A complete set of transfer coefficients for all four quad-
trants around the z axis was created from the single quad-
rant’s results determined by the ACQ program. Since four
times the injection current would have been required for
four quadrants to produce the same voltages, we quadru-
pled the originally computed injection current’s value.

Because there were a large number (12,696) of nodes in
the grid, and because our solution procedure was an itera-
tive one, we performed a number of checks to verify that
our transfer coefficients were correct. These included: (1)
comparing the computed transfer coefficients for the full
isotropic (Z1) and full anisotropic (Z2) cases to those ex-
pected analytically if the medium extended to infinity, (2)
determining the variation in the transfer coefficients for the
tissue case (Z3) if the number of iterations was extended
from 400 to 800 to 1600, and (3) comparing sets of transfer
coefficients for the tissue case after initializing the program
“isotropic” or “anistropic.” Moreover, for all sets of transfer
coefficients, we verified manually that at randomly chosen
nodes the sum of currents entering the node was zero to
within a very small error. All of these checks indicated
solution errors of only 1 to 3%. These errors were much
less than differences we observed later between isotropic
and anisotropic calculations.

Excitation Sequences

Excitation sequences and the resulting extracellular wave-
forms were divided into three broad divisions. The divisions
were: (1) plane waves—one-dimensional propagation in the
x or y direction, (2) elliptical waves—two-dimensional propa-
gation, where lines of equal excitation time (isochrones)
formed ellipses, and (3) ellipsoidal waves—three-dimen-
sional propagation where surfaces of equal excitation time
formed ellipsoids.

The plane wave and elliptical wave cases were taken to
apply to the tissue bath preparation where the active tissue
was assumed to extend to a depth of 0.3 mm [see Spach et
al. (1979)]. Therefore, for plane wave and elliptical excita-
tion, the excitation wave along the third (z) dimension was
assigned an extent of 0.3 mm and was centered at \( z = 9.85 \),
i.e., it extended 0.3 mm beneath the surface of the tissue.
Note that 9.7 mm of tissue remained below the active layer
since the plane excitation, the excitation wave along the third (z)
dimension was assigned at \( z = 10 \), i.e., it extended \( 0.3 \) mm
beneath the surface of the tissue.

For the elliptoidal or three-dimensional case, the entire
block of tissue is assumed to be active. This case would be
applicable, for example, to studies of epicardial stimulation
of the intact ventricle. For the elliptical excitation, excitation
began at one of three (x, y) points: \((-3, 0), (-3, -3), \) or \((0, -3)\). For ellipsoidal excitation, excitation began at \( z = 10 \)
and at one of the same three locations as for the elliptical excitation wave. In this case, excitation proceeded in the
\( -z \) direction as well as along both directions of the x and y
axes. Excitation waves were assigned velocities of \( \beta_x = 0.4 \)
mm/msec and \( \beta_y = 0.2 \) mm/msec, with \( \beta_z = 0.2 \) mm/sec
for the elliptical case.

Calculation of Waveforms

The present study was limited to the QRS complex
associated with the spread of excitation, i.e., with the de-
polarization of individual cells. Hence, only the upstroke of
the cellular action potential is of interest. The upstroke was
defined by the following equation:

\[
V_m = 52 \tanh (2.7 (t - \tau)) - 38
\] (22)

where \( V_m \) is in millivolts, and \( t \) and \( \tau \) are in milliseconds.
Time \( \tau \) is the time when the middle of the upstroke of the
action potential reaches a particular node and varies from
node to node.

This action potential is 104 mV peak-to-peak. The middle
of its upstroke occurs at \( t = \tau \) with \( V_m = -38 \) mV. The time
required for the action potential to rise through 10% to 90%
of its upstroke is 1.1 msec.

Consider a plane wave propagating in the x direction. Define
\[
w(x) = \int_{-14}^{14} Z(x, y, 9.85) dy.
\] (23)

Then, from Equations 18 and 19, we have alternative expres-
sions for the extracellular potential

\[
\phi_n(t) = \frac{-\Delta \theta_x^2}{K} \int_{-14}^{14} w(x)(\partial^2 V_m(t - x/\theta_x) / \partial x^2) dx
\] (24)

\[
\phi_n(t) = \frac{-\Delta \theta_y^2}{K} \int_{-14}^{14} \partial w(x)(\partial V_m(t - x/\theta_y) / \partial x) dx
\] (25)

where \( \Delta z = 0.3 \) mm, the extent of the wave into the tissue,
and \( K = 132 \).

Straightforward use of Equation 24 proved unsatisfactory
because the values of the second derivative changed drasti-
cally in the interval between successive nodes in those
portions of the tissue where node spacing was 1 or 2 mm.
Although this problem could probably have been resolved
by locally interpolating the values of the transfer coeffi-
cients, \( Z \), which changes smoothly from node to node, we
found that the use of Equation 25 gave good results.

For numerical computation, Equation 25 becomes

\[
\phi_n(t) = \frac{-\Delta \theta_z^2}{K} \sum_{i=1}^{n} \left[ V_m(t - x_{i+1} - x_i) - V_m(t - x_{i+1}/\beta_x) - V_m(t - x_i/\beta_x) \right]
\] (26)

Note that Equation 26 requires that \( V_m \) rather than any
of its derivatives, be evaluated at each node. A similar
expression is used for propagation in the y direction. Compu-
tation time can be conserved by noting that the term in
the brackets involving \( V_m \) vanishes to a good approximation
for all \( x_i \) for which \( |t - x_i/\beta_y| > 1.5 \).

For elliptical excitation initiated at \((x_o, y_o)\), Equation 27
determined the excitation time, \( \tau \), at each intracellular
location and Equation 19 was used to compute extracellular
potentials.

\[
\tau(x, y) = \left[ \frac{(x - x_o)^2}{\beta_x^2} + \frac{(y - y_o)^2}{\beta_y^2} \right]^{1/2}
\] (27)

Again the wave was assumed to extend a distance \( \Delta z = 0.3 \)
mm into the tissue. Equation 27 was extended to three-dimensional form for ellipsoidal excitation.

Transfer coefficients and waveforms were computed for a number of variations of the original tissue and fluid geometry and resistivity. For the plane wave case, in addition to the standard tissue resistivity values of 150 Ωcm/450 Ωcm, calculations were completed for resistivities of 150 Ωcm/405 Ωcm (anisotropy ratio of 2.7:1.0). Variations of perfusate level were studied for all three cases. Note that the standard configuration has a fluid level of z = 40 mm, whereas a level of z = 10.0 mm corresponds to the absence of any perfusate on the tissue surface. For the plane wave case, the fluid level was varied to be 10.00, 10.05, 10.20, 11, and 20 mm; for the elliptic wave case it was varied to be 10.00 mm; and for the ellipsoidal wave case it was varied to be 10.00 and 10.05 mm. Finally, the effect of having the electrode penetrate into the tissue was simulated by adjusting the height of the tissue to be 10.05, 10.1, 10.2, 10.5, 11.0 mm, while retaining the observation point at a level of z = 10.00 mm.

Results

Verification of Calculations

Analytic solutions are available for unbounded homogeneous isotropic and anisotropic conductors. As a test of our model, we computed potentials for cases in which the entire volume was either isotropic, or anisotropic with a resistivity ratio of 1:3:3. Although the volume conductor is bounded in the model, potentials at points not too close to the boundary should agree closely with the analytic solution for an unbounded conductor. This comparison of computed with analytic results revealed flaws in a number of early approaches. Good agreement was obtained with the final version.

Figure 3 shows plots of $\phi_e(t)$ assuming the volume conductor is homogeneous and isotropic. The result from the model is compared with the result obtained analytically assuming $Z$ varies inversely with $r$, i.e., assuming the volume conductor is homogeneous, isotropic, and unbounded. To check the adequacy of the original grid's spacing, we computed waveforms using more dense spacing. A third curve in the figure shows results from the analytic expression where the grid spacing has been reduced by a factor of 16.

The three curves are essentially superimposable except for the early portion of the rising phase. The curve calculated using the denser spacing of nodes is smooth, whereas the other two show irregularities. The irregularities are an artifact of the calculation arising from the fact that the grid spacing used for points distant from the origin is comparable to the value of $\Delta x$ for which $\Delta \psi_e$ departs significantly from zero. See Equation 26. To reduce computer time, we retained the standard grid spacing and smoothed the computed curves.

Plane Waves

Standard Configuration

Figure 4 shows the results for plane waves moving in the fast ($x$) and the slow ($y$) direction computed from the model. We will refer to this result as the anisotropic case. Also shown are extracellular potentials calculated assuming an unbounded homogenous isotropic extracellular space of resistivity $\rho = 50$ ohm-cm. We will refer to this result as the isotropic case.

For the isotropic case, the peak amplitude of the slow wave is 0.30 times the peak amplitude of the fast wave, while for the anisotropic case the ratio is 0.48 (see Table 1). The waveforms are all much the same. Note that, in the isotropic case, $w$ is the same for both directions of propagation. Since $\theta_s = 2\theta_f$, we would expect the fast wave amplitude to be 4 times that of the slow wave if the contribution of $v_m$ were the same. Actually, the spatial spread of $V_m$ is smaller in the $y$ direction, and it more closely resembles a step function, thus giving a greater amplitude for $\phi_e$. The effective increase is 0.30/0.25 or about 20%.

In the isotropic case, the amplitude of the potential is proportional to $\rho$ which may be considered a scale factor (see Equation 16). We define the effective isotropic resistivity, $\rho_{eff}$, as that value of $\rho$ which would make the amplitude of the isotropic case agree with that of the anisotropic case. In the fast direction, agreement in amplitude between the isotropic case and the anisotropic case can be achieved by setting...
### TABLE 1
Comparison of Peak-to-Peak Wave Amplitudes

<table>
<thead>
<tr>
<th></th>
<th>Standard configuration</th>
<th>Reduced fluid level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anisotropic</td>
<td>Isotropic</td>
</tr>
<tr>
<td>Plane wave</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast direction</td>
<td>1.64 mV</td>
<td>1.54 mV</td>
</tr>
<tr>
<td>Slow direction</td>
<td>0.78 mV</td>
<td>0.46 mV</td>
</tr>
<tr>
<td>Slow/fast</td>
<td>0.48</td>
<td>0.30</td>
</tr>
<tr>
<td>Elliptic wave</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast direction</td>
<td>1.52 mV</td>
<td>1.35 mV</td>
</tr>
<tr>
<td>Slow direction</td>
<td>0.81 mV</td>
<td>0.44 mV</td>
</tr>
<tr>
<td>45°</td>
<td>0.85 mV</td>
<td>0.52 mV</td>
</tr>
<tr>
<td>Slow/fast</td>
<td>0.53</td>
<td>0.33</td>
</tr>
<tr>
<td>Ellipsoidal wave</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast direction</td>
<td>2.58 mV</td>
<td>2.11 mV</td>
</tr>
<tr>
<td>Slow direction</td>
<td>1.97 mV</td>
<td>1.23 mV</td>
</tr>
<tr>
<td>45°</td>
<td>1.97 mV</td>
<td>1.21 mV</td>
</tr>
<tr>
<td>Slow/fast</td>
<td>0.76</td>
<td>0.57</td>
</tr>
</tbody>
</table>

See text for explanation of p<sub>eff</sub>. Dash indicates calculation was not done.

\( \rho_{eff} = 53 \) ohm-cm. Similarly, \( \rho_{eff} = 85 \) ohm-cm achieves agreement in amplitude for the slow direction. If we use a geometric mean value of 67 ohm-cm, then amplitudes computed using the isotropic formulation would be too large in the fast direction and too low in the slow direction by about 27%.

The calculations were repeated, using extracellular resistivities increased by a factor of 3 to 450 and 1350 ohm-cm. The peak-to-peak amplitude of \( \phi_{ex} \) increased to 1.84 (12%), that of \( \phi_{ey} \) to 0.84 (7%), and the ratio changed to 2.20, an increase of 4%. Hence, there is only a small effect if tissue resistivity is increased, provided the ratio is preserved. The result is a consequence of the low resistivity of the perfusate.

To evaluate the effect of the ratio of the resistivities in the longitudinal and transverse direction, these values were changed to 150 ohm-cm and 405 ohm-cm, giving a ratio of 2.7 instead of 3.0. The peak-to-peak amplitudes in the fast and slow directions were now 1.70 (4% increase) and 0.78 (no change). Again, there was a remarkably small change, because of the short-circuiting effect of the perfusate.

**Effect of the Fluid Level**

The effect of changes in fluid level is shown in Figure 5. Very little change was observed until the level of fluid above the tissue dropped below 1 mm. Both \( \phi_{ex} \) and \( \phi_{ey} \) increased by amplitude as the level dropped with little change in wave shape. A very dramatic increase occurred when the fluid level was lowered from 0.05 mm to 0. With no fluid above the tissue, the ratio of peak amplitudes became 0.76 (Table 1). When this ratio is multiplied by a factor of \( \theta_x^2/\theta_y^2 = 4 \), it becomes 3.05, which is almost identical to the ratio of extracellular resistivity in the y direction to that in the x direction.

**Effect of Electrode Position**

To evaluate the effect of penetration of the electrode into the tissue, calculations were repeated for various tissue thicknesses, keeping the observation point at \( z = 10.00 \) mm. Figure 6 shows the results for thicknesses of 10.05, 10.10, and 10.20, corresponding...
Elliptic Spread

We assume that when anisotropic muscle is stimulated at a point, the excitation wave will spread so that isochrones on the surface are ellipses. The extracellular waveform will depend on the direction of propagation relative to the fiber axis. We investigated three recording sites: one along the fast axis, one along the slow axis, and one at 45° with respect to either axis. Excitation was assumed to extend to a depth of 0.3 mm.

The three waveforms calculated for the anisotropic and isotropic cases are shown in Figure 7, A and B. For elliptic waves, as opposed to plane waves, the waveform is not symmetrical. Note that the amplitude of the S wave is larger than that of the R wave. The waveform recorded along the slow axis shows an initial negative component, whereas the 45° waveform shows a small initial positive wave followed by a larger positive peak.

The waveshapes for the isotropic case are very similar to those computed assuming anisotropy. There are differences in amplitude which are summarized in Table 1. The geometric mean value for $\rho_{\text{eff}}$ is 75 ohm-cm. If this value is used, then waveforms calculated by means of the isotropic approximation should overestimate amplitudes in the fast direction by about 32% and underestimate amplitudes in the slow and 45° directions by 17% and 9%, respectively. Therefore, the discrepancy in amplitude is smaller than it was for plane wave propagation. The ratio of peak-to-peak amplitudes in the slow and fast directions for the anisotropic case is 0.53.

Figure 7C shows the three waveforms for the anisotropic case when the fluid level above the tissue is reduced to zero. The major effect is to increase all amplitudes substantially and to reduce the relative size of the potential waveform in the fast direction.

FIGURE 7. Extracellular potentials for elliptic wave propagation in fast direction, in slow direction, and in 45° direction. Curves are plotted for anisotropic tissue (panel A) and for an isotropic volume conductor (panel B). Panel C shows the extracellular waveforms for elliptic wave propagation when the level of perfusate above the tissue is reduced to zero. Anisotropic case is shown. In all panels, the recording sites for fast and slow directions are 3 mm from stimulus point. Recording site for 45° angle is 4.2 mm from stimulus point. Slow wave arrives earlier than 45° wave because it is closer to stimulus point.
With the surface of the tissue insulated, the ratio of peak-to-peak amplitudes in the slow and fast directions is 0.78, compared with 0.53 for the standard configuration with fluid above the tissue (see Table 1). Figure 8 shows experimental results of varying the fluid level in a tissue bath preparation.

The 45° wave exhibits a greater delay than the slow wave because, in the simulation, the recording electrodes for the fast and slow waves were placed 3.0 mm from the point of stimulation, whereas this distance was 4.2 mm for the 45° wave. From Equation 27, the values of $\tau$ are 7.5, 15, and 16.8 msec, respectively, in the fast, slow, and 45° directions.

Figures 9 and 10 and Table 1 show results for propagation in three dimensions, which we assume leads to ellipsoidal isochrones. The waveforms are characterized by a prolonged negative potential following the deflection. Only the fast wave exhibits a positive deflection of any consequence. The slow wave and 45° wave are almost entirely negative except for a very small $R$ wave in the case in which the fluid level is reduced to 50 μm. The geometric mean value for $\rho_{EF}$ is 73 ohm-cm, almost identical to that for elliptic spread.

As in the elliptic case, the wave amplitudes increase dramatically when the fluid level is reduced to zero. A significant reduction in amplitude occurs when the fluid depth increases even to 50 μm, indicating the great sensitivity of amplitude to the presence of very thin layers of fluid.

Because of the wave shapes, the measure of the amplitude becomes somewhat arbitrary. In Table 1, we have used the total peak-to-peak excursion when the fluid depth increases even to 50 μm, indicating the great sensitivity of amplitude to the presence of very thin layers of fluid.

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Because of the wave shapes, the measure of the amplitude becomes somewhat arbitrary. In Table 1, we have used the total peak-to-peak excursion. Somewhat different results are obtained when an estimate of the amplitude of the rapid deflection is used. For example, from Figure 10B, the ratio of slow wave amplitude to fast wave amplitude is 0.90 on the basis of peak-to-peak deflections as shown in Table 1, whereas if the rapidly descending portion of the waveform is used, this ratio becomes 0.82.

Discussion

Spach and coworkers (1979) have reported results of a comparison of measured extracellular potentials with calculated potentials in a tissue bath preparation. They found good agreement between measured and computed waveforms. In computing waveforms, they assumed the transfer impedance was of the form $Z = \rho/4\pi r$.

Several theoretical papers have considered anisotropy in cardiac muscle and have indicated that extracellular anisotropy may have a significant effect (Plonsey, 1970; Muler and Markin, 1977). Yet, Spach obtained good agreement when he ignored extracellular anisotropy in his calculations. The present model study was undertaken in an attempt to determine quantitatively the effect of extracellular anisotropy on extracellular potentials. The geometry, electrical characteristics, and assumptions concerning the cellular action potential were chosen to agree as closely as possible with those used by Spach. For purposes of comparison, we will use the case of elliptic propagation which corresponds most closely to the experimental situation.

The most striking feature of the results from the model is that the isotropic approximation does rather well in reproducing the waveforms computed in the anisotropic case, which should resemble actual measured potentials. The isotropic case corresponds to the computed waveforms of Spach et al. (1979). See, in particular, Figures 3 and 7 of their paper.

The waveforms from the model exhibit all the salient features of the waveforms reported by Spach, including a larger peak-to-peak amplitude and a larger ratio of $R$ wave amplitude to $S$ wave amplitude in the fast direction, a $Q$ wave in the slow direction, and an initial small positive deflection in the 45° direction. Furthermore, the discrepancies between the anisotropic case and the isotropic case of the model are apparent in the measured and computed waveforms of Spach. In particular, the computed amplitudes in the fast direction are too large, which is precisely what is observed in the model. For example, waveforms 1 and 5 in Figure 7 of Spach show data for propagation in the fast direction. Computed waveforms are 27% and 47% larger than measured waveforms, for these two examples. These values may be compared with the 32% predicted by the model. Note that the model assumes an ideal elliptical spread, while, experimentally, the isochrones departed from the ideal. Computed extracellular waveforms would depend on the shape assumed for the isochrones.
In calculating waveforms, Spach et al. take $K = 92.6 \text{ ohm-cm-mm}^2/\text{msec}^2$ and $\rho = 150 \text{ ohm-cm}$. The ratio $\rho/K$ enters as a scale factor (see equations 16 and 18). The value of $\rho$ was chosen to obtain a good fit between measured and calculated amplitudes, and is thus equivalent to $\rho_{\text{eff}}$.

The value of $K$ used by Spach was obtained from the experimental data of Clerc (1976) and utilized Clerc's data on intracellular resistivity. Clerc expressed his results in terms of the resistivity of the intracellular domain. On the other hand, the resistivities in the present paper are effective resistivities where the intracellular and extracellular compartments are each taken to occupy the entire tissue space (Miller and Geselowitz, 1976; Roberts, Hersh and Scher, 1979). Spach's parameters can be brought into congruence with those used in the model by dividing by 0.7, the volume fraction of intracellular space. $K$ would then become 132, which is the value used in the model, and $\rho_{\text{eff}}$ would become 214 ohm-cm.

The value of $\rho_{\text{eff}}$ determined from the model was 75 ohm-cm. There is therefore a discrepancy of a factor of 2.9. It thus appears that $K$ should be reduced by a factor of 2.9, bringing it to 45. Note that the waveform amplitudes from the model would then be increased by a factor of 2.9 relative to those shown in the figures, bringing them into close agreement with the measured potentials.

Clerc studied trabecular bundles from the right ventricle of calf heart, whereas Spach et al. used canine ventricular muscle. Refer to Equation 8. It would appear reasonable to assume that the membrane capacitance is the same. Clerc reports $a = 10 \mu\text{m}$ and $\tau_{\text{foot}} = 650 \mu\text{sec}$ for the calf fibers. On the other hand, Spach et al. (1981) have reported $\tau_{\text{foot}} = 920 \mu\text{sec}$ for the canine fibers, which range in diameter from 7 to 12 $\mu\text{m}$, with an average radius of 5 $\mu\text{m}$. Hence,

$$\frac{K_{\text{Clerc}}}{K_{\text{Spach}}} = \frac{10 \times 920}{650 \times 5} = 2.8,$$

which is in good agreement with the ratio predicted by the bisyncytial model.

Values of intracellular resistivity do not appear explicitly in the model, although they are implied by Equation 7 and would depend on the values assumed.
for interstitial resistivity. The model study indicates, however, that amplitudes of extracellular potentials in the tissue bath preparation are very insensitive to the precise values of the extracellular resistivities because of the low resistivity of the perfusate. Hence, no conclusions concerning intracellular and extracellular resistivities, other than ratios, can be drawn from this type of tissue bath experiment by itself.

Refer to Figures 5, 7C, and 8. Both the experimental and model results show that decreasing the perfusate level has very little effect on the waveform amplitude until the fluid level above the tissue surface drops below 1 or 2 mm, at which point the amplitude increases as the fluid level diminishes. The effect for the model is much more dramatic, perhaps because the increase is most rapid when the level drops below 100 μm. It is possible that a thin film of fluid remains on the tissue surface.

The waveforms shown in Figure 10 for ellipsoidal propagation seem to agree well with experimental curves presented by Roberts et al. (1979), who measured epicardial potentials on an insulated canine heart. Peak-to-peak wave amplitudes from their Figure 1 are 60, 45, and 40 mV, respectively, for the fast, 45°, and slow waves. If the amplitudes from the model for the zero fluid case are multiplied by 2, the results are 53, 47, and 48 mV, respectively. Care must be taken in making a quantitative comparison, since the electrode locations reported by Roberts do not quite agree with those used in our model. Furthermore, Roberts reports θ, θ = 0.42, whereas our model uses a ratio of 0.50.

Roberts also discussed the problem of determining the amplitude of the waveform. He used a particular measure of the rapid deflection which he termed “wavefront voltage.” It might be observed that he reported a considerable scatter in his “wavefront voltage” measurements.

Plane wave propagation is one-dimensional. From Equation 2 using the relation \( V_m = \phi_i - \phi_e \), we obtain as the solution for a plane wave in an unbounded volume conductor,

\[
\phi_e = \frac{\rho_e}{\rho_i} \phi_i = -\frac{\rho_u}{\rho_i + \rho_e} \dot{\phi}_m. \tag{28}
\]

If we consider axial propagation in an insulated cylinder of muscle, then Equation 28 still holds, since it satisfies the boundary conditions at the surface of the cylinder. This result is identical with that of cable theory. Hence, the bisyncytial model is consistent with the observed cable-like behavior of cardiac muscle. Weidmann (1970) used the cable properties to determine the electrical parameters of cardiac muscle, and Clerc (1976) extended this approach to include anisotropy by studying propagation in the longitudinal and in the transverse direction in strips of heart muscle.

The boundary conditions for three-dimensional propagation in an insulated heart differ from those of axial propagation in an insulated cylinder. Hence, Equation 28 is no longer valid. The extracellular potential is not simply proportional to the intracellular potential; it has a different wave shape, which varies with the direction of propagation as observed experimentally and predicted by the model calculations.

Roberts et al. (1979) used their data from the intact insulated canine heart to derive resistivity values for canine ventricle. To do so they assumed that the ratio of extracellular potentials in the slow and fast directions predicted by Equation 28 was valid, i.e.,

\[
\frac{\phi_{ex}}{\phi_{ie}} = \frac{\rho_{ex}}{\rho_{ie}} \frac{\rho_{ie}}{\rho_{ex}} + \rho_{es}
\]

where the caret over the \( \phi \) indicates a measure of the amplitude. For the resistivity values of the present simulation with the use of Equation 7, the ratio on the right hand side of Equation 29 is 0.75. This value agrees rather well with the results for zero fluid level for plane waves (0.76), elliptical waves (0.78), and the rapid deflection of ellipsoidal waves (0.82). Hence, it appears that Equation 29 may be a good approximation. A note of caution must be raised, however, because of the dramatic changes observed in extracellular potentials for an electrode penetration as small as 50 μm or in the presence of a 50-μm layer of fluid. Note especially the change in ratio of slow wave amplitude to fast wave amplitude for the 50-μm layer of fluid. The fluid will tend to diminish the apparent effect of anisotropy.

To simulate the effect of electrode penetration into the tissue, the electrode was kept at (0,0,10) while the height of the tissue was increased above z = 10. The excitation wave was unchanged. To be more precise, the geometry of the excitation wave should be altered to extend to the new height of the tissue. Nonetheless, the results should be substantially correct, especially for the smaller depths of penetration.

When the electrode penetrates the surface of the muscle, or when the fluid level drops below about 1 mm, the potential waveforms change significantly. Hence, in these cases, extracellular anisotropy cannot be ignored. In the case where the muscle is immersed in an isotropic fluid of lower resistivity, then potentials at the surface of the muscle or in the fluid can be approximated by assuming extracellular space to be isotropic, at least for the geometries studied here. It must be emphasized that in all cases the cardiac sources did depend on intracellular anisotropy as predicted by the bisyncytial model.

We draw the following conclusions from the computer model study.

1. The bisyncytial model which incorporates extracellular and intracellular anisotropy, accounts well for extracellular potentials given the spatial distribution and time course of the transmembrane action potential.

2. In a tissue bath preparation, interstitial anisotropy can be ignored to a good approximation because of the low conductivity of the isotropic perfusate. A major effect of the assumption of interstitial isotropy is to enlarge the amplitude of calculated potentials in...
the longitudinal (fast) direction without affecting the waveshape.

3. When the fluid level is reduced to zero or when the electrode penetrates the tissue by a small amount, effects of interstitial anisotropy become important. A fluid level of 50 μm also results in anisotropy effects which are significantly different from those with no fluid above the tissue surface.

4. A prediction of the bisynaptic model concerning the relation of the scale factor for potentials to the size of the myocardial fibers and the time constant of the foot of the action potential seems to be consistent with available data.

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