Electrical interactions between a real ventricular cell and an anisotropic two-dimensional sheet of model cells

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Electrical interactions between a real ventricular cell and an anisotropic two-dimensional sheet of model cells. Am. J. Physiol. Heart Circ. Physiol. 278: H452–H460, 2000.—We have extended our “coupling clamp” technique, in which we couple a real cell to a real-time simulation of a computer model of a myocyte and observed a common feature of alteration in propagation with changes in the ratio of the propagation velocity (\(v_T\)) in the transverse direction to the longitudinal velocity (\(v_L\)). Variations in strand geometry (6, 7, 22) were found to change the propagation velocity and enhance the degree of anisotropy both by loss of lateral gap junctions and the development of resistive barriers may play a facilitating role in the development of ectopic foci that may lead to cardiac arrhythmias.

Many experimental and theoretical studies have focused on action potential propagation in cell pairs, linear strands, or multidimensional structures of cardiac cells. Multidimensional cardiac tissue differs in conduction behavior from the simple linear models in several respects. Myocyte structure is asymmetric, with average adult myocytes being 100–150 µm in length and 15–25 µm in width (11, 18), with the cellular arrangement of these cells giving the tissue a structural anisotropy. Anisotropy is further enhanced by the pattern of gap junction distribution such that the propagation velocity (\(v_T\)) in the transverse direction is lower than longitudinal velocity (\(v_L\)), with ratios of \(v_T/v_L\) in the range of 2.7 in the ventricle to as much as 12 in the atrial crista terminalis (3, 10, 14, 32). There are also further anisotropies in cardiac structure produced by the presence of connective tissue strands and the occurrence of scars from prior myocardial infarction (16, 26) that can be represented as resistive barriers because of the effective absence of gap junctions across such regions, which produces “discontinuous anisotropy” (29).

Directional dependence of action potential propagation has been studied in both computer simulations (12, 17, 28) and cell culture systems with cultures grown on a directed collagen matrix to form an anisotropic network (5). Structural complexities affecting propagation and extracellular waveforms have been previously described for intact tissue in the atria and in the Purkinje fibers (27, 30–32) and at the Purkinje-ventricular muscle junction (34). Most of these studies have focused on the effects of the anisotropy and specific discontinuities on propagation of an already established wave of excitation, such as the formation of a “pivoting point” for propagation (4, 8, 23), propagation slowing through an “isthmus” of tissue (1, 2), or effects of sudden variations in strand geometry (6, 7, 22). We have studied many of these same phenomena with our “coupling clamp” technique, in which we either coupled two real cardiac myocytes together or coupled a real myocyte to a real-time simulation of a computer model of a myocyte and observed a common feature of alterations in propagation with changes in the ratio of the source current available to the current sink required to continue propagation (33, 35).

Whereas the multiple effects of anisotropy and resistive barriers on a propagating wave have received much attention, much less work has been done on the effects of anisotropy and resistive barriers on the initiation of a propagating wave of excitation. The initiation of a propagating wave from either a small region of direct stimulation or an automatically active focus involves many of the same general factors, such as the input resistance of the syncytial tissue, the ability of the focus region to serve as a current source, and the sensitivity of the focus region to electrotonic interactions with the surrounding quiescent region, which will tend to either abolish automaticity or prevent the initiation of propagation. One of the major problems in developing such an experimental system is...
that we have been restricted to either completely theoretical solutions of multidimensional arrangements of cell models or experimental models such as intact tissue or cell cultures in which neither the cell membrane properties nor the cellular connectivity can be directly measured. To study the way in which anisotropic connectivity and the presence of resistive barriers affect initiation of a propagating wave, we have extended our methodology of connecting a real cell to one or two model cells (35, 37) to enable the real-time simulation of a two-dimensional sheet of model ventricular cells into which a real ventricular cell is incorporated as the central element of the sheet.

**METHODS**

Cell isolation and electrodes. Single ventricular myocytes were prepared from adult guinea pigs weighing 300–500 g that were anesthetized (intraperitoneally) with 50 mg/kg pentobarbital sodium and 500 units of heparin. The heart was rapidly removed via thoracotomy with artificial ventilation, and the aorta was cannulated for Langendorff perfusion. Single cells were isolated according to the method described previously (33). Briefly, the isolated heart was mounted on a Langendorff apparatus and perfused sequentially with normal Tyrode solution for 5 min, with nominally Ca$^{2+}$-free Tyrode solution for 6–7 min, with nominally Ca$^{2+}$-free Tyrode solution containing collagenase and protease for 8–12 min, and with storage solution for 5 min at a rate of 3–4 ml·g$^{-1}$·min$^{-1}$ at 35–36°C. For ventricular cell isolation, the enzyme-perfused left ventricle was cut into small pieces, stirred in storage solution, and filtered through nylon mesh. The resulting suspension of cells was kept in storage solution at room temperature. The isolated cells were transferred to an experimental chamber containing normal Tyrode solution. The chamber was continuously perfused with normal Tyrode solution at 2 ml/min, and the temperature was maintained at 36 ± 0.5°C. Only cells that were quiescent and had a rod-shaped appearance were used in this study. The pipettes were pulled from borosilicate glass and, after fire polishing, had resistances of 4–6 MΩ when filled with the internal solution. High-resistance seals were formed with the cell membrane with the use of light suction, and the membrane was disrupted by applying a transient suction. The junctional potential was corrected by zeroing the potential before the change in potential (dV/dt) which necessarily introduces some distortion into the real-time simulation of the particular model system. With a dV of 80 μs we found that the cardiac membrane model of Luo and Rudy (LR) (20, 21), which was specifically designed to represent the membrane properties and intracellular ion concentrations of guinea pig ventricular cells, produces stable solutions that differ from their solutions at a dV of 1 μs by only a small percentage for such parameters as the maximum rate of change in potential (dv/dt), conduction velocity, and stimulus threshold (37).

We have been able to extend our methodology for simulating a linear strand of model cells to the real-time simulation of a two-dimensional sheet of model cells with a real cell incorporated as the central element of the sheet using the specified models, using the computed coupling current from the real cell as well as computed coupling currents among the model cells. As we discussed at length in our earlier paper (37), this technique requires a fixed time step (△t) which introduces some distortion into the real-time simulation of the particular model system. With a △t of 80 μs we found that the cardiac membrane model of Luo and Rudy (LR) (20, 21), which was specifically designed to represent the membrane properties and intracellular ion concentrations of guinea pig ventricular cells, produces stable solutions that differ from their solutions at a △t of 1 μs by only a small percentage for such parameters as the maximum rate of change in potential (dv/dt), conduction velocity, and stimulus threshold (37).

Solutions. Normal Tyrode solution contained (in mM) 148.8 NaCl, 4.0 KCl, 1.8 CaCl$_2$, 0.53 MgCl$_2$, 0.33 NaH$_2$PO$_4$, 5 HEPES, and 5 glucose, with pH 7.4 adjusted with NaOH. The composition of Ca$^{2+}$-free solution was the same as that of normal Tyrode solution except that CaCl$_2$ was omitted. The enzyme solution contained 4–6 mg/100 ml collagease (Yakult, Tokyo, Japam) and 0.5 mg/100 ml protease (type XIV, Sigma Chemical, St. Louis, MO) in Ca$^{2+}$-free solution. The storage solution contained (in mM) 120 potassium glutamate, 5 MgCl$_2$, 20 taurine, 0.5 EGTA, 10 glucose, and 10 HEPES, with pH 7.4 adjusted with KOH. The composition of the internal pipette solution (in mM) was 145 KCl, 5 Mg-ATP, 5.0 Na$_2$ creatine phosphate, and 5.0 HEPES, with pH 7.2 adjusted with KOH. The external solution was normal Tyrode solution.

Real-time simulation of a sheet of cells with a real ventricular cell. We previously described the “coupling clamp” method used to provide a coupling conductance either between two real cardiac cells that are not directly in contact with each other or between a real cardiac cell and a real-time simulation of the cardiac cell model (33, 37), and we recently extended this technique to include a real cardiac cell within a linear strand of model cells (36). The common feature of all of these methods is that at each time step, the computer samples the membrane potential of the real cell (through an analog-to-digital converter) and then uses this potential (V$_{cell}$) and the membrane potential(s) of one or more model cells (V$_{model}$) to which the real cell is connected to compute the value of the coupling current leaving the real cell (I$_{C}$) from the sum of the coupling currents to each of the model cells (each computed as (V$_{cell}$ - V$_{model}$)·G$_{c}$, where G$_{c}$ is the value of coupling conductance previously selected). During this same time step, a voltage proportional to the coupling current is sent to the experimental setup by a digital-to-analog converter and then converted to a current of appropriate value by an amplifier and a voltage-to-current converter for passage into the cell through the recording pipette. We also showed that we could model the effective “size” of the real cell by setting the current passing into or out of the real cell via the coupling circuit. Also, during the same time step, the computer solves for the new value of membrane potential for each of the specified models, using the computed coupling current from the real cell as well as computed coupling currents among the model cells. As we discussed at length in our earlier paper (37), this technique requires a fixed time step (△t) which necessarily introduces some distortion into the real-time simulation of the particular model system. With a △t of 80 μs we found that the cardiac membrane model of Luo and Rudy (LR) (20, 21), which was specifically designed to represent the membrane properties and intracellular ion concentrations of guinea pig ventricular cells, produces stable solutions that differ from their solutions at a △t of 1 μs by only a small percentage for such parameters as the maximum rate of change in potential (dv/dt), conduction velocity, and stimulus threshold (37).
include all of the interactions among elements in the entire sheet by solving only for the potential and coupling currents of the 16 elements of the upper right quadrant, even if barriers. Each coupling conductance has a value \( G_x \) in the \( x \)-direction and a value \( G_y \) in the \( y \)-direction. The central element (shaded box) is represented by a real cell with a variable size, and all other elements (open boxes) are represented by real-time simulations of the ventricular membrane model of Luo and Rudy (20).

The upper right quadrant of 16 elements (thick lines) is actually solved in real time (see METHODS).

RESULTS

We varied the size factor for the real guinea pig ventricular cell used as element (0, 0) and paced this cell at 1 Hz while coupling the cell to the sheet shown in Fig. 1 (with no barriers) for various values of \( G_x \) and \( G_y \). Figure 3 shows successful propagation through the sheet for \( G_x = 30 \) nS and \( G_y = 30 \) nS, with a size factor of 7 for the real cell. From bottom to top, each set of four plots of voltage versus time in Fig. 3 is for \( y \)-values of 0, 1, 2, and 3, respectively, and the four action potentials shown on each plot are for \( x \)-values of 0, 1, 2, and 3, as labeled. For Fig. 3 as well as Figs. 4, 5, 8, and 9, the potential waveform of the real cell is plotted as a thicker line. Propagation throughout the sheet was symmetric, with the time of occurrence of activation for element (1, 0) the same as that for element (0, 1), the time of occurrence of activation for element (2, 0) the same as that for element (0, 2), and so on. Along both the \( x \)- and \( y \)-axes there was a delayed propagation from the real cell to the adjacent model cells that is associ-
ated with a partial repolarization in the real cell. When we then reduced the size factor for the real cell to 5, we obtained the results shown in Fig. 4. At this point the early repolarization in the real cell was more extreme and led to failure of action potential propagation away from the real cell into the model cells. For this particular real cell, we found that the critical size for initiating a propagating action potential was 6.3. However, when we continued with a size factor of 5 for the real cell and included the barriers as diagrammed in Fig. 2 into the sheet representation, we obtained the results shown in Fig. 5. The values for $G_x$ and $G_y$ in Fig. 5 are the same as those in Figs. 3 and 4, but propagation is now successful for a size factor of 5 (cf. Fig. 4), although with a different spatial pattern. Note that the action potential in Fig. 5 for $y = 0$ or $y = 1$ is propagating from left to right (activating elements along the x-axis in the order 0, 1, 2, and then 3), whereas the activation order for $y = 2$ or $y = 3$ in Fig. 5 is 3, 2, 1, and then 0 as the action potential propagates counterclockwise around the barrier and then from right to left. The peak amplitude of the action potentials for elements (0,2) and (0,3) is larger because these action potentials are actually "colliding" with action potentials propagating around the upper barrier in a clockwise direction in the upper left quadrant of the sheet (Fig. 2), which we are not directly simulating.

We found a general phenomenon in that action potential propagation from a central cell was more difficult (requiring a larger size factor for the central real cell) when the conductances in the $x$ and $y$ direction were equal than when they were unequal. The data summarized in Fig. 6 were obtained from eight guinea pig ventricular cells. For each cell, using a size factor of 5, we systematically varied $G_x$ and $G_y$ to test the success or failure of propagation through the sheet when the real cell was repetitively stimulated at 1 Hz. In Fig. 6, filled square symbols represent combinations of $G_x$ and $G_y$ for which propagation was successful and open triangular symbols represent combinations for which propagation failed. Fractions beside these symbols indicate the ratio of number of cells with successful propagations to total number of cells tested with the indicated combination of $G_x$ and $G_y$. Note that the failures occur either along the diagonal at which $G_x$ equals $G_y$ or slightly off the diagonal ($G_y = 25$ or 35 for $G_x = 30$). For four of these cells we also tested propagation along the diagonal values of $G_x = G_y$ with the barriers present.

![Fig. 4. Results for stimulation of a real cell with a size factor of 5 incorporated into the two-dimensional sheet with $G_x = G_y = 30$ nS. Each panel shows results for 1 of 4 rows of elements ($y = 0, 1, 2,$ and $3$), and within each panel the results for each of the 4 elements ($x = 0, 1, 2,$ and $3$) are labeled. The real cell has coordinates (0,0) and is plotted as a thicker line. Data are from same cell as in Fig. 3.](image)

![Fig. 5. Results for stimulation of a real cell with a size factor of 5 incorporated into the two-dimensional sheet with $G_x = G_y = 30$ nS and also with barriers (as indicated in Fig. 2). Each panel shows results for 1 of 4 rows of elements ($y = 0, 1, 2,$ and $3$), and within each panel the results for each of the 4 elements ($x = 0, 1, 2,$ and $3$) are labeled. The real cell has coordinates (0,0) and is plotted as a thicker line. Data are from same cell as in Fig. 3.](image)

![Fig. 6. Diagram showing success or failure of propagation into the sheet for 6 real guinea pig ventricular cells. For each cell, using a size factor of 5, we systematically varied $G_x$ and $G_y$ to test the success or failure of propagation through the sheet when the real cell was repetitively stimulated at 1 Hz. ■, combinations of $G_x$ and $G_y$ for which propagation was successful; △, combinations of $G_x$ and $G_y$ for which propagation failed. Fractions beside each symbol indicate ratio of number of cells with successful propagations to total number of cells tested with that combination of $G_x$ and $G_y$.](image)
and found in each case that the presence of the barriers
collapsed failed propagation to successful propagation.
To evaluate this phenomenon more quantitatively,
we systematically varied the size factor for the real cell
to determine the critical size for initiating successful
propagation with a fixed value of \( G_x \) (30 nS) and a
variable value of \( G_y \) from 20 to 40 nS. The results are
shown in Fig. 7, where the experimental results for the
critical size of the central element (mean \( \pm \) SE) are
shown as filled square symbols. We included a horizontal
dashed line at a size of 5 to show that the mean
values of critical size were \(<5\) for \( G_y \) values of 20 or 40
nS but \(>5\) for \( G_y \) values of 25, 30, and 35 nS with the
fixed \( G_x \) of 30 nS. We also did simulations in which we
replaced the real cell at (0,0) with a model cell identical
to the other model cells of the sheet and then deter-
mined the critical size of this central model cell. These
results are shown as open circular symbols in Fig. 7,
showing lower values but the same general phenom-
enon in that a greater critical size was required when
\( G_y \) was equal to \( G_x \).
It may seem paradoxical that the critical size for
initiating propagation for a fixed value of \( G_x \) was
reduced when we either raised or lowered \( G_y \) from the
symmetric value. We show in Figs. 8 and 9 the actual
results obtained for the same cell as in Figs. 3–5 for
which propagation failed with \( G_x = G_y = 30 \) nS. For Fig.
8, we lowered \( G_y \) by using settings of \( G_x = 30 \) nS and
\( G_y = 20 \) nS. Note that activation of the sheet became
asymmetric, as expected. The propagation occurred
with less delay along the \( x \)-axis (\( y = 0 \)) than along the
\( y \)-axis. A similar phenomenon occurred when we raised
\( G_y \) with the fixed value of \( G_x \). We used settings of
\( G_x = 30 \) nS and \( G_y = 40 \) nS and, again for the same cell, got
the results shown in Fig. 9. The activation sequence
was again asymmetric, with a more rapid initiation of
propagation along the \( y \)-axis, producing the same effect
as in Fig. 8 of actually diminishing the electrical
loading on the central cell because of the shorter delay
in propagation (now along the \( y \)-axis), which again
produced the situation in which the cell that had been
activated was no longer a load on the central cell but
actually helped to further the spread of activation.
The mechanisms for the lower critical size of the
central element when we either raised or lowered \( G_y \)
from the symmetric case can be more clearly seen in
Fig. 10, in which we have included the voltage wave-
forms of elements (0,0), (0,1), and (1,0) as well as the
directional division of the currents associated with the
central element. We plotted the total coupling current

![Fig. 7. Critical size factors for 6 real guinea pig ventricular cells incorporated as the central element of the sheet as diagrammed in Fig. 1 with a fixed \( G_x \) of 30 nS and a variable \( G_y \) from 20 to 40 nS ( ), means \( \pm \) SE). ○ results with same protocol in which we replaced the real cell with another model cell. Mean values of critical size were \(<5\) (dashed line) for \( G_y \) of 20 or 40 nS but \(>5\) for \( G_y \) of 25, 30, and 35 nS. LR model, Luo and Rudy model.](image)

![Fig. 8. Results for stimulation of a real cell with a size factor of 5 incorporated into the two-dimensional sheet with \( G_x = 30 \) nS, \( G_y = 20 \) nS, and no barriers. Each panel shows results for 1 of 4 rows of elements (\( y = 0, 1, 2, \) and 3), and within each panel the results for each of the 4 elements (\( x = 0, 1, 2, \) and 3) are labeled. The real cell has coordinates (0,0) and is plotted as a thicker line. Data are from same cell as in Fig. 3.](image)

![Fig. 9. Results for stimulation of a real cell with a size factor of 5 incorporated into the two-dimensional sheet with \( G_x = 30 \) nS, \( G_y = 40 \) nS, and no barriers. Each panel shows results for 1 of 4 rows of elements (\( y = 0, 1, 2, \) and 3), and within each panel the results for each of the 4 elements (\( x = 0, 1, 2, \) and 3) are labeled. The real cell has coordinates (0,0) and is plotted as a thicker line. Data are from same cell as in Fig. 3.](image)
for element (0,0) in the top left panel and the membrane potential of element (0,0) in the bottom left panel of Fig. 10. To represent the three sets of coupling conductances, we used thick lines for the symmetric case \((G_x = G_y = 30 \text{ nS})\), thin lines for the condition in which \(G_y\) increased to 40 nS, and dotted lines for the condition in which \(G_x\) decreased to 20 nS. The total coupling current was plotted with a positive value leaving the cell (0,0), thus producing a repolarization. For clarity, we omitted the stimulus current that was applied as a pulse of 2 ms in duration to initiate the action potential. For the symmetric case, there was no activation of either element (0,1) or element (1,0), and thus the coupling current leaving element (0,0) is a monotonically decreasing function. For each of the asymmetric cases, because both elements (0,1) and (1,0) eventually activated, there are significant changes in the time course of the coupling current of element (0,0). As either of the adjacent elements (0,1) or (1,0) activate, there is a significant decrease in the outward coupling current from element (0,0) because these adjacent elements are no longer an electrical load but actually supply current back to element (0,0). It is clear from the bottom left panel of Fig. 10 that the activation of the adjacent elements is associated with a termination of the fast repolarization process of element (0,0) and thus accounts for the successful activation of element (0,0) for either of the asymmetric conditions.

The mechanisms for the activation of these adjacent elements are shown in the middle and right panels of Fig. 10. In the middle panels, we plotted the coupling current in the \(x\) direction for element (0,0) (top) and the membrane potential of element (1,0), which received one-half of this current [the other one-half went to element (−1,0)] (bottom). Changing the value of \(G_y\) from 30 nS to either 40 or 20 nS did not significantly change the magnitude of the coupling current in the \(x\) direction before activation of element (1,0). However, the response of the membrane potential of element (1,0) to this current was quite different. When \(G_y\) was lowered to 20 nS, element (1,0) had a larger voltage response, which raised the membrane potential to threshold as shown by the dotted line in the bottom middle panel of Fig. 10. The larger voltage response of element (1,0) when \(G_y\) was lowered was produced by the decreased load on this cell in the \(y\) direction through its connections to elements (1,1) and (1,−1) [the elements above and below element (1,0)], and thus activation of element (1,0) occurred with the decreased \(G_y\) value. This activation of element (1,0) then sent current back to element (0,0) to assure activation of element (0,0) and thus produced a delayed activation of element (0,1), as shown by the dotted line in the bottom right panel of Fig. 10.

The right panels of Fig. 10 show the mechanism of successful activation of the array when \(G_y\) was increased to 40 nS. The top right panel shows the coupling current for element (0,0) flowing in the \(y\) direction. When \(G_y\) was raised or lowered, there was a significant increase or decrease, respectively, of this coupling current. Increases in this coupling current produced a greater response of the membrane potential of element (0,1), as shown by the thin solid line of the bottom right panel, and thus led to activation of element (0,1). This activation of element (0,1) then sent current back to element (0,0) and terminated the early repolarization of this element, as shown in the bottom left panel of Fig. 10, which then allowed more current to flow in the \(x\) direction and produced a delayed activation of element (1,0), as shown by the thick solid line in the bottom middle panel. As shown in the top right panel of Fig. 10, decreases in \(G_y\) lowered the coupling current in the \(y\) direction and thus lowered the membrane potential response of element (0,1), as shown in the bottom right panel. However, the activation of
element (1, 0) led to a greater membrane potential in element (0, 0), which then activated, with delay, element (0, 1), as shown by the dotted line in the bottom right panel of Fig. 10.

We next compared the effects of a resistive barrier on the critical size for the central element of the sheet to initiate propagation into the sheet when we let \( G_x = G_y \) (isotropy) except for the specified conductances of the barrier region. Figure 11 shows the critical size as a function of \( G_x \) (or \( G_y \)) for the condition with no barrier. Note that a larger critical size is required when \( G_x \) and \( G_y \) are low than when they are higher. As shown in the outcome plot of Fig. 6, in which no points along the diagonal indicate successful propagation for a size of 5, all of the critical sizes for the sheets where \( G_x = G_y \) are >5 (for which a horizontal line is drawn). Figure 11 also shows the critical sizes determined for the same real cells when connected to sheets where \( G_x = G_y \) but with a barrier added. Note that there is a slight tendency for the critical size to decrease as \( G_x \) and \( G_y \) increase but that all of the values are much lower than for the condition without the barrier and now indicate successful initiation of propagation with a cell size of 5 for the central element.

**DISCUSSION**

There are some limitations to our present implementation of a two-dimensional sheet of cardiac cells. The constraints of a fixed time step of 80 µs, which is required to solve the equations of Luo and Rudy (20, 21) for each of the 15 cell models as well as to provide the interaction with the real cell, introduce a small distortion into the rising phase of the model cell action potential, which we previously discussed (37). The same time considerations limit the size of the sheet that we can simulate (in real time) and thus indirectly limit the degree of anisotropy that we can represent. For very high degrees of anisotropy, the action potential propagates all the way to the edge of our sheet before propagating into the other direction, thus introducing “edge effects” into the results. Although we were not able to run a larger model system in “real time,” we did implement the same two-dimensional sheet representation with a total of 13 × 13 = 169 elements in which we made the same assumptions of symmetry and solved for the upper right quadrant with all 49 of these elements represented by model cells. We repeated the determinations of critical cell size presented in the open symbols of Fig. 7 and found no difference to two decimal places with the larger sheet size, suggesting that for the effects on the central cell of the sheet, our real-time implementation of a sheet of 49 cells is sufficient. We also emphasize that our simulation is entirely based on the assumption that a single cell is, for these values of coupling conductance, very nearly isotropic, as demonstrated by the theoretical work of Shaw and Rudy (24). Thus, for our studies, each “element” is an intact cell, and the actual spatial dimensions and orientation or the particular cells used does not affect the results. We deliberately chose lower values of coupling conductance than those occurring in “normal” ventricular tissue to emphasize the effects that might be observed in cells that are partly uncoupled, such as might have occurred by prior ischemia.

Our major results show that there is a critical size for the central element directly stimulated to produce propagation out into the two-dimensional sheet. For a continuous one- or two-dimensional system, this would be analogous to the “liminal length” that must be activated by a stimulus to produce propagation (9). To further the analogy for discontinuous tissue, the critical size of the central element might be considered the “liminal lump.” Figure 7 shows that this phenomenon can be demonstrated by a simulation that contains only model cells (no real cell), but the numerical values for the critical sizes are significantly lower when the LR model cell is used as the central element. This is consistent with our earlier work (37), in which we showed that the LR model has activation characteristics (current threshold, maximum dV/dt, peak amplitude, etc.) quite similar to those of real guinea pig ventricular cells but does not exhibit as much early repolarization in response to an electrical load as real guinea pig ventricular cells (37). Thus the LR model cell is more effective as a leader cell for propagation than the real cell but serves very well as a follower cell. To some extent, this limitation of size would thus help to determine the critical size of an automatic focus region that might serve as an ectopic focus. However, for a spontaneously firing focus, the effects of the electrophysiological interactions on the diastolic depolarization phase would also be of significance (13, 15, 35).

It is interesting that the size required for our central stimulated element to propagate into a symmetric sheet is higher than that required to propagate into an asymmetric sheet. It is clearly not the case that the critical size of the central element is determined only by the effective passive input impedance of the sheet, because the critical size is lowered (as shown in Figs. 8 and 9) by either lowering or raising one of the conductances from the symmetric value. For the effective electrical load imposed on an active element, the effect...
of repolarization of the central element (which ultimately determines the success or failure of propagation from the central element) depends not only on the conductance but also on the time interval for each current pathway. Our results show that some degree of asynchrony seems to favor activation from a central site. This then helps to explain the facilitating effects of the resistive barrier. As demonstrated in Fig. 5 and shown more quantitatively in Fig. 11, the presence of the resistive barriers as shown in Fig. 2 lowers the critical size of the central element of the sheet. In particular, for the case in which \( G_x = G_y \), the presence of the barrier makes activation of the sheet asynchronous as well as restricting the current flow. The decrease in the critical size of the central element as the coupling conductances are raised without the barrier (Fig. 11) again demonstrates the difference between discontinuous and continuous conduction. If the sheet were a continuous structure and we simply measured the conductance, we would see no increase in critical size when the sheet is divided into two separate regions.

These experiments have demonstrated somewhat paradoxical phenomena in arrays of poorly coupled cells. The presence of anisotropy facilitates the initiation of a propagating action potential compared with the isotropic case. The presence of a resistive barrier near the site of stimulation does not inhibit but, rather, facilitates the initiation of a propagating action potential by reducing the critical size of the central element of the sheet. It has been shown in studies of the remodeling that occurs in peri-infarction zones that there is a particular loss of lateral connections compared with end-to-end connections among heart cells (19, 25). We propose that the normal existence of anisotropy and enhancement of the degree of anisotropy both by loss of lateral gap junctions and the development of resistive barriers may play a facilitating role in the development of ectopic foci that may lead to cardiac arrhythmias.

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