How to Explain Why "Unequal Anisotropy Ratios" is Important Using Pictures but No Mathematics

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Abstract—"Unequal anisotropy ratios" is an important property of cardiac tissue. Many of the fundamental mechanisms governing how the heart responds to an electrical shock require unequal anisotropy ratios. In this paper, I explain the role of unequal anisotropy ratios using pictures rather than mathematics. My goal is to help you develop physical insight, so you can better understand qualitatively why the condition of unequal anisotropy ratios is so important.

I. INTRODUCTION

The bidomain model describes the electrical properties of cardiac tissue [1]. The term "bidomain" arises because the model accounts for two ("bi") spaces ("domains"): intracellular and extracellular. Both spaces are anisotropic; the electrical conductivity depends on the direction relative to the myocardial fibers. Moreover, the intracellular space is more anisotropic than the extracellular space, a condition referred to in the literature as "unequal anisotropy ratios" [2], [3]. This condition has important consequences for the electrical behavior of the heart.

Many papers describe the implications of unequal anisotropy ratios. The mathematical derivations and numerical calculations in these reports emphasize the consequences of unequal anisotropy ratios, but they often fail to explain physically why these consequences occur. For example, Sepulveda et al. discovered that during unipolar stimulation, depolarization occurs under the cathode but hyperpolarization exists adjacent to it along the fiber direction [4]. The hyperpolarized regions affect the mechanism of excitation [5], the shape of the strength-interval curve [6], and the induction of reentry [7]. Yet, when I am asked *why* the hyperpolarization appears, I find it difficult to give an intuitive, nonmathematical answer.

In this paper, I try to answer the "why" questions that arise from the bidomain model. I present no new results, but many old results are clarified. My hope is that the reader will develop the intuition necessary to understand qualitatively how cardiac tissue behaves, without having to resort to lengthy mathematical derivations or numerical calculations.

I. ROTATION AND DISTRIBUTION

Unequal anisotropy ratios causes two distinct effects, which I refer to as "rotation" and "distribution". Rotation occurs because the two spaces have different degrees of anisotropy. Let i indicate the intracellular space, e the extracellular space, L the longitudinal direction (parallel to the fibers), T the transverse direction (perpendicular to the fibers), and g the electrical conductivity. The intracellular space is anisotropic, so $g_{iL} \neq g_{iT}$. In other words, the anisotropy ratio is not equal to one: $g_{iL}/g_{iT} \neq 1$. The extracellular space is also anisotropic, $g_{eL}/g_{eT} \neq 1$. Unequal anisotropy ratios implies that $g_{iL}/g_{iT} \neq g_{eL}/g_{eT}$. For cardiac tissue the intracellular space is more anisotropic than the extracellular space, so $g_{iL}/g_{iT} > g_{eL}/g_{eT}$. If tissue were isotropic, the electric field $\mathbf{E}$ and current density $\mathbf{J}$ would point in the same direction; $\mathbf{J}=g\mathbf{E}$, where g is the scalar conductivity. In anisotropic tissue, $\mathbf{J}$ and $\mathbf{E}$ are not necessarily parallel; the conductivity tensor *rotates* $\mathbf{J}$ toward the fiber direction relative to $\mathbf{E}$. Because of the unequal anisotropy ratios, the intracellular current density is rotated more than the extracellular current density.

Distribution refers to the relative conductivity of the intracellular and extracellular spaces. Current takes the path of least resistance, so more current flows in the space with the highest conductivity. The relative amount of current in the intracellular and extracellular spaces is given by the ratio of the intracellular and extracellular conductivities. Parallel to the myocardial fibers the conductivities of the two spaces are similar, so current *distributes* nearly evenly inside and outside the cells. Perpendicular to the fibers the conductivity is higher in the extracellular space than in the intracellular space, so more current flows outside the cells than inside. In other words, $g_{iL}/g_{eL} > g_{iT}/g_{eT}$.

The astute reader will notice that the two inequalities for rotation and distribution are the same: one can be derived from the other by simple algebraic manipulations. Rotation emphasizes unequal anisotropy ratios, whereas distribution emphasizes unequal current dividing. Ultimately, they lead to the same mathematical condition.

I. ROTATION

A nice example of rotation is illustrated by the magnetic field associated with a planar wave front [8]. Fig. 1 shows an unbounded two-dimensional sheet of tissue with a wave front (shaded) propagating from left to right (the x

direction). The rising phase of the action potential (the boundary between shaded and unshaded regions) has an electric field directed perpendicular to the wave front: to the right in the intracellular space, $\mathbf{E}_i$, and to the left in the extracellular space, $\mathbf{E}_e$. The gray diagonal lines indicate the direction of the myocardial fibers. Anisotropy causes the intracellular current density $\mathbf{J}_i$ to rotate counterclockwise toward the fiber direction. The extracellular current density $\mathbf{J}_e$ also rotates counterclockwise, but not by as much as $\mathbf{J}_i$ because of the smaller anisotropy ratio in the extracellular space. Consequently $\mathbf{J}_i$ is not parallel to $\mathbf{J}_e$, so the net current $\mathbf{J}_i + \mathbf{J}_e$ does not vanish. Continuity of current implies that the components of $\mathbf{J}_i$ and $\mathbf{J}_e$ in the x-direction are equal and opposite, so the net current points in the y direction. This net current produces a magnetic field [8]-[10]. If the tissue had equal anisotropy ratios $\mathbf{J}_i$ and $\mathbf{J}_e$ would be rotated away from $\mathbf{E}_i$ and $\mathbf{E}_e$ by the same angle, so that $\mathbf{J}_i$ and $\mathbf{J}_e$ would add to zero and the magnetic field would vanish. If the wave front propagated parallel or perpendicular to the fibers, $\mathbf{J}_i$ and $\mathbf{J}_e$ would not rotate (mathematically, $\mathbf{J}$ and $\mathbf{E}$ are parallel when directed along the principle axes of the conductivity tensor), so the net current and magnetic field would again vanish.
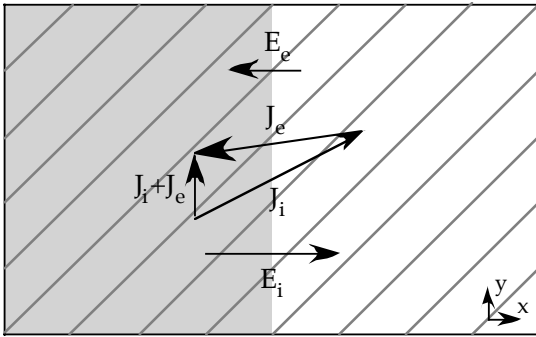

Fig. 1. Rotation: A planar wave front propagating through cardiac tissue. Based on Fig. 1 of [8].

Rotation plays an important role during electrical stimulation. Consider the strip of cardiac tissue shown in Fig. 2, where the top and bottom surfaces are insulated. The irregular surfaces on the left and right indicate that this is a long strip with only a part shown here, and that the ends are far enough away that their effect is negligible. Imagine that an electrode on the far left injects current into the tissue, and an electrode on the far right removes it. Continuity implies that the net current is directed to the right (x-direction). The electric field is not necessarily to the right because charge builds up on the insulated surfaces; positive on the top and negative on the bottom. $\mathbf{J}_i$ and $\mathbf{J}_e$ are not parallel; they have been rotated by different amounts because of the unequal anisotropy ratios. Therefore, in the y-direction $\mathbf{J}_i$ has a component pointing up, and $\mathbf{J}_e$ has an equal component pointing down. Now consider what happens at the insulating surface, where the y-components of $\mathbf{J}_i$ and $\mathbf{J}_e$ must both vanish. Near the top, the y-directed intracellular current must stop. The only place this current can go is out the membrane

into the extracellular space. Outward membrane current depolarizes the tissue (D), so a positive transmembrane potential is induced along the top surface. Similarly, the y-directed extracellular current must stop at the lower insulated boundary. It has no place to go except through the membrane and into the intracellular space, hyperpolarizing the tissue along the bottom surface (H). Trayanova and Skouibine discovered this mechanism of polarization along an insulating surface [11]. Later, I analyzed it in more detail [12].
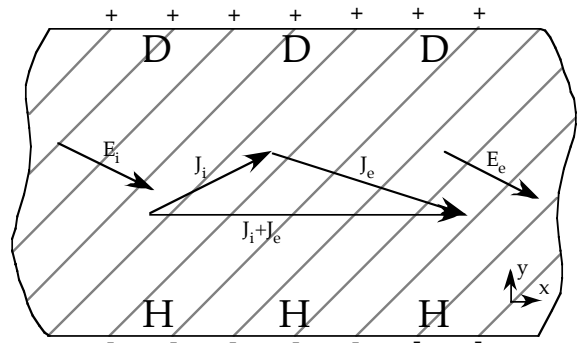

Fig. 2. Rotation: Polarization caused by fibers approaching an insulated surface at an angle. Based on Fig. 3 of [12].

Cardiac fibers rarely approach an insulating surface at an angle (except at a cut surface, such as created in a "wedge preparation"). However, fiber curvature can lead to the same effect, as shown in Fig. 3. The short gray line segments indicate the local fiber direction. The fibers change direction along the y-axis, but do not vary along the x-axis. Current is applied from left to right. The boundary effects discussed in Fig. 2 do not play a role, because the fibers do not approach the upper and lower insulated surfaces at an angle. Where the fibers are in the x- or y-direction (top and bottom), the current and electric field are parallel to each other. Where the fibers are at an angle, a charging of the tissue will cause the electric field to be oriented down and to the right, in the same way as in Fig. 2. The current density will be rotated toward the fiber direction, but to a greater extent in the intracellular space than the extracellular space. Thus, in the middle of the tissue $\mathbf{J}_i$ has a y-component pointing up and $\mathbf{J}_e$ has a y-component pointing down. The y-component of $\mathbf{J}_i$ ends near the top of the strip, where the fibers point along the x-axis. The only place this intracellular current can go is through the membrane into the extracellular space, depolarizing the tissue (D). The y-component of $\mathbf{J}_e$ ends near the bottom of the strip, where the fibers point along the y-axis. The only place for this extracellular current to go is through the membrane into the intracellular space, hyperpolarizing the tissue (H). The effect is almost identical to that in Fig. 2, except that the fiber geometry, rather than an insulated surface, causes the y-component of the current density to end. Langrill Beaudoin and I analyzed this mechanism mathematically, with similar results [13].
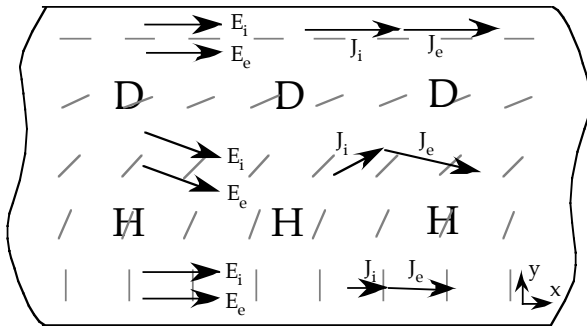
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Fig. 3. Rotation: Polarization caused by curving fibers. Based on Fig. 3 of [13].

We now have the tools necessary to understand the distribution of transmembrane potential during unipolar stimulation [4]. In Fig. 4, the black dot in the lower left corner is the electrode. The fibers are horizontal, as indicated by the light gray lines. The ellipses are approximate isopotential contours arising from a cathodal (negative) stimulus current. Along the x- and y-axes, the electric field and current density are parallel to each other. In between, $\mathbf{E}_i$ and $\mathbf{E}_e$ are pointing down and to the left, perpendicular to the isopotential contour. The current density vectors are rotated toward the fiber axis, with $\mathbf{J}_i$ rotated more than $\mathbf{J}_e$ because of the unequal anisotropy ratios. The net current density points directly toward the electrode, but $\mathbf{J}_i$ has a component in the θ-direction pointing counterclockwise, while $\mathbf{J}_e$ has a θ-component pointing clockwise. Just as in the previous two figures, where the θ-component of $\mathbf{J}_i$ ends the tissue is depolarized and where the θ-component of $\mathbf{J}_e$ ends the tissue is hyperpolarized. The same effect occurs in all four quadrants of the x-y plane, resulting in the familiar regions of hyperpolarization along the fiber axis (virtual anodes) and the "dog-bone" region of depolarization perpendicular to the fiber axis [14]. There is also a strong depolarization directly under the cathode because the intracellular current must redistribute into the extracellular space in order to reach the electrode. This effect, however, is localized to within a few length constants of the electrode, and has nothing to do with unequal anisotropy ratios.
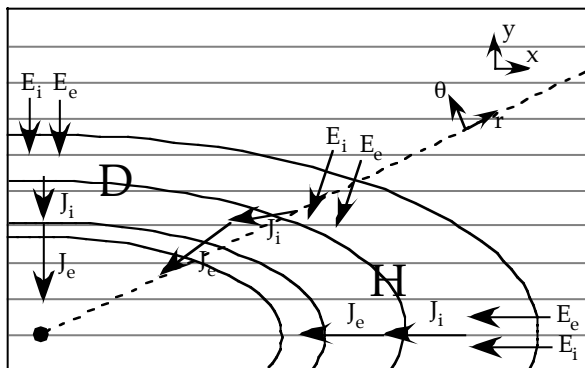

Fig. 4. Rotation: Polarization caused by unipolar stimulation of cardiac tissue. This figure corresponds to Fig. 3f of [4]

I. DISTRIBUTION

Distribution is illustrated in Fig. 5, in which current flows along a strip of tissue. We ignore any polarization caused at the top and bottom surfaces by effects like those described in Fig. 2. On the left the fibers are oriented in the y-direction. Because current is flowing perpendicular to the fibers, the intracellular conductivity is small compared to the extracellular conductivity, and most of the current is extracellular. The fibers change direction as we move along the x-axis, so that on the right the fibers are oriented in the x-direction. In this direction, the intracellular and extracellular conductivities are similar, so the intra- and extracellular current densities are about the same. In the middle, where the fiber direction is changing, current must redistribute from the extracellular space into the intracellular space, thereby hyperpolarizing the tissue. If the tissue had equal anisotropy ratios, the ratio of intracellular to extracellular current would be the same regardless of direction, and no redistribution or polarization would occur. This mechanism was discovered by Trayanova et al. [15], and Langrill Beaudoin and I analyzed it analytically [13].
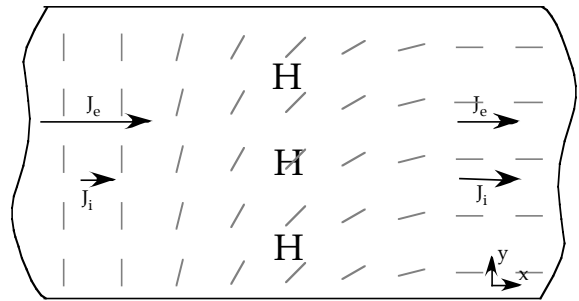

Fig. 5. Distribution: Polarization caused by fiber curvature. Based on Fig. 2 of [13] and Fig. 10 of [16].

Otani showed that the fibers do not have to change direction for the distribution mechanism to work; the current itself can change direction in tissue with straight fibers [17]. In Fig. 6, two electrodes--one positive and one negative, shown as black rectangles--are on the tissue surface, and the fiber geometry is uniform. Where current leaves the positive electrode (the anode), the current density is perpendicular to the fibers, and most of the current is in the extracellular space. This current will eventually turn right and flow toward the negative electrode (the cathode). Between the electrodes current is directed along the fibers, so the current density will be nearly evenly distributed between the two spaces. In the region where the current changes direction, extracellular current passes through the membrane into the intracellular space, hyperpolarizing the tissue. The opposite occurs near the negative electrode, depolarizing the tissue. Hyperpolarization and depolarization will also occur very near the anode and cathode regardless of the anisotropy ratios, but this boundary effect will be restricted to a region within a few length constants of each electrode. Otani points out that the polarization arising from unequal anisotropy ratios dominates in the tissue bulk.
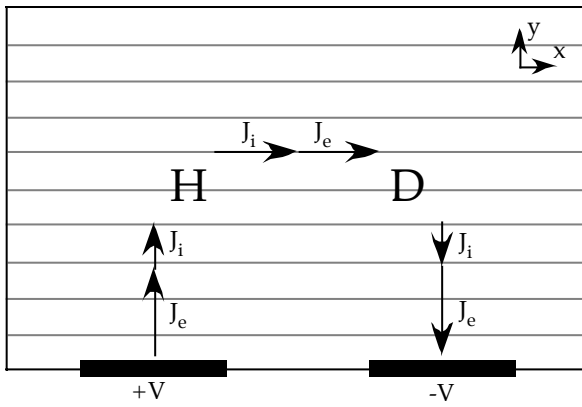
Fig. 6. Distribution: Polarization caused by the current changing direction in a tissue with straight fibers parallel to the tissue surface.

As a final example, consider an insulating cylinder in an otherwise uniform tissue with straight fibers (Fig. 7). An electric field is applied from left to right. Far from the insulator, the current is in the x-direction and is distributed equally between the intracellular and extracellular spaces. As current approaches the insulator, it turns left to circle around the obstacle. The current then is flowing approximately perpendicular to the fibers, so most of the current will be extracellular. As the current turns right to flow once again in the x-direction, it will be parallel to the fibers and will again be distributed more or less equally between the two spaces. As current leaves and then reenters the intracellular space, it causes depolarization and then hyperpolarization. The transmembrane potential distribution surrounding the insulator is even in y and odd in x. The result is the complex pattern of polarization surrounding an insulator in cardiac tissue during electrical stimulation [18]-[20].
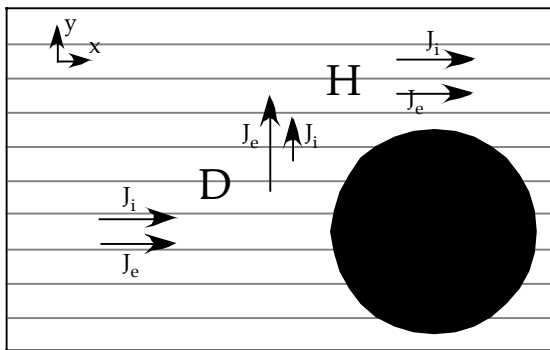

Fig. 7. Distribution: Polarization caused by an insulating obstacle. This figure explains the results observed in [18].

II. CONCLUSION

Rotation and distribution explain qualitatively why the condition of unequal anisotropy ratios is so important in cardiac tissue. These conclusions are not new. In fact, Langrill Beaudoin and I came to similar conclusions in our analytical analysis of the bidomain equations (see Fig. 4 of [13]). In complex fiber geometries, both rotation and distribution occur simultaneously, leading to complicated distributions of polarization [13]. Of course, the nonlinear

properties of the ion channels will introduce additional effects, such as deexcitation [21]. Nevertheless, I believe the ability to predict and explain qualitatively the passive effects caused by unequal anisotropy ratios in cardiac tissue is essential for a fundamental understanding of important phenomena such as defibrillation.

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