Modeling bipolar stimulation of cardiac tissue

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Unipolar stimulation of cardiac tissue is often used in the design of cardiac pacemakers because of the low current required to depolarize the surrounding tissue at rest. However, the advantages of unipolar over bipolar stimulation are not obvious at shorter coupling intervals when the tissue near the pacing electrode is relatively refractory. Therefore, this paper analyzes bipolar stimulation of cardiac tissue. The strength-interval relationship for bipolar stimulation is calculated using the bidomain model and a recently developed parsimonious ionic current model. The strength-interval curves obtained using different electrode separations and arrangements (electrodes placed parallel to the fibers versus perpendicular to the fibers) indicate that bipolar stimulation results in more complex activation patterns compared to unipolar stimulation. An unusually low threshold stimulus current is observed when the electrodes are close to each other (a separation of 1 mm) because of break excitation. Unlike for unipolar stimulation, anode make excitation is not present during bipolar stimulation, and an abrupt switch from anode break to cathode make excitation can cause dramatic changes in threshold with very small changes in the interval. These results could impact the design of implantable pacemakers and defibrillators. *Published by AIP Publishing.*

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Cardiac pacemakers are used to save the lives of those with some cardiac arrhythmias. However, to fully understand how pacemakers work, researchers need to know how an electrical stimulus interacts with cardiac tissue. Mathematical modeling provides an important way to study the basic mechanisms of electrical stimulation. Defibrillators use strong shocks to terminate the most deadly of arrhythmias—ventricular fibrillation—and they are also based on the interaction of electrical shocks with cardiac tissue. Of particular importance is how a shock affects tissue that is partially refractory because of a previous action potential. The strength-interval (SI) curve is a common way to assess partially refractory tissue: the stimulus strength is plotted against the time that the stimulus is applied. The bidomain model has been used to predict strength-interval curves for unipolar stimulation, when a single electrode applies a current pulse with the return electrode a long distance away. Pacemakers and defibrillators, however, sometimes use bipolar stimulation, in which case the cathode and anode are closely spaced. The goal of this paper is to use the bidomain model to simulate bipolar stimulation of the heart and predict its strength-interval curve. With such knowledge, engineers may be able to build better pacemakers and defibrillators.

INTRODUCTION

Artificial cardiac pacemakers and defibrillators are used to treat many heart arrhythmias (Jeffrey, 2001). These medical devices are implanted in the chest with leads that direct the electrical stimulus to the heart. The stimulation electrodes

can be unipolar (one electrode, with the return electrode being the pacemaker device in the chest) or bipolar (two electrodes, one the anode and the other the cathode). Unipolar stimulation has a low threshold current when stimulating resting tissue, but when exciting relatively refractory tissue, the advantages of unipolar versus bipolar stimulation are less clear. The current required to excite tissue as it recovers toward rest is summarized by the strength-interval (SI) curve. The purpose of this study is to compare the strength-interval curves of unipolar and bipolar stimulation using a mathematical model of the electrical properties of cardiac tissue.

For a unipolar electrode, cathodal stimulation depolarizes the tissue under the cathode and hyperpolarizes adjacent regions known as virtual anodes, whereas anodal stimulation hyperpolarizes tissue under the anode and depolarizes adjacent regions known as virtual cathodes (Sepulveda *et al.*, 1989). The interaction of depolarization and hyperpolarization results in four mechanisms of excitation: cathode make (CM), cathode break (CB), anode make (AM), and anode break (AB) (Roth, 1995 and Wikswo *et al.*, 1995). Researchers have observed all four mechanisms experimentally (Goto and Brooks, 1969; Dekker, 1970; Lindemans *et al.*, 1975; and Wikswo *et al.*, 1995). Previous studies predicted the shapes of the unipolar cathodal and anodal SI curves (Roth, 1996; Kandel and Roth, 2014; and Galappaththige *et al.*, 2017), and these predictions are consistent with experiments (van Dam *et al.*, 1956; Cranefield *et al.*, 1957; Dekker, 1970; Mehra and Furman, 1979; and Sidorov *et al.*, 2005).

Bipolar stimulation is when the myocardium is in contact with two closely spaced electrodes—an anode and a cathode (Sepulveda and Wikswo, 1994 and Muzikant and Henriquez, 1998). For bipolar stimulation, excitation is

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complex; it can be initiated by either the anode or cathode individually or by the interaction between them. Mehra *et al.* (1977) and Mehra and Furman (1979) measured experimentally strength-interval curves during bipolar stimulation.

Galappaththige *et al.* (2017) predicted the *unipolar* strength-interval curve using a parsimonious model of the ion channels in the myocardial membrane. The advantage of this minimal model is that it highlights the essential features of cardiac excitability and recovery (Gray and Pathmanathan, 2016 and Shotwell and Gray, 2016). The same parsimonious model is adopted for this study of *bipolar* stimulation. The specific aim is to predict how the strength-interval curve depends on the electrode orientation and the distance between the two electrodes.

METHODS

The two-dimensional bidomain model (Henriquez, 1993) is used to represent the cardiac tissue. The bidomain model describes the electrical properties of tissue mathematically, where the intracellular space is one domain and the extracellular space is the other. The active membrane properties are represented by the parsimonious ionic model (Gray and Pathmanathan, 2016 and Shotwell and Gray, 2016), which consists of a sodium current that underlies the action potential upstroke and a nonlinear time-independent potassium current for repolarization. The mathematical representation of the membrane model and its parameters are given in the Appendix.

Both the electrodes (E1 and E2) have the same size and shape: 1 mm in length and width. Electrodes are separated by a distance d from edge to edge (1 or 4 mm). The myocardial fibers are parallel to the x -axis. The bidomain model is solved numerically using previously described methods (Galappaththige *et al.*, 2017 and Galappaththige, 2017). The space step is 0.05 mm parallel to the fibers and 0.02 mm perpendicular to them. The time step is 1 μ s. The two orientations for the electrode placement are as follows:

(1) Parallel to the fibers [Fig. 1(a)]

The stimulus is applied to a 20×5 mm sheet of tissue. Because the electrodes are placed symmetrically along the x -axis, only the top half of the tissue is simulated. The number of nodes in the x -direction is 400, and in the y -direction it is 250.

(2) Perpendicular to the fibers [Fig. 1(b)]

The stimulus is applied to a 6.25×16 mm sheet of tissue. Because the electrodes are placed symmetrically along the y -axis, only the right side of the tissue is simulated. The number of nodes in the x -direction is 125, and in the y -direction it is 800.

The distribution of nodes is different for the two electrode arrangements, but the total number of nodes is the same (100 000). The cardiac tissue has unequal anisotropy ratios (Roth, 1997a).

The tissue is excited using a two-stimulus protocol. This technique is common in cardiac electrophysiology and is the method used to construct the strength-interval curve. The first stimulus (S1) initiates an action potential. The second stimulus (S2) is applied when the refractory period of the first action

FIG. 1. (a) Electrodes placed along the x -axis. (b) Electrodes placed along the y -axis. In both cases, fibers are horizontal (parallel to the x axis) and $d = 4$ mm. The color scale shows the transmembrane potential; in this figure, the tissue is at rest. The same color scale is used in all figures and movies. The stimulus current and polarity (C = cathode and A = anode) as a function of time for (c) the simulations of Figs. 2 and 11(a) when S1 and S2 have the same polarity at each electrode and for (d) the simulations of Figs. 10 and 11(b) when S1 and S2 have the opposite polarity at each electrode are shown.

potential ends. The response of the tissue as it recovers from refractoriness can be characterized by varying the timing of S2 and determining the S2 threshold strength. Both electrodes (E1 and E2) are given two stimuli [Fig. 1(c)], and each stimulus pulse lasts 2 ms. The S1-S2 interval is defined as the time between the start of S1 (time 0) and the start of S2. When E1 and E2 are parallel to the fibers, the S1 threshold is 2.22 mA/mm for $d = 4$ mm and 1.62 mA/mm for $d = 1$ mm. When E1 and E2 are perpendicular to the fibers, the S1 threshold is 2.13 mA/mm for $d = 4$ mm and 1.91 mA/mm for $d = 1$ mm. In our simulations, the S1 stimulus strength is twice threshold.

Excitation is classified as cathodal if the wave front begins near the cathode and anodal if it begins near the anode. Excitation is classified as *make* if it occurs following the start of the stimulus pulse and *break* if it occurs following the end of the stimulus pulse. These classifications are unambiguous for widely spaced electrodes and long stimulus durations. For brief stimuli and closely spaced electrodes, the distinctions are less clear and sometimes arbitrary. In general, *cathode make* is when a wave front originates from tissue depolarized at the cathode, and *cathode break* is when a wave front propagates initially through tissue hyperpolarized at a virtual anode. Similarly, *anode make* is when a wave front originates from tissue depolarized at a virtual cathode, and *anode break* is when a wave front propagates initially through tissue hyperpolarized at the anode. When regions of depolarization and hyperpolarization overlap in complex patterns, identifying the excitation mechanism is often difficult and subjective.

RESULTS

Electrodes parallel to the fibers

The strength-interval curves when the electrodes are parallel to the fibers, for the separation between electrodes of

FIG. 2. Strength-interval curves for electrodes parallel to the fibers, for (a) $d = 4$ and (b) 1 mm. Movies are indicated by the movie numbers (M1, M2, etc.).

1 or 4 mm, are shown in Fig. 2. E1 is the anode and E2 is the cathode for both S1 and S2 [Fig. 1(c)].

When the electrodes are separated by 4 mm [Fig. 2(a)], there is little overlap between the polarization caused by the individual electrodes. For S1-S2 intervals of 155 ms or longer, the mechanism of S2 excitation is cathode make starting at the left edge of the cathode (Fig. 3 (Multimedia view), corresponding to M1 in Fig. 2(a), S1-S2 interval = 170 ms; S2 strength = 2.44 mA/mm). At intervals of about 155 ms, there is a smooth transition from cathode make to cathode break excitation; excitation from 138 to 154 ms is classified as break because the wave front initially propagates through hyperpolarized tissue near the cathode, in a direction parallel to the fibers. From 147 to 154 ms, propagation occurs only to the left of the cathode toward the anode. Depolarization under the cathode diffuses into and excites the recovered tissue at the left virtual anode [Fig. 4 (Multimedia view), M2 in Fig. 2(a), 149 ms, 6.4 mA/mm]. From 138 to 146 ms, propagation is only to the right of the cathode away from the anode through the right virtual anode [Fig. 5 (Multimedia view), M3 in Fig. 2(a), 140 ms, 55.5 mA/mm]; propagation toward the anode is blocked by the anode's right virtual cathode. The SI curve undergoes a change in the slope at 147 ms as the initial direction of propagation changes from the left

to right. Between 126 and 137.5 ms, the excitation mechanism is anode break [Fig. 6 (Multimedia view), M4 in Fig. 2(a), 135 ms, 85 mA/mm]; the depolarization at the virtual cathodes diffuses into the hyperpolarized and excitable tissue at the anode, triggering an action potential that propagates perpendicular to the fibers. Any excitation initiated by the cathode is unable to propagate because of the extensive refractoriness surrounding it. The SI curve contains a dip in the anode break section, meaning that it has a positive slope, so excitation becomes more difficult as the interval becomes longer. For intervals shorter than 126 ms, anode break excitation begins following S2 but cannot propagate because the surrounding tissue is refractory [Fig. 7 (Multimedia view), M5 in Fig. 2(a), 125 ms, 60 mA/mm].

The interaction between the two electrodes is enhanced for a separation of only 1 mm [Fig. 2(b)]. For intervals longer than 153 ms, the depolarization under the cathode diffuses into the hyperpolarized region under the anode and produces cathode break excitation [Fig. 8 (Multimedia view), M6 in Fig. 2(b), 170 ms, 1.81 mA/mm], although the dynamics also contain features of cathode make excitation. From 141 to 152 ms, the depolarization produced under the cathode diffuses into the hyperpolarization under the anode and initiates a wave front that begins on the right of the anode and then

FIG. 3. Cathode make excitation, for widely spaced electrodes parallel to the fibers. The transmembrane potential is shown as a function of x (horizontal, parallel to the fibers) and y (vertical, perpendicular to the fibers). The black rectangles are the electrodes, separated by a distance $d = 4$ mm, and the number in each frame is the time in ms. S1-S2 interval = 170 ms and S2 strength = 2.44 mA/mm. The color scale is the same as shown in Fig. 1; purple is rest, yellow is depolarized, and blue is hyperpolarized. These frames are from movie M1. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.1>]

FIG. 4. Cathode break excitation toward the anode, for widely spaced electrodes parallel to the fibers; $d = 4$ mm, $S1-S2$ interval = 149 ms, $S2$ strength = 6.4 mA/mm, movie M2. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.2>]

FIG. 5. Cathode break excitation away from the anode, for widely spaced electrodes parallel to the fibers; $d = 4$ mm, $S1-S2$ interval = 140 ms, $S2$ strength = 55.5 mA/mm, movie M3. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.3>]

FIG. 6. Anode break excitation, for widely spaced electrodes parallel to the fibers; $d = 4$ mm, $S1-S2$ interval = 135 ms, $S2$ strength = 85 mA/mm, movie M4. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.4>]

FIG. 7. Failed anode break excitation, for widely spaced electrodes parallel to the fibers; $d = 4$ mm, $S1-S2$ interval = 125 ms, $S2$ strength = 60 mA/mm, movie M5. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.5>]

FIG. 8. Cathode break excitation, for closely spaced electrodes parallel to fibers; $d = 1$ mm, S1-S2 interval = 170 ms, S2 strength = 1.81 mA/mm, movie M6. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.6>]

FIG. 9. Anode break excitation, for closely spaced electrodes parallel to the fibers; $d = 1$ mm, S1-S2 interval = 146 ms, S2 strength = 5.49 mA/mm, movie M7. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.7>]

propagates initially perpendicular to the fibers [Fig. 9 (Multimedia view), M7 in Fig. 2(b), 146 ms, 5.49 mA/mm]. This behavior is classified as anode break, although it contains features of both anode break and cathode break. The SI curve contains a slight dip between 142 and 146 ms [see the inset in Fig. 2(b)]. At 141 ms, the excitation remains anode break, but the dynamics are somewhat different. The initial propagation is very slow, allowing enough time for the surrounding tissue to recover from refractoriness, until about

164 ms when the propagation again speeds up and strengthens (Figure 5.10 in Galappaththige, 2017). The SI curve is steep in the range of 141 to 142 ms. For intervals less than 141 ms, no excitation survives (stimulus strengths up to 512 mA/mm were checked).

Figure 10(a) shows the strength-interval curves when the electrode polarities are switched for the second stimulus [Fig. 1(d)], for widely spaced electrodes. As before, for the S1 stimulus, E1 is anodal and E2 is cathodal. During the S2

FIG. 10. (a) Strength-interval curves for electrodes parallel to the fibers when $d = 4$ mm, for S1 having E1 anodal and S2 having E1 either cathodal (black curve) or anodal (green curve). (b) Strength-interval curves for electrodes parallel to the fibers when $d = 1$ mm, for S1 having E1 anodal and S2 having E1 either cathodal (black curve) or anodal (green curve).

FIG. 11. Strength-interval curves for electrodes perpendicular to the fibers. Movies are indicated by the movie numbers (M8, M9, etc.).

stimulus, however, E1 switches to cathodal and E2 to anodal (black curve). Also plotted in Fig. 10(a) is the SI curve from Fig. 2(a), when E1 is anodal and E2 cathodal during both S1 and S2 (green curve). For intervals greater than 148 ms, the two curves are nearly identical. The SI curve for S2 E1 cathodal shows a steep increase in stimulus strength for intervals from 147 to 148 ms. The threshold stimulus strength for S2 E1 cathodal is larger than that for S2 E1 anodal, due to the surrounding tissue being more refractory because of the time for the S1 wave front to propagate from E2 to E1.

Strength-interval curves for $d = 1$ mm are shown in Fig. 10(b). The SI curves for S2 E1 anodal and E2 cathodal have nearly the same shape as for S2 E1 cathodal and E2 anodal, except for a slight leftward shift of the S2 E1 cathodal curve around 142 ms. The smaller interval arises because the S1 wave front takes longer to reach the anode E2.

Electrodes perpendicular to the fibers

Bipolar stimulation for electrodes placed perpendicular to the fiber direction produces the SI curves as shown in Fig. 11(a); E1 is anodal and E2 is cathodal for both S1 and S2. There is a monotonic decrease in S2 threshold strength with the increasing interval for both electrode separations of 4 (black curve) and 1 mm (red curve).

For a separation of 4 mm, at intervals greater than 152 ms, the excitation mechanism is cathode make, with initial propagation perpendicular to the fibers and toward the anode [Fig. 12 (Multimedia view), M8 in Fig. 11(a), 160 ms, 2.32 mA/mm]. For intervals between 122 and 151 ms, the cathode break mechanism excites the tissue [Fig. 13 (Multimedia view), M9 in Fig. 11(a), 125 ms, 120 mA/mm]. Break excitation begins under both the anode and cathode, but propagation starting near the anode is not successful because the tissue is too refractory, whereas propagation starting near the cathode survives. In Fig. 13, the wave front does not accelerate until it reaches the right tissue edge, but for other intervals, cathode break excitation accelerates well

to the left of the boundary, indicating that in general the success of excitation is not an edge effect. For intervals less than 122 ms, the tissue is inexcitable. There is no anodal break section of the SI curve and no dip.

Similar behavior is observed when the separation between electrodes is only 1 mm. For intervals greater than 152 ms, excitation is cathode make [Fig. 14 (Multimedia view), M10 in Fig. 11(a), 157 ms, 2.32 mA/mm]. For intervals between 141 and 151 ms, the mechanism is cathode

FIG. 12. Cathode make excitation, for widely spaced electrodes perpendicular to the fibers; $d = 4$ mm, S1-S2 interval = 160 ms, S2 strength = 2.32 mA/mm, movie M8. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.8>]

FIG. 13. Cathode break excitation, for widely spaced electrodes perpendicular to the fibers; $d = 4$ mm, S1-S2 interval = 125 ms, S2 strength = 120 mA/mm, movie M9. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.9>]

break [Fig. 15 (Multimedia view), M11 in Fig. 11(a), 145 ms, 17.8 mA/mm]. Between 138 and 140 ms, two distinct wave fronts are produced, one by anode break and the other by cathode break [Fig. 16 (Multimedia view), M12 in Fig. 11(a), 139 ms, 42.3 mA/mm]. These cases are classified as cathode break in Fig. 11(a), although they are really a mixture of anode break and cathode break. The anode break excitation does not arise from an interaction of the hyperpolarization under the anode and depolarization at the virtual cathode, as is the case for unipolar stimulation. Instead, excitation starts when depolarization under the cathode diffuses into the hyperpolarized region under the nearby anode. For intervals from 134 to 137 ms, only cathode break excitation occurs [Fig. 17 (Multimedia view), M13 in Fig. 11(a), 135 ms, 88.8 mA/mm]. For intervals from 131 to 133 ms, cathode break excitation propagates only on the side away from the anode, being blocked by the virtual cathode on the side nearer the anode (Figure 5.20 in Galappaththige, 2017). For intervals less than 131 ms, no excitation occurs because the surrounding tissue is too refractory for the wave front to survive (Figure 5.21 in Galappaththige, 2017).

For the SI curves shown in Fig. 11(a), just before S2 is applied, the region around the anode (E1) is still depolarized and refractory, in part because the S1 wave front needed 28 ms to propagate from E2 to E1. This enhanced refractoriness at E1 explains why anodal stimulation is rare (completely absent for $d = 4$ mm). Anode break excitation becomes possible when the polarity of S2 is reversed so that for S1, the electrode E2 is cathodal, but for S2, E2 is anodal [Fig. 1(d)],

FIG. 14. Cathode make excitation, for closely spaced electrodes perpendicular to the fibers; $d = 1$ mm, S1-S2 interval = 157 ms, S2 strength = 2.32 mA/mm, movie M10. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.10>]

producing a dip in the SI curve for both electrode separations of 1 and 4 mm [Fig. 11(b)]. When the separation between electrodes is 4 mm, the excitation mechanism is cathode make for S1-S2 intervals greater than 163 ms, initiating from the cathode at E1 [Fig. 18 (Multimedia view), M14 in Fig. 11(b), 170 ms, 2.29 mA/mm]. The reason for the delay before cathode make excitation dominates [163 ms in Fig. 11(b) compared to 152 in Fig. 11(a)] is that the tissue at E1 must recover from S1 refractoriness which includes the time for the S1 wave front to propagate from E2 to E1. For intervals between 147 and 162 ms, excitation is cathode break [Fig. 19 (Multimedia view), M15 in Fig. 11(b), 150 ms, 57.0 mA/mm]. For intervals between 132 and 147 ms, the mechanism of excitation is anode break [Fig. 20 (Multimedia view), M16 in Fig. 11(b), 146 ms, 78.7 mA/mm]; excitation starts by cathode break at E1 and anode break at E2. In this example, both wave fronts survive, but for other intervals, the cathode break excitation decays as it propagates into still-refractory tissue, while the anode break excitation survives, in part because the tissue had more time to recover from the S1 action potential that originated at E2. For intervals shorter than 134 ms, the tissue around E2 is so refractory that even the anode break wave front cannot survive, and stimulation fails. The anode break section of the SI curve contains a pronounced dip.

For an electrode separation of 1 mm, the SI curve is similar to the 4 mm curve but shifted down and to the left. Intervals greater than 152 ms result in cathode make, intervals between 143 and 151 ms cause cathode break, and intervals between 129 and 142 ms trigger anode break excitation.

FIG. 15. Cathode break excitation, for closely spaced electrodes perpendicular to the fibers; $d = 1$ mm, S1-S2 interval = 145 ms, S2 strength = 17.8 mA/mm, movie M11. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.11>]

FIG. 16. Cathode break and anode break excitation, for closely spaced electrodes perpendicular to the fibers; $d = 1$ mm, S1-S2 interval = 139 ms, S2 strength = 42.3 mA/mm, movie M12. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.12>]

DISCUSSION

Bipolar stimulation [Fig. 21(b)] produces strength-interval curves that are different than those associated with unipolar (Galappaththige *et al.*, 2017) stimulation [Fig. 21(a)]. These differences include the following:

- (1) When the electrodes are parallel to the fibers and are closely spaced ($d = 1$ mm), the excitation mechanism for long intervals (rheobase) is cathode break rather than cathode make [Fig. 2(b)]. The bipolar rheobase stimulus strength for $d = 1$ mm (1.81 mA/mm) is lower than for unipolar stimulation (3.01 mA/mm). The presence of the anode reduces the stimulus required for cathodal stimulation, even when the interval is long and the tissue is fully recovered. The 1 mm spacing between electrodes results in a minimum in the bipolar stimulation threshold; either smaller or larger values of d increase it.
- (2) The lower stimulus strength when the electrodes are placed parallel to the fibers ($d = 1$ mm) [Fig. 21(b)] is important when we consider the battery life of a pacemaker. The lower current delivery ensures that there will be less implant-related complications due to low current injection. It is noted that bipolar pacing is favored to minimize pectoral muscle stimulation (Mulpuru *et al.*, 2017).
- (3) Distinguishing between cathode make and cathode break excitation can be difficult for short duration stimuli and closely spaced electrodes. For instance, Fig. 8 is labeled cathode break excitation, but one might argue it

is in fact cathode make. Simulations with longer duration S2 pulses would unambiguously distinguish between make (excitation following the onset of the pulse) and break (excitation following the termination of the pulse). For short duration pulses, such distinctions are arbitrary.

- (4) When the electrodes are perpendicular to the fibers, an electrode spacing of 1 mm does not reduce the rheobase stimulus strength significantly (Fig. 11). This may be an artifact of the spacing used. The length constant is shorter perpendicular to the fibers than parallel to them, so at $d = 1$ mm, the electrodes are effectively farther apart when arranged perpendicular to the fibers than parallel to them. When d is reduced to 0.5 mm, the rheobase stimulus strength is 2.13 mA/mm for electrodes placed parallel to the fibers and 1.70 mA/mm for electrodes placed perpendicular to the fibers. For $d = 1$ mm, the rheobase threshold stimulus strength is 1.81 mA/mm for electrodes placed parallel to the fibers and 1.91 mA/mm for electrodes placed perpendicular to the fibers.
- (5) Anode make excitation is not present in these simulations of bipolar stimulation. In general, the anode make threshold is higher than the cathode make threshold, so make excitation will favor the cathode over the anode. Anode make might be possible if d were very large and S1 and S2 had different polarities. In that case, the propagation time from the S1 site to the S2 site might be so long that S2 make excitation at the cathode is impossible because the tissue is refractory, leaving make excitation

FIG. 17. Slowly developing cathode break excitation, for closely spaced electrodes perpendicular to the fibers; $d = 1$ mm, S1-S2 interval = 135 ms, S2 strength = 88.8 mA/mm, movie M13. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.13>]

at the anode as the low-threshold mechanism. However, anode make is not present in Fig. 11(b), which is the closest simulation we performed to such a scenario.

- (6) For bipolar stimulation with closely spaced electrodes ($d = 1$ mm), the cathode break mechanism can be difficult to distinguish from anode break. Excitation initiates from an electrotonic interaction between the depolarization under the cathode and the hyperpolarization under the anode; virtual electrodes play no role. In this manuscript, such an interaction is usually referred to as cathode break excitation, but it might more properly be called a combination, cathode break/anode break. This mechanism allows break excitation to occur with an unusually low threshold [see the anode break section of the SI curve in Fig. 2(b)]. When the electrodes are more widely spaced ($d = 4$ mm), wave fronts unambiguously arise from either the anode or cathode, and cathode break is easy to distinguish from anode break.
- (7) A dip like that in the unipolar anodal strength-interval curve [Fig. 21(a)] is sometimes present in bipolar SI curves, but in other cases it is missing. It appears prominently when the electrodes are parallel to the fibers and are far apart [Fig. 2(a)]. However, it is suppressed when the electrodes are close together [Fig. 2(b)], and it disappears entirely when the electrodes are perpendicular to the fibers [Fig. 11(a)]. The reason for its disappearance is that the S1 wave front requires 28 ms to propagate from E2 (the cathode for S1 stimulation) to E1. Therefore, the tissue just before S2 is more refractory at

FIG. 18. Cathode make excitation, for widely spaced electrodes perpendicular to the fibers and S2 E1 cathodal; $d = 4$ mm, S1-S2 interval = 170 ms, S2 strength = 2.29 mA/mm, movie M14. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.14>]

E1 (the anode for S2 stimulation) than at E2. This raises the threshold for anodal excitation, favoring cathodal excitation. The dip, which is associated with only anode break excitation, is therefore not present.

- (8) The site of excitation can switch abruptly from the cathode to the anode as the interval decreases [Fig. 2(a); compare Figs. 5 and 6]. This behavior is most obvious when the electrodes are farther apart. To a first approximation, the SI curve for $d = 4$ mm and the electrodes parallel to the fibers is equal to the unipolar cathodal SI curve for long intervals and is equal to the unipolar anodal SI curve for short intervals [Fig. 21(b)]. This result is consistent with the experiments by Mehra *et al.* (1977). Because the abrupt switch is often between anode break and cathode make (not anode make) excitation, this switch may be associated with a marked drop in threshold [see for instance $d = 4$ mm, S1 AC, S2 CA in Fig. 21(b)].
- (9) The shape of the SI curve can change dramatically when the polarity of S2 is switched. This effect is most dramatic when comparing Figs. 11(a) and 11(b).
- (10) The shape of the strength-interval curve is particularly sensitive to electrode spacing and fiber orientation during the relative refractory period [Fig. 21(b)]. This could be important during antitachycardia pacing and perhaps during pacing to treat ventricular fibrillation, when excitation is often applied to refractory tissue.
- (11) When d is large, by the time the S1 wave front starting at E2 reaches E1 it is nearly a plane wave. In this case,

FIG. 19. Cathode break excitation, for widely spaced electrodes perpendicular to the fibers and S2 E1 cathodal; $d = 4$ mm, S1-S2 interval = 150 ms, S2 strength = 57.0 mA/mm, movie M15. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.15>]

the S2 stimulus creates regions of depolarization and hyperpolarization that are similar to numerical simulations of the pinwheel experiment performed by Lindblom *et al.* (2000). For instance, Fig. 6 shows a simulation similar to that shown in Fig. 11 of the study by Lindblom *et al.*, corresponding to an S1 planar wave front parallel to the fibers and a unipolar anodal S2 stimulus. Also, Fig. 19 is similar to Fig. 9 of the study by Lindblom *et al.*, showing the S1 planar wave front perpendicular to the fibers and a cathodal S2.

- (12) None of the simulations presented here resulted in sustained reentry. The lack of reentry may arise because the tissue is too small to support a reentrant wave front, the S2 stimuli are too weak, the two electrodes are too close together, or the parsimonious model does not easily support reentry. The wave fronts in these simulations, however, often contain phase singularities (see, for instance, Figs. 6 and 19), and stimulations like these have resulted in reentry before (Roth, 1997b and Lindblom *et al.*, 2000).

Our calculations have several limitations. We use a two-dimensional model of tissue with a uniform fiber geometry and a parsimonious model of the ionic current containing only two currents rather than a more detailed model. The advantage of the parsimonious model is that it emphasizes generic features of the membrane kinetics while not being overwhelmed in unimportant details. Our previous study (Galappaththige *et al.*, 2017) indicated that the parsimonious

FIG. 20. Anode break excitation, for widely spaced electrodes perpendicular to the fibers and S2 E1 cathodal; $d = 4$ mm, S1-S2 interval = 146 ms, S2 strength = 78.7 mA/mm, movie M16. (Multimedia view) [URL: <http://dx.doi.org/10.1063/1.5000163.16>]

model was sufficient to predict the shapes of unipolar strength-interval curves. Gray and Pathmanathan (2016) and Shotwell and Gray (2016) discussed the motivation and validity of the parsimonious model. The model may need to be refined in order to address issues such as using drugs to block specific channels active during repolarization.

In conclusion, the strength-interval curves for bipolar stimulation depend sensitively on electrode separation and the orientation of the electrodes to the fiber axis. Many of the features of strength-interval curves using unipolar stimulation are present, but in addition new phenomena emerge. These results could impact the design of artificial implantable pacemakers.

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APPENDIX: PARSIMONIOUS IONIC CURRENT MODEL

The parsimonious ionic current model was developed by Gray and Pathmanathan (2016). The model has only two ion currents, and yet it reproduces many experimentally measured ventricular action potentials. The sodium current (I_{Na}) is in the form used in the Hodgkin-Huxley model, and the repolarization current (I_K) is phenomenological

FIG. 21. (a) Unipolar cathodal and anodal strength-interval curves (data from Galappathige *et al.*, 2017). (b) All strength-interval curves plotted on common axes.

$$I_{Na} = g_{Na}^{max} m^3 h (V_m - E_{Na}), \quad (A1)$$

$$I_K = g_K (V_m - E_K) \exp \left[\frac{-(V_m - E_K)}{k_r} \right], \quad (A2)$$

where V_m is the transmembrane potential, g_{Na}^{max} is the maximal conductance of I_{Na} , m is the fast activation gate, h is the inactivation gate, E_{Na} is the Nernst equilibrium potential for sodium, g_K is the conductance of I_K at the reversal potential, k_r is the parameter controlling action potential shape, and E_K is the reversal potential for potassium. The dynamics of the gating variables m and h are governed by

$$\frac{dm}{dt} = \frac{m_{\infty}(V_m) - m}{\tau_m}, \quad (A3)$$

$$\frac{dh}{dt} = \frac{h_{\infty}(V_m) - h}{\tau_h(V)}. \quad (A4)$$

The steady-state sodium activation m_{∞} and inactivation h_{∞} are

$$m_{\infty}(V_m) = \frac{1}{1 + \exp \left[\frac{-(V_m - E_m)}{k_m} \right]}, \quad (A5)$$

TABLE I. Table of parameters.

Parameter	Definition	Value
β	Surface to volume ratio	200 mm^{-1}
C_m	Membrane capacitance per unit area	$0.01 \text{ } \mu\text{F mm}^{-2}$
g_{ix}	Intracellular conductivity in the x -direction	0.2 mS mm^{-1}
g_{iy}	Intracellular conductivity in the y -direction	0.02 mS mm^{-1}
g_{ex}	Extracellular conductivity in the x -direction	0.8 mS mm^{-1}
g_{ey}	Extracellular conductivity in the y -direction	0.2 mS mm^{-1}
g_{Na}^{max}	Maximal conductance of I_{Na}	0.11 mS mm^{-2}
E_{Na}	Nernst equilibrium potential for sodium	65 mV
E_K	Reversal potential for potassium	-83 mV
E_h	Sodium channel half-inactivation voltage	-74.7 mV
E_m	Sodium channel half-activation voltage	-41 mV
k_m	Sodium channel activation slope	4 mV
k_r	Parameter controlling action potential shape	21.28 mV
k_h	Sodium channel inactivation slope	4.4 mV
τ_m	Sodium activation time constant	0.12 ms
τ_{ho}	Sodium inactivation time constant scale	6.80738 ms
δ_h	Sodium channel inactivation time constant asymmetry	0.799163
g_K	Conductance of I_K at the equilibrium potential E_K	0.003 mS mm^{-2}

$$h_{\infty}(V_m) = \frac{1}{1 + \exp \left[\frac{+(V_m - E_h)}{k_h} \right]}, \quad (A6)$$

where E_m is the sodium channel half-activation voltage, k_m is the sodium channel activation slope, E_h is the sodium channel half-inactivation voltage, and k_h is the sodium channel inactivation slope. The inactivation time constant τ_h is

$$\tau_h(V_m) = \frac{2\tau_{ho} \exp \left[\frac{\delta_h(V_m - E_h)}{k_h} \right]}{1 + \exp \left[\frac{(V_m - E_h)}{k_h} \right]}, \quad (A7)$$

where τ_{ho} is the sodium inactivation time constant scale and δ_h is the sodium channel inactivation time constant asymmetry. The activation time constant τ_m is independent of membrane potential and hence a constant. The two currents $I_{Na} + I_K$ make up the total membrane current I_{ion} that we use when solving the bidomain equations

$$g_{ex} \frac{\partial^2 V_e}{\partial x^2} + g_{ey} \frac{\partial^2 V_e}{\partial y^2} = -\beta \left(C_m \frac{\partial V_m}{\partial t} + I_{ion} \right), \quad (A8)$$

$$\begin{aligned} & (g_{ix} + g_{ex}) \frac{\partial^2 V_e}{\partial x^2} + (g_{iy} + g_{ey}) \frac{\partial^2 V_e}{\partial y^2} \\ & = - \left(g_{ix} \frac{\partial^2 V_m}{\partial x^2} + g_{iy} \frac{\partial^2 V_m}{\partial y^2} \right). \end{aligned} \quad (A9)$$

Model parameters are given in Table I, and additional details about the model are discussed in Galappathige (2017).

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