ABSTRACT

Cable theory and active equivalent circuits have been used to simulate the propagation of action potentials along a single nerve or muscle fiber by representing the cell as a unidimensional cable composed of isopotential segments. We extended this method to a two-dimensional sheet of cells which in many ways represents the atrium. Our method consisted of solving for the potential profile of a sheet composed of a large number of isopotential membrane patches, each of which was represented by an active equivalent circuit in which the ionic conductances were functions of voltage and time. The patches were arranged in a rectangular array with resistive interconnections that could be varied over the sheet. We used this model to study the effect of various inhomogeneities on conduction velocity and the resulting wave fronts in a sheet of excitable tissue. Some of these inhomogeneities included different effective internal resistances in the x and y directions, preferential pathways, and discrete regions of changing resistive connections. The results showed that very localized changes in membrane properties or cellular interconnections produce changes in the wave front over broad areas. This model provides a method for computing the wave fronts of action potential propagation in any two-dimensional inhomogeneous sheet of coupled excitable cells.

KEY WORDS

atrium  wave fronts  preferential pathways  partial differential equations  conduction velocity  mathematical model

Methods

The numerical solution for the voltage profile of a two-dimensional sheet of cells is based on the Crank-
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Nicolson method (6) for solution of a one-dimensional cable and the extension of this method to two spatial dimensions by Peaceman and Rachford (7). A complete discussion of these methods and comparisons with other methods for the numerical solution of this type of equation are given elsewhere (8).

For the one-dimensional representation of a cylindrical cell, each segment is assumed to be isopotential. The length of each segment is chosen to be as short as possible, consistent with time and memory considerations of the computer used. The work of Cooley and Dodge (2) and our own unpublished results show that the conduction velocity of a one-dimensional active cable is very insensitive to the segment length chosen for the simulation.

For a two-dimensional sheet of cells that are assumed to be electrically coupled with low-resistance junctions (Fig. 1A), a patch that is assumed to be isopotential can also be described. It is important to note that this patch does not necessarily correspond to the dimensions of a single cell. As shown in Figure 1A, each patch is connected by coupling resistances to four adjacent segments.

**FIGURE 1**

A: Electrical circuit representation of a sheet of coupled cells. Each resistance (R)-capacitance (C) circuit represents the upper and the lower face of a patch of the sheet. The resistors $R_1$ and $R_2'$ represent coupling resistances in the $x$ and $y$ directions, respectively.

B: Diagram showing how the passive circuit for each patch can be replaced by an active equivalent circuit. The corresponding equations for the total membrane current are also shown.
patches. (This assumption of a rectangular arrangement of patches does not imply that the individual cells are coupled only in a rectangular fashion. The coupling resistors used in the model only represent the equivalent coupling resistances in the x and y directions. The rectangular arrangement of patches is necessary for the application of the Peaceman-Rachford method [7] of alternating implicit solutions for rows and columns.) These coupling resistances represent the cytoplasmic resistance and the intercellular resistances from the center of one patch to the center of an adjacent patch. Since each cell in a sheet has an upper membrane surface and a lower membrane surface which undergo identical potential changes, the membrane resistance and capacitance shown in the circuit diagram represent the combination of the upper and lower faces of the cells included in the patch.

We considered the sheet of cells to be represented by a two-dimensional grid of patches with coordinates x and y; moreover, we denoted a line of patches along the x direction as a row and a line along the y direction as a column. We could reduce the complexity of the numerical solution by treating each row (or column) as a one-dimensional cable and using the standard Crank-Nicolson method (6) (also see Moore et al. [4]) to advance the solution one time step for that row (or column), as long as we included the interactions with the corresponding patches in the adjacent rows (or columns).

The Crank-Nicolson method (6) for implicit integration consists, basically, in writing down node equations for each segment as difference equations and treating them as simultaneous equations of the form

$$B_x V_{x-1} + D_x V_x + A_x V_{x+1} = C_x,$$

where $B_x$, $D_x$, and $A_x$ are constants related to geometrical factors, the grid dimensions, and the coupling resistances, respectively, and $C_x$ is a function of $V_{x-1}$, $V_x$, $V_{x+1}$, and the membrane current. This form does not have to be changed to include the current from the adjacent patches, since this current is merely added to the $C_x$ term for each patch. Thus, this extension of the Crank-Nicolson method (6) to two dimensions, by successive solutions for all of the rows (or columns), advances the complete solution one time step. The actual procedure used was to alternate the use of the columns and rows for alternate time steps.

This method of numerical integration is extremely flexible, since many nonhomogeneous and even nonlinear membrane properties can be introduced. In particular, each patch can be considered to be "active:" the membrane is not simply represented by a resistor but includes ionic conductances in series with batteries corresponding to ionic equilibrium potentials (Fig. 1B). These ionic conductances can be functions of voltage and time. We simulated the active conductances for each patch with the equation proposed for the squid giant axon by Hodgkin and Huxley (1). Also, the sheet need not be homogeneous, since the model parameters can be made functions of the x and y coordinates.

### Tests and Results

**Passive Sheet**

For a passive infinite homogeneous sheet of specific membrane resistance $R_m$ (ohm-cm²), specific cytoplasmic resistance $R_a$ (ohm-cm), and thickness $W$ (cm), the analytical expression for the steady-state voltage profile resulting from a constant current, $I_0$, injected at the center is (9, 10):

$$V(r/\lambda) = \frac{I_0 R_m}{4\pi \lambda^2} K_0(r/\lambda),$$

where $V$ is the voltage as a function of distance $(r)$, $K_0$ is the modified Bessel function of the second kind of order zero, and $\lambda = \sqrt{WR_m/2R_a}$. $K_0(r/\lambda)$ becomes infinitely large as r approaches zero and therefore $V(0)$ must also be infinitely large, since

$$V(r/\lambda)/K_0(r/\lambda) = R_m/4\pi \lambda^2$$

is a constant for all r.

For the numerical solution, the current is not actually injected at a point but rather is applied to a single membrane patch. This type of stimulation makes the potential of the central patch a finite value. Therefore, it is possible to compare the analytical solution with the voltage profile obtained from a simulation of a passive homogeneous sheet using all patches except the central one. Realizing that the analytical solution is for an infinite sheet, we expected our numerical results for finite sheets to approach this solution as the dimensions were increased or the space constant shortened.

Figure 2 shows the numerical and analytical solutions, at the steady state, for a $21 \times 21$-patch sheet of width 0.005 cm, $R_a = 100$ ohm-cm, $\Delta x = 0.02$ cm, and $R_m = 1000$ ohm-cm² (A) or 20 ohm-cm² (B). Note that the analytical and numerical solutions agree very well for $R_m = 20$ ohm-cm²; however, for $R_m = 1000$ ohm-cm², the numerical solution falls much more slowly than does the analytical solution. This difference is due to the effect of termination of the sheet on the numerical solution and is much more apparent for higher values of $R_m$, since the space constant is correspondingly larger and the termination is therefore closer (in terms of length constants) to the point of current injection. This situation is analogous to the one that exists for the one-dimensional cable, in which the voltage profile is described by an exponential function for an infinite cable but by a hyperbolic cosine for a cable of finite length.

Figure 3 shows the potential along the diagonal of a $21 \times 21$-patch passive homogeneous sheet as a function of time for various patches (A) and as a function of distance at various times (B). In Figure 3A, the potential rises very rapidly at the central patch of the sheet (9, 10) and more slowly as the
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Comparison between the steady-state voltage profile of a numerical solution (stars) and the Bessel function $K_0(r)$ (solid circles) for a $21 \times 21$-patch passive sheet with width 0.005 cm, $R_a = 100$ ohm-cm, $\Delta x = 0.02$ cm, and $R_m = 1000$ ohm-cm$^2$ (A) or $R_m = 20$ ohm-cm$^2$ (B). Voltages of patches along the central row of the sheet are plotted as the ordinate; the abscissa of the graph is the $x$ coordinate of the point plotted. $K_0(r)$ has been scaled to match the value of the numerical solution at a distance $\Delta x$ from the center of the sheet.

EXCITABLE SHEET

If each membrane patch is now given sodium and potassium conductances that are functions of voltage and time, as described by the Hodgkin-Huxley equations (1), an action potential can be elicited by a short current injection at one patch; this action potential will propagate in all directions in the sheet. Figure 4 shows the potential, as a function of time, for points along the diagonal of an $11 \times 11$-patch sheet following stimulation at the central patch, with $\Delta x = 0.02$ cm (A) and $\Delta x = 0.2$ cm (B). In both cases, the coupling resistance $R_a$ is 100 ohm-cm. For the smaller $\Delta x$ the sheet is approximately isopotential, but for the larger $\Delta x$ the action potential propagates in all directions from the point of stimulation.

As the total dimensions of the sheet become smaller, the shape of the action potential depends only on the properties of the active conductances and not on the coupling resistances among the patches in the sheet. In the limiting case, the action potential at every patch must occur at the same time as if recordings were from a single isolated membrane patch. This wave form obtained in an isopotential sheet will be referred to as the membrane action potential (MAP), and the wave form seen at a specified patch of a nonisopotential sheet will be referred to as the propagated action potential (PAP) at that patch. It is clear distance from this point increases, reaching lower values in the steady state. Figure 3B shows the numerical solutions at various times after the stimulus was applied.

Plots of voltage vs. time for various patches (A) and of voltage vs. distance from the central patch at various times (B) for a $21 \times 21$-patch sheet. In A, the potential of patches along the central row with $x$ coordinate 11 (a), 10 (b), 9 (c), and 8 (d) is plotted. In B, the times after the start of the current injection are 0.005 msec (a), 0.1 msec (b), and 0.45 msec (c). In both A and B, $R_m = 1000$ ohm-cm$^2$, $R_a = 100$ ohm-cm, $C_m = 2 \mu$farads/cm$^2$, $\Delta x = 0.02$ cm, and width = 0.005 cm.
from Figure 4 that, for patches other than the central patch, the PAP has a shape similar to that of the MAP.

The central patch requires a large depolarization to initiate a propagating action potential (11). Due to the large "load" of the four adjacent cells, the stimulus required to initiate an action potential is larger than it would be if the central patch were isolated from the other patches. The peak amplitude of the PAP in the central patch is also lower than the peak amplitude of the MAP for the same reason. As the action potential propagates close to the boundary of the sheet, its maximum amplitude and velocity increase because the termination prevents further cytoplasmic spread of current.

**INHOMOGENEOUS EXCITABLE SHEET**

In a study on the passive electrical properties of the rat atrium (12), different values for the passive length constant along the trabecula and transverse to the trabecula have been found. This phenomenon has been interpreted as a difference in intercellular coupling in the two directions, resulting in an effective increase in $R_a$ in the transverse direction. The authors of this study (12) obtained a length constant ratio of about 3:1, which would indicate a coupling resistance ratio of about 9:1. Figure 5 shows the steady-state potential profile for a passive sheet of $15 \times 15$ patches, with a ratio for the specific coupling resistance $R_a$ along the x and y directions of 4:1. The profile along the x axis, the y axis, and a diagonal are plotted.

For a sheet of conducting tissue, we can define a wave front as a function of an angle $\theta$ about the point of stimulation such that $Z(\theta)$ is the distance, along a line drawn at an angle $\theta$, that the action potential has propagated in a specified time. We will say that the action potential has arrived at a point when the potential at that point first exceeds 50 mV. If the sheet is homogeneous, then the conduction velocity in any direction is the same and therefore the wave front must be circular at all times.

One effect of the difference in specific coupling resistance along the two directions is that the conduction velocity is no longer constant in all directions from the point of stimulation. For a unidimensional cable, the conduction velocity varies inversely as the square root of $R_a$. Therefore, a similar dependence of the conduction velocity on $R_a$ would be expected for a two-dimensional sheet.

To study the effect of variations of $R_a$ in the x and y directions, we took as a sign of the arrival of the impulse at a specific patch the time at which the potential of that patch first exceeded 50 mV. By taking a series of patches along the x axis, the y axis, and various angles with respect to the x axis, we obtained plots of conduction velocity as a function of $\theta$. For the angles shown in Figure 6A, the velocity initially increases, reaches a nearly
steady value, and then increases again due to the effect of the termination of the sheet. The wave front during the period of nearly constant velocity (Fig. 6B) is approximately an ellipse with the long axis along the direction of lower $R_a$.

In the preceding simulations, the coupling resistances along the $x$ axis were different from those along the $y$ axis. If we now make all of the coupling resistances the same except for those coupling a single row of patches, we will create a "preferential pathway" along which the conduction velocity will be greater than it is over the rest of the sheet. Figure 7b shows the wave front for a $31 \times 31$-patch sheet in which the central row has coupling resistances of 100 ohm-cm while the other coupling resistances are 400 ohm-cm. It is clear that the presence of this preferential pathway, which is not insulated from the rest of the sheet, produces a marked change in the wave front at all angles from the point of stimulation. This phenomenon results in a broad wave front which might be interpreted as indicating the absence of a sharply defined preferential pathway. Figure 7c shows the wave front for a $31 \times 31$-patch sheet in which the central row has coupling resistances of 1600 ohm-cm while the other coupling resistances are 400 ohm-cm. Again the presence of a narrow slower pathway affects the wave front at all angles from the point of stimulation.

**Discussion**

We have presented an extension of the numerical solution for a unidimensional cable with active segments to a two-dimensional matrix of active membrane patches, and we have applied this method to the simulation of action potential propagation along a thin sheet of electrically coupled excitable cells, the atrium.

Analytical expressions have been obtained for the steady-state potential profile produced by a current injection at a single point for a passive sheet (9, 12-14). All of our simulations were done with sheets of finite dimensions. We showed that for a suitably large passive sheet, the computed voltage profile agreed well with the analytical result. As the dimensions of the sheet were reduced, the changes in the computed voltage profile were qualitatively similar to the effect of termination of a one-dimensional cable. Of course, no analytical solutions exist for the voltage profile of an active sheet, and our confidence in these simulations comes from similar simulations of one-dimensional active cables (2, 4) as well as the symmetrical propagation in the homogeneous active sheet.
and the predictable variations in the wave front with changes in the coupling resistances in the \( x \) and \( y \) directions.

A feature of the model, to which we would like to draw attention, is the size of the individual patches. A more realistic simulation would require patches whose size would be, at the most, the size of the individual cells. Since this simulation is not possible because of the large memory space and computer time required, we have made the simplification of assuming that the cells included within the size of our patches are isopotential at all times. This assumption is analogous to assuming isopotential segments in a cylindrical cell during unidimensional simulations. Having satisfied ourselves with the accuracy of our numerical solutions, we applied the technique to the study of propagation of action potentials in the atrium, where a two-dimensional representation is a reasonable approximation.

Since our model is ideally suited to study propagation, as opposed to excitation, we did not try to match the shape of the experimentally recorded action potential of atrial cells. Since little is known about the conductance changes in atrial cells and in cardiac muscle in general, a model for the electrical behavior of atrial cells has not yet been proposed. However, there is good evidence that at least the rising phase of the action potential is due to a transient increase in conductance similar to that occurring in giant axons (15, 16). Since this rising phase determines the propagation of the action potential, we felt justified in using, as a representation of the atrial action potential, the model proposed to account for the electrical behavior of the axon membrane (1). Therefore, in this paper, we studied only the wave front shape, which should be independent of the membrane model used.

It has been clearly shown that action potential propagation over the atrium does not occur in a homogeneous fashion but rather in a complex pattern of wave fronts which changes with time (17). It is not known to what extent this pattern of wave fronts is determined by variations in active membrane parameters or by variations in intercellular couplings.

Assuming that the atrium is homogeneous in its active membrane properties, we have computed the wave fronts resulting from changes in only the coupling resistances between patches. The changes in the coupling resistances were chosen so as to simulate some structures proposed to account for aberrant propagation, such as preferential pathways (18-20), parts of the sheet along which the action potential travels faster than it does along the rest of the sheet due to either different membrane properties or coupling resistances. The results obtained with our model allow us to predict that a highly preferential pathway would not be experimentally observed if the only parameter affected were the coupling resistances. According to our results, a preferential pathway would have to be the result of two conditions: (1) either different coupling resistances or different membrane properties of the cells involved in the pathway and (2) electrical resistances of the cells in the pathway from the other atrial cells.

Determining membrane parameters and coupling resistances from data of atrial wave fronts is a problem that has no unique mathematical solution. However, it can be approached by modeling techniques in which reasonable assumptions are made for some parameters and the other parameters are varied to fit the experimental data. For example, if the active membrane parameters were known and assumed to be constant for all of the atrial cells, it might be possible to construct a matrix of coupling resistances that would produce wave fronts similar to experimental data. This coupling resistance distribution might be at least grossly verified by resistance measurements and examination of intercellular connections and fiber orientation by electron microscopy.

This paper introduces a method of solving for propagation on two space dimensions as well as some of the tests to which we have submitted this method to check its accuracy. The results presented assure us of the adequacy of the method. In view of the lack of information about active and passive atrial membrane parameters, the range of applicability of this method is limited to those cases in which the results are not affected by the membrane model used. An example of such an application, the shape of the propagating wave front, was used in this paper.

We think that our method is ideally suited to attack some problems already described in the literature that could not be solved due to practical limitations of these early studies. For example, a problem that has attracted the attention of many workers is the self-sustained transmission of impulses in electrically connected, nonspontaneously active networks. As early as 1946, Wiener and Rosenblueth (21) described a mathematical model to account for two of the problems in this group: flutter and fibrillation. The versatility of the model presented in the present paper allows us to in-
troduce inhomogeneities in the two-dimensional sheet and study the effect of "obstacles" in the propagation of an action potential. We hope that this approach will give a better understanding of the mode of initiation of these arrhythmias. In addition, we hope that the method will provide insight into the conditions required to initiate and maintain excitation in a tissue that can be represented by a two-dimensional sheet of cells. It is clear that the quantitative results of this work can only be expressed in terms of the wavelength and velocity of the membrane model used for the simulations.

In summary, we have developed a method of computing the potential profile for a two-dimensional sheet of electrically coupled cells. This method is extremely flexible in that each patch has active conductances which can be represented by the Hodgkin-Huxley equations (1) or by any other mathematically defined voltage- and time-dependent functions; in addition, the coupling resistances between patches need not be constant over the entire sheet. It is important to note that the action potential propagation simulated in the present paper results from an actual numerical solution of the cable equations modified for a two-dimensional sheet and not from the assumption of propagation of a uniform wave, which would be true only for an infinite homogeneous sheet.

Acknowledgment

The authors are indebted to Dr. E. A. Johnson and Dr. M. Kootsey for carefully reading and commenting on this paper. We have benefited from discussions with Dr. M. S. Spach and Dr. F. Starmer. We also appreciate the secretarial assistance of Mrs. D. Munday.

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Simulation of action potential propagation in an inhomogeneous sheet of coupled excitable cells.

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Circ Res. 1975;36:654-661
doi: 10.1161/01.RES.36.5.654

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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