Extracellular Field Required for Excitation in Three-Dimensional Anisotropic Canine Myocardium


It is not known how well potential gradient, current density, and energy correlate with excitation by extracellular stimulation in the in situ heart. Additionally, the influence of fiber orientation and stimulus polarity on the extracellular thresholds for stimulation expressed in terms of these factors has not been assessed. To answer these questions for myocardium in electrical diastole, extracellular excitation thresholds were determined from measurements of stimulus potentials and activation patterns recorded from 120 transmural electrodes in a 35 x 20 x 5-mm region of the right ventricular outflow tract in six open-chest dogs. Extracellular potential gradients, current densities, energies, and their components longitudinal and transverse to the local fiber orientation at each recording site were calculated from the stimulus potentials produced by 3-msec constant-current stimuli. The resulting values in regions directly excited by the stimulus field were compared with the values in regions not directly excited but activated by the spread of wavefronts conducting away from the directly excited region. Magnitudes of 3.66 mA/cm² for current density, 9.7 μJ/cm³ for energy, and 804 mV/cm for potential gradient yielded minimum misclassifications of 8%, 13%, and 17%, respectively, of sites directly and not directly excited. A linear bivariate combination of the longitudinal (l) and transverse (t) components of the potential gradient yielded 7% misclassification (threshold ratio of 2.88), and linear combination of corresponding current density components yielded 8% misclassification (threshold ratio of 1.04). Anodal and cathodal thresholds were not significantly different (p = 0.39). Potential gradient, current density, and energy strength-duration curves were constructed for pulse durations (D) of 0.2–20 msec. The best fit hyperbolic curve for current density magnitude (J_m) was J_m = 3.97/D + 3.15, where J_m is in mA/cm², and D is in msec. Thus, for stimulation during electrical diastole 1) both current density magnitude and longitudinal and transverse components of the potential gradient are closely correlated with excitation, 2) the extracellular potential gradient along cardiac cells has a lower threshold than across cells, while current density thresholds along and across cells are similar, 3) anodal and cathodal thresholds are approximately equal for stimuli ≥ 5 mA, and 4) the extracellular potential gradient, current density, and energy excitation thresholds can be expressed by strength-duration equations. (Circulation Research 1988;63:147-164)
cellular field created by the stimulation electrode and relate these values to the minimal pacing thresholds. Jones et al. have used this method to estimate the excitability threshold for in vitro preparations of cultured chick myocardial cells, and activation thresholds for transthoracic stimulation have been calculated based on electrode geometry and other parameters. The electric field necessary for excitation at sites distant from a current source has not, however, been determined for in vivo myocardium. Although the anisotropic behavior of cardiac muscle has been shown to affect the conduction velocity, the conductivity, and the intracellular and extracellular waveforms, it is not known whether anisotropy also influences the extracellular field necessary to excite cardiac cells. In addition, no study has compared extracellular potential, potential gradient, current density, and energy at different pulse durations and stimulus polarities and determined which furnishes the best threshold value for estimating whether excitation occurs.

To determine these threshold values during electrical diastole and to determine the effect of tissue anisotropy on these values, on pacing electrode polarity, and on pulse duration, low- and high-current anodal and cathodal stimuli of multiple durations were delivered from the midmyocardium. The values of the resulting extracellular potentials, potential gradients, current densities, and energies in the region directly excited by the field of the stimulus were compared with values in the region not directly excited by the stimulus field but activated by conduction spreading away from the border of the directly excited region. The resulting field strengths at the border of the directly excited and not directly excited regions were defined as the threshold values for direct excitation of cardiac tissue.

This study suggests that, because of the anisotropy of cardiac muscle, the extracellular potential gradient applied along the cardiac cell during electrical diastole results in a lower excitation threshold than potential gradient threshold across the cell, while current density thresholds are similar. Therefore, a combination of the longitudinal and transverse components of the potential gradient or the magnitude of the current density applied to a cardiac cell correlates with excitation most accurately. The extracellular excitation thresholds for potential gradient, current density, and energy at different pulse durations were found to be approximated by standard strength-duration equations. In addition, the mechanism of excitation by anodal and cathodal stimulation during electrical diastole was found to be similar for high-current stimulation but different for low-current stimulation.

Materials and Methods

Data Acquisition and Surgical Preparation

The recording apparatus consisted of 120 recording terminals located on 40 plunge electrodes held within a rigid acetal plate (Figure 1). Each plunge electrode contained six terminals forming three bipolar pairs, allowing the recording of potentials at subendocardial, midmyocardial, and subepicardial planes in a 20 x 35 x 5-mm volume of heart muscle. Surface ECG leads I, II, and III were also recorded.

A computer-assisted mapping system capable of simultaneously recording from 128 channels was used to record both the stimulus potentials and the activation complexes. The signals were recorded digitally at a rate of 1,000 samples per second with the low-pass filter at 500 Hz and the high-pass filter at 0.01 Hz. Gain settings were individually optimized for each channel. During stimuli, the gains were automatically switched to lower values to prevent amplifier saturation, and at the end of each stimulus the gains were reset to their original values. This allowed the detection of activation complexes 2 msec after the end of high-current stimuli. The data were stored on videotape for off-line analysis, and the recordings from each channel were subsequently displayed on a Tektronix 4014 graphic terminal (Beaverton, Oregon) to allow mea-
measurement of stimulus potentials and detection of activation times.

The method of surgical preparation has been previously described for these same animals. Briefly, six mongrel dogs (mean weight ± SD, 27.1 ± 4.7 kg) were anesthetized with pentobarbital (30–35 mg/kg). Sucinylcholine (1 mg/kg) was also given to decrease muscular contractions induced by the electrical shocks. Systemic blood pressure was continuously monitored through a femoral arterial line, and normal metabolic status was maintained throughout the study by taking blood samples every 30–60 minutes and by correcting abnormal electrolyte and blood gas parameters. The chest was opened through a median sternotomy. The heart was suspended in a pericardial cradle, and the recording and pacing electrodes were then inserted into the right ventricular outflow tract and free wall. Because this portion of the right ventricle is slightly curved, superficial epicardial sutures were used to pull the tissue flush against the undersurface of the plate and to anchor the plunges in stable positions. After a 30-minute period to allow any injury potentials to subside, the protocol was begun. The surface of the heart was kept moist throughout the study with normal saline.

**Stimulation Protocol**

The purposes of this protocol were to determine 1) which extracellular parameter, stimulus potential, potential gradient, current density, or energy best delineates the region of direct excitability by the stimulus field, 2) the threshold values for stimulation for each of these parameters at different pulse durations, 3) whether a combination of thresholds for components of the potential gradient and current density longitudinal and transverse to the long axis of the myocardial fibers correlates with excitation more accurately than single magnitude thresholds, and 4) if anodal and cathodal stimulation thresholds are different.

First, the effects of the stimulus strength and polarity on excitation were investigated. The heart was paced from the right atrium through bipolar wire electrodes at a rate of 150 beats/min (400-msec interval) for five beats (S1) after which the ventricular stimulus (S2) was delivered. S1-S2 coupling intervals ranged from 400 to 500 msec in the six dogs but were kept constant within each dog. During electrical diastole, S2 stimuli from 5 to 70 mA at 5-mA increments with pulse durations of 3 msec were delivered through the platinum electrodes P1 and P2 (Figure 1). For all current levels, ventricular S2 stimuli were delivered with both anodal and cathodal polarities. Second, the duration of the pulse was varied to determine its effects on the activation sequence and on the excitation thresholds. Stimuli from 0.2 to 40 msec (0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.6, 2.0, 2.5, 3.0, 3.5, 5.0, 7.0, 10.0, 20.0, and 40.0 msec) were delivered through electrodes P1 and P2 at twice anodal pacing threshold (0.4–0.8 mA for 3 msec S2) for all possible pulse durations and at 20, 40, and 60 mA with both anodal and cathodal polarities. In addition, as a control, 2-mA cathodal stimuli were delivered from the pacing electrodes P1 and P2 every 15 minutes or less. The recordings from these control stimuli were evaluated to determine whether the large number of stimulation pulses or the passage of time was altering the activation sequence or stimulus potentials.

Ventricular stimulation waveforms were examined on a Tektronix 7613 oscilloscope to ensure that electrode polarization was not occurring. Stimuli were assumed to cause negligible electrode polarization when they maintained the shape of the square wave produced by the stimulator. Unipolar and bipolar recordings for each stimulus polarity at each current level were made sequentially within 30 seconds of each other to allow measurement of potentials with unipolar recordings and detection of activations with bipolar recordings.

**Tissue Examination**

At the end of each study, the dog was killed by the induction of ventricular fibrillation, and the portion of myocardium containing the plate was removed from the heart. If any terminals of the recording electrodes were in the ventricular cavity, the data from them were excluded from analysis. The method of tissue examination has been previously described. Briefly, the endocardium under the plate was stained with Lugol’s iodine solution to identify the Purkinje fibers, and the transmural fiber orientation was determined for 112 regions (each 2.5 × 2.5-mm) throughout each tissue plane bounded by the plunge electrodes. Tissue planes were taken parallel to the epicardial surface at 0.5-mm intervals. The fiber orientations within the volume of tissue bounded by the recording electrodes were used in the calculation of potential gradients, current densities, and energies.

**Data Analysis**

**Analysis of recordings.** The activation time for bipolar recordings was taken as the time of the fastest slope for biphasic waveforms and the absolute peak magnitude for uniphasic and triphasic waveforms. For unipolar recordings, the time of activation was taken as the fastest downslope. Isochronal maps were drawn for all activations analyzed. The stimulus potential was defined as the unipolar potential recorded by an electrode relative to the left hind leg potential during the constant-current stimulation pulse. The 10-msec baseline immediately preceding each stimulus was used as the zero value in the calculation of stimulus potentials. Although the stimulus waveforms were uniformly flat, the stimulus potential was chosen as the middle point of each recorded waveform for consistency. Unipolar recordings of multiple-stimulus pulses at each current level were made to assess the stability of stim-
ulus potentials for different stimuli. Because the left leg was not far from the stimulus source, its potential changed as the stimulus current changed. Thus, all 120 recorded stimulus potentials contained a constant offset value arising from this nonperfect reference potential at the left leg. The offset value increased in absolute magnitude as the stimulus current increased, necessitating its removal from the recorded potentials before analysis of possible relations of these potentials at the directly excited boundary. This constant value, V, to be subtracted from all 120 potentials, was determined for each stimulus current with the least-squares fit to the equation:

\[ V = \frac{1}{4\pi\sigma} \left\{ \frac{1}{r_1} + \frac{1}{r_2} \right\} \]

where \( r \) is distance from the source, \( r_1 \) is the distance from the image source, \( I \) is current magnitude, and \( \sigma \) is conductivity of the medium. The y-intercept determined from the least-squares fit of stimulus potential versus inverse distance \((1/r_1 + 1/r_2)\) was subtracted from the recorded stimulus potentials for each current level, 5–70 mA, to allow determination of the approximate magnitude of the stimulus potential at the directly excited boundary (see below). The calculated offset potentials (y-intercepts) were approximate values because Equation 1 holds true only for an isotropic medium. A constant value subtracted from all recorded stimulus potentials for each individual stimulus current did not affect the calculation of the potential gradient, current density, and energy.

The recordings were divided into directly excited and not directly excited populations for the activations initiated by the S2 stimuli. Recording sites were classified as directly excited by the stimulus 1) if no activation complexes were detected directly after the stimulus and 2) if earliest activation wavefronts directly after the stimulus were first detected at recording sites farther away from the pacing site than the recording site in question (Figure 2).

**Calculation of potential gradient, current density, and energy.** Previously unpublished studies of stimulation from this laboratory indicated that when potential gradients were computed by finite difference or by finite element methods from the original 3 × 5 × 8 grid, large errors occurred. For example, exact potentials and gradients were calculated for stimulation from pacing site P2 through the use of the closed form solution for anisotropic, unbounded tissue. A comparison of exact gradients to gradients calculated numerically from exact potentials showed that the root mean square error was 42% for the longitudinal gradient and 27% for the transverse gradient. Increasing the number of points by subdividing the original grid gave a fivefold improvement of the results but required knowledge of the distribution of potentials throughout the subdivided 5 × 9 × 15 grid. Therefore, the calculation of the gradients consisted of three steps: 1) estimation of potentials at the grid points added during subdivision of the original 3 × 5 × 8 grid with the finite element method; 2) calculation of the gradient components from the potentials of the 5 × 9 × 15 grid with the finite element method; and 3) analysis of the accuracy of the solution and elimination of points with possible excessive errors.

The finite element method used in steps 1 and 2 takes into account the real fiber orientation determined histologically for the 448 elements of the subdivided grid. The values of longitudinal and transverse conductivities were computed by first estimating the gross conductivity from the measured potentials (Equation 1). The gross conductivity, \( \sigma \), for an anisotropic medium was approximated by \( \sigma = (\sigma \cdot \sigma \cdot \sigma)_{1/3} \). The conductivity ratio, \( k_\sigma = \sigma / \sigma \), was assumed to be 3.02, an average of values in the literature. Transverse and longitudinal conductivities were calculated as \( \sigma_L = \sigma_L \sigma \), and \( \sigma_T = \sigma_T \sigma \). These equations yielded values of 0.7565/Ω • m \( \sigma \) and 0.2505/Ω • m \( \sigma \) for longitudinal and transverse conductivities, respectively.

The method of gradient calculation is described in the "Appendix." Current density was obtained as a product of the potential gradient and the conductivity tensor corresponding to the fiber orientation. Energy was calculated by taking the inner product of the potential gradient and current density vectors and multiplying the result by the pulse duration.

**Classification procedures.** Threshold values were found for stimulus potential, potential gradient, current density, and energy that divided all recording sites into two populations, which were directly excited and not directly excited by the field of the stimulus, so that a minimum and equal number of sites from the two groups were misclassified. This classification was performed with one variable with the magnitudes of stimulus potential, potential gradient, current density, and energy, and with the gradients and current densities along and across fibers. Also, a classification with two variables, the longitudinal and transverse components of the potential gradient and current density, was used. Since potential and energy are scalar, they have no longitudinal and transverse components. The transverse component is defined as the vector sum of two orthogonal vectors perpendicular to the fiber axis (see "Appendix," Figure 9A, and Equation 19). For each univariate classification, the value that minimized the number of sites assigned to the wrong group was determined. For the bivariate classification, the value that minimized the number of sites assigned to the wrong group was determined. For the bivariate classification, the value that minimized the number of sites assigned to the wrong group was determined. For the bivariate classification, the value that minimized the number of sites assigned to the wrong group was determined.
directly excited if \( g_l \geq G_l^A \) or \( g_r \geq G_r^A \)  
\[ (2) \]

The linear (L) discriminant function predicted that the tissue would be excited if the linear combination of the longitudinal and the transverse gradients was above a certain level:

\[ \text{directly excited if } \frac{g_l}{(G_l^L)} + \frac{g_r}{(G_r^T)} \geq 1 \]  
\[ (3) \]

The quadratic (E) discriminant function required the following elliptical relation to be satisfied:

\[ \text{directly excited if } \frac{g_l^2}{(G_l^L)^2} + \frac{g_r^2}{(G_r^T)^2} \geq 1 \]  
\[ (4) \]

In Equations 2, 3, and 4, \( g_l \) and \( g_r \) are the longitudinal and transverse components of potential gradient. Equations for current density were obtained by substituting \( j \) for \( g \) and \( J \) for \( G \). Different values of \( G_l^A \) and \( G_t^A \), \( G_l^B \) and \( G_t^B \), and \( G_l^E \) and \( G_t^E \), respectively, were tested during the analysis, and those that misclassified a minimal and equal number of sites from both groups, directly excited and not directly excited, were selected as the threshold values. Although these values represent relations between directly excited sites and extracellular field strengths, the actual measurement of direct excitation was not performed; this would have required recordings of the transmembrane potential. In addition, these values represent the threshold relations only for myocardium in electrical diastole; these values would certainly change in relatively refractory tissue and probably for myocardium electrophysiologically altered by electrolyte abnormalities, autonomic tone, or changes in the resting membrane potential. For simplicity, however, we will refer to the values obtained by the above discriminant functions as the threshold values for excitation of myocardial tissue.

### Statistical methods

Data were analyzed with the paired \( t \) test, the correlation coefficient, 26 and nonlinear regression analysis. 27 Values of \( p<0.05 \) were considered significant. Values are given as mean \( \pm \) SD.

### Results

#### Stimulation Thresholds

To determine the best predictor of direct excitation, the following parameters were analyzed: the stimulus potential, the absolute magnitudes of the potential gradient, current density, and energy, the transverse and longitudinal components of the potential gradient and current density, and combinations of the longitudinal and transverse components of the potential gradient and current density. Figure 2 shows an example of the activation map and electrode recordings from a 40-mA anodal stimulus illustrating the transition from directly excited myocardium to that activated by wavefronts arising from the border of the directly excited tissue. The associated stimulus potential, potential gradient, current density, and energy maps are shown in Figure 3.

**Stimulus potentials at boundary of direct excitation.** The isochronal and isopotential lines in Figures 2A and 3B are similarly oriented, suggesting that the stimulus potential could be used as an indicator of direct excitation. The results of the univariate classification procedure show that for individual current levels in each dog, the division of
FIGURE 3. Fiber orientation, stimulus potential, potential gradient, current density, and energy maps. Panel A: Fiber orientation in the tissue under the acetal plate for the midmyocardial plane of recording electrodes (4 mm from the epicardium) for the same example as in Figure 2. Averages of the 2.5×2.5-mm regions surrounding each recording electrode are shown. Horizontal axis of the plate is designated as 0°. Panel B: Myocardial map of stimulus potentials for the same 40-mA stimulus in Figure 2. Values are given in mV, and isopotential lines are at 250-mV intervals. Magnitude of the energy (Panel C), the magnitude of the potential gradient (Panel D), the longitudinal component of the potential gradient (Panel E), the transverse component of the potential gradient (Panel F), the magnitude of the current density (Panel G), the longitudinal component of the current density (Panel H), and the transverse component of the current density (Panel I) for the midmyocardial layer were calculated from the stimulus potentials shown in Panel B. Potential gradients are in mV/cm, the current densities in mA/cm², and energy in μJ/cm³. Magnitude (mag), longitudinal (long), and transverse (tran) univariate thresholds for potential gradient and current density (Table 1) for all dogs are indicated with solid isolines on their respective maps. Best fit elliptical (E), linear (L), and alternative (A) discriminant functions for all dogs (Equations 2-4) enclosing sites predicted to be directly excited are shown on separate panels as dashed isolines. Underlined values were not used in the threshold analysis because they were suspected of containing excessive errors as described in the "Appendix."
directly excited and not directly excited sites based on the potentials resulted in less than 3% total misclassification. However, the threshold value of stimulus potential separating directly excited and not directly excited sites increases with the stimulus strength. Figure 4 shows the distributions of the stimulus potentials at the directly excited boundary for current levels of 30 and 50 mA from one dog. Note the difference in the dividing potential for the two current levels. For each dog, the square of the threshold stimulus potential \( V^2 \) that best separated the populations at each current level showed a linear increase for increasing stimulus strengths, correlation coefficients for each dog ranging from 0.92 to 0.98 (mean 0.95). Figure 4C shows this relation for a characteristic dog. The plots of potential squared versus stimulus current for all dogs resulted in equations \( V^2 = 23,235 - 2,626 \) for \( V \) in mV and \( I \) in mA (\( r = 0.83, p < 0.0001 \)). This equation for all dogs resulted in 23.1% misclassification of directly excited sites and 2.8% misclassification of sites not directly excited (total percent misclassified, 7.8%). The linear stability of \( V^2/I \) implies a constant potential gradient at the directly excited boundary for an isotropic medium, independent of the stimulus current.

**Potential gradients, current density, and energy at boundary of direct excitation.** A summary of the ability of the potential gradient, current density, and energy to correctly classify the directly excited and not directly excited populations for stimuli of 3-msec pulse duration is listed in Table 1 and illustrated in Figure 5. Univariate classification to predict excitation was applied to the magnitudes and to the longitudinal and transverse components of the potential gradient, current density, and energy. The magnitude of the current density, 3.66 mA/cm\(^2\), correlates better with excitation than the magnitudes of the energy, 9.7 \( \mu \)J/cm\(^3\), and of the potential gradient, 804 mV/cm. The magnitudes of potential gradient and current density are superior to the univariate thresholds calculated from either of their respective longitudinal or transverse components, indicating that the stimulus field both along and across the myofibers is important for excitation.

Bivariate classifications with alternative, linear, and elliptical discriminant functions (see "Materials and Methods" and Equations 2, 3, and 4) were also used to predict excitation. Linear and elliptical discriminant functions of the potential gradient and current density are approximately equally successful in delineating excitation. The linear function identifying the region of direct excitation for the potential gradient in mV/cm is \( g^p/640 + g^r/1,840 \geq 1 \). For current density in mA/cm\(^2\), the equation is \( j^p/4.60 + j^r/4.80 \geq 1 \), yielding transverse to longitudinal threshold ratios (y- and x-intercepts, respectively) of 2.88 for potential gradient and 1.04 for current density. The elliptical functions are \( g^p/530^2 + g^r/1,150^2 \geq 1 \) for potential gradient and \( j^p/3.76^2 + j^r/3.49^2 \geq 1 \) for current density, yielding
transverse-to-longitudinal threshold ratios of 2.17 for potential gradient and 0.93 for current density.

Strength-duration curves were constructed for the magnitudes of potential gradient, current density, and energy. Bivariate plots were not constructed for the longitudinal and transverse components of potential gradient and current density owing to the smaller number of data points at these pulse durations. Magnitude threshold data were not available for the 40-msec pulses because of frequent polarization of the platinum electrodes at this longer duration. Figure 6 shows that the strength-duration curves for potential gradient and current density are hyperbolic, with the rheobase occurring at pulse durations of approximately 3–3.5 msec. The energy strength-duration curve has a minimum at pulse durations of 0.8–2 msec (Figure 6C). A linear increase in the energy excitation threshold occurs for pulse durations greater than 3 msec, and apparent hyperbolic increases in the threshold occur for pulse durations less than 0.8 msec. The solid lines in Figures 6A and 6B represent the least-squares fit to the equation $T = bc/D + b$, where $T$ represents $G_m$ or $J_m$ for each pulse duration, $D$ is the pulse duration in msec, $b$ is the rheobase, and $c$ is the chronaxie. The best fit equations estimated from linear regression analysis were $G_m = 795/D + 698$ and $J_m = 3.97/D + 3.15$. Both equations tend to underestimate the potential gradient and current density thresholds for longer pulse durations (Figure 6). The energy strength-duration curve was fit to the equation $E_m = b/rDX(1 + r/D)^2$, where $r$ is resistance, yielding the equation $E_m = 6.94/D + 3.78D - 2.907$. The mean chronaxie value yielded by the three equations was 1.25 msec (range 1.14–1.35 msec).

Current density values reported in Table 1 and Figures 5 and 6 were obtained with the conductivity values of 0.7565/Ω • m for $\sigma_l$ and 0.2505/Ω • m for $\sigma_r$ (ratio 3.02) as discussed in "Materials and Methods." Conductivity ratios of 2.5, 2.8, 3.2, and 3.5 (keeping conductivity magnitude constant) were also tested, all yielding an increase in percent misclassification for the bivariate discriminant functions without producing large changes in the magnitude threshold value.

**Anodal versus cathodal excitation.** Figures 7 and 8 show the results of cathodal and anodal stimulation during electrical diastole. At twice-minimal anodal pacing threshold (0.4 mA), the latency, that is, the time from the onset of the stimulus artifact to the time of excitation at the recording site, for anodal excitation is longer (total range, 3–11 msec for all dogs) than cathodal excitation ($p<0.0001$). For stimulus currents ≥5 mA, however, the differences in latency at each recording electrode for anodal and cathodal stimulation are not significant ($p=0.25$ for all dogs, Figures 7 and 8). These relations hold true for all pulse durations tested. In Figures 7D and 7L, the activation complex occurs before the break of the anodal pulse for both high-current and low-current stimulation, indicating that excitation was not produced by the break of the anodal pulse. In addition, the anodal and cathodal stimulation thresholds, expressed as stimulus potential, potential gradient, current density, or energy, are not significantly different for stimuli ≥5 mA ($p=0.39$).

**Stability and Reproducibility of Recordings: Control Stimuli**

Cathodal stimuli of 2 mA were delivered intermittently to assess the effects of time and high-current...
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Figure 5. Potential gradient and current density thresholds. Shown are the bivariate plots of the longitudinal (abscissa) and transverse (ordinate) components of the potential gradient (Panel A) and current density (Panel B) for the directly excited and not directly excited populations from all dogs. Discriminate functions used to divide the populations are indicated on the graphs. Long and trans, univariate thresholds corresponding to the longitudinal and transverse components, respectively. A, E, and L, alternative (Equation 2), elliptical (Equation 3), and linear (Equation 4) discrimination functions, respectively. The magnitude thresholds (mag) form quarter circles on the bivariate plots. Asterisks represent directly excited sites, and dots represent sites not directly excited. To better delineate the areas of overlap, the entire data set for both graphs is not shown; 11% of the directly excited population for the potential gradient graph is greater than 2,000 mV/cm, and 18% of the directly excited population for the current density graph is greater than 10 mA/cm² and thus lie outside the graphed region. All points are shown for the populations not directly excited.

density stimuli on stimulus potentials, potential gradients, and activation times. The magnitude of the stimulus potentials declined at a linear rate (mean $r = 0.92$) for all recording terminals at an average decline of 3.03 mV/hr. The potential gradients, however, remained stable over time, reflecting the parallel decline in potentials at all recording electrodes within individual dogs ($p = 0.92$). The stability of the activation sequence was assessed by comparing the activation times at each recording terminal for the first and last control stimuli from the same pacing electrode. These two stimuli were separated by a minimum of 100 minutes. For the six dogs, the average linear regression slope was $0.99 \pm 0.02$ with an average correlation coefficient of $0.99 \pm 0.01$ (root mean square error = 4.6%). Paired

Figure 6. Strength-duration curves. Relation between stimulus duration and excitation threshold for potential gradient (Panel A), current density (Panel B), and energy (Panel C). •, points determined for pulse durations 0.2–20 msec with stimulus currents of 20, 40, and 60 mA as described in “Materials and Methods” and “Results.” ○, values given in Table I and Figure 5 that were obtained from a different set of 3-msec stimuli. Best fit curves to the equations are given above each strength-duration curve for D (pulse duration) in msec.
**FIGURE 7.** Anodal and cathodal excitation. Panels A and B are consistent with cathodal make and anodal break excitation. Anodal latency is approximately 6-msec greater than the cathodal latency at an identical pulse duration and stimulus current. Panels C and D show, however, the break excitation is not the mechanism for either cathodal or anodal stimulation as the activations occur before the break of both 40-msec pulses. Respective latencies remain the same as for the 3-msec pulses in Panels A and B. Pacing currents in Panels A–D are at twice minimal anodal pacing threshold (0.4 mA). Panels E and F show the disappearance of the difference in cathodal and anodal latencies for 5-mA stimuli at 3-msec pulse durations. Recording terminal is different from that in Panels A–D. Difference in anodal and cathodal activation times for all dogs is less than 1 msec for stimulus currents ≥5 mA for all pulse durations. Panels G–J show decreasing latencies as the pulse durations of cathodal and anodal 40-mA stimuli are increased from 0.2 to 3 msec. An increase to 20-msec pulse durations in Panels K and L shows identical latency to the 3-msec stimuli, suggesting no change in the area directly excited. Activation occurred before the break of the 20-msec 40-mA pulse for both polarities at this recording site. Decreasing latency for increasing pulse durations up to 3-msec indirectly demonstrates the increasing area that was directly excited. –→, initiation and termination of stimulus pulses except for the 0.2-msec pulses in Panels G and H that are marked with a single bold arrow because they are so short. Stimulus pulses are at the end of gain switching and are often not seen because of the bipolar recording and low gains necessary to record activations without saturation. –, indicate the time in msec from stimulus initiation to time of activation. All panels are at the same time scale. Stimulus polarity, stimulus current in mA, and pulse duration in msec are shown on the panels. Stimuli were delivered from the midmyocardium with pacing electrode P2 (Figure 1).

comparisons of the stimulus potentials, potential gradients, and activation times immediately before and after high constant-current shocks (60 and 70 mA) revealed no change in any variable (p = 0.11). These results, in conjunction with those from a previous study, validate the use of plunge electrodes to study activation patterns and stimulus fields in a small region of myocardium over a time span of several hours.

**Discussion**

**Stimulation Threshold Parameters**

Stimulus potentials and potential gradients. Threshold excitation of in vivo cardiac tissue has traditionally been expressed in terms of the total stimulus strength, for instance, as the threshold value of current delivered to the preparation. This threshold is not constant but is sensitive to variations in electrode size, stimulation site, tissue geometry, and conductivity. The nature of cellular excitation by a stimulus has suggested the importance of the role of the extracellular potential gradient for cellular excitation and raised the hypothesis that a distinct threshold of potential gradient exists for stimulation. This potential gradient apparently depolarizes the sarcolemma to threshold, activating the inward sodium current and initiating an activation wavefront.
Stimulation thresholds for the potential gradient have since been measured for in vitro cell cultures and calculated for transthoracic shocks in dogs and humans. The range of the reported stimulation thresholds is 1.2–9.1 V/cm, higher values coming from cell cultures. To our knowledge, the excitation threshold expressed as a potential gradient has not been measured in vivo, and the effect of fiber orientation on this threshold has not been previously assessed. However, the anisotropic syncytial behavior of cardiac muscle, which is dependent primarily on the geometry of the cardiac cells, their interconnections, and the microscopic discontinuities in conductivity, causes the current to be greater along than across fibers.

The isopotential lines in Figure 3B are elliptical, although less so than predicted for anisotropic conductivity. This is presumably due to the changing fiber orientation between source and recording sites, which reduces the effect of anisotropy as the distance from the source increases. The elliptical isopotential lines, however, proved to be fairly accurate determinants of the boundary of direct excitation (Figures 2A and 3B). This result can be predicted from the equation relating potential gradients and stimulus potentials for an isotropic medium. In this case, the gradient field $\nabla V$ can be expressed as

$$\nabla V = \frac{4 \pi \sigma}{I} V^2$$

where $V$ is the stimulus potential, $I$ is the stimulus current, and $\sigma$ is conductivity of the tissue. If $V^2$ and $I$ form a linear relation, $\nabla V$ must be constant. The average linear regression equation for all dogs is $V^2 = 23,2351 - 2,626 (r=0.83, p<0.001)$. The potential at the boundary of direct excitation can therefore be predicted for a given stimulus current (and vice versa), thus implying the existence of a constant potential gradient at the boundary of direct excitation. For the anisotropic case, however, the isogradient lines are more circular than the isopotential lines (Figures 3B and 3D). The failure of the magnitude of the gradient to separate accurately the directly excited and not directly excited populations demonstrates this phenomenon (Figure 5A). Therefore, the fiber orientation is important in determining the potential gradient thresholds for excitation.

Bivariate combinations of the transverse and longitudinal potential gradients yield ratios of their threshold values of 1.9–2.9, indicating higher excitation thresholds for the transverse gradient. These ratios, particularly those for the linear combination (ratio, 2.9), are roughly equivalent to the anisotropy conductivity ratio that, like the anisotropic potential gradient thresholds, arises from the geometry of cardiac cells. If the cardiac cell cross section is approximated by an elongated ellipse, a potential gradient applied across the cell produces a smaller change in the transmembrane potential than the same potential gradient applied along the cell axis.

In 1975, Rush et al. presented a modeling study proposing that "field quantities such as potential gradient and current density in the heart are more suitable measures of the electrical stimulus than electrode voltage, current, or charge."
Therefore, the potential gradient threshold in the transverse direction should be larger than the gradient in the longitudinal direction. This anisotropy of gradient thresholds explains the failure of the magnitude of the potential gradient to characterize direct excitation accurately. Bivariate combinations of the longitudinal and transverse potential gradients proved to be accurate and sensitive predictors of direct excitation of cardiac cells. Although the data do not allow determination of the best of the three bivariate methods, a model of potential distribution in periodic structures indicates that the linear discriminant function is most appropriate. In addition, the use of the linear discriminant function (Equation 3) to calculate magnitude thresholds closely approximates previously reported potential gradient thresholds of 1,200–1,300 mV/cm if a large component of current flow is assumed to be oriented perpendicular to the long axis of the cardiac cells. This situation probably exists for trans-thoracic pacing and in cultures of randomly oriented myocardial cells.

Current density and energy. The current density, \( j \), proved to be as accurate as the potential gradient for the identification of directly excited and not directly excited myocardium (Figure 5B and Table 1). A current density of 3.66 mA/cm\(^2\) yielded 8.3\% total misclassifications and was the most accurate predictor of direct excitation of the three magnitude thresholds. The success of the magnitude of the current density in predicting excitation suggests that, for the three bivariate combinations of the longitudinal-transverse components of the current density, the elliptical discriminant function might characterize excitation most accurately since one possible form of the elliptical function is the circle representing the magnitude threshold. Indeed, the elliptical function misclassified the least number of sites, yielding the equation \( j^2/3.76^2 + j^2/3.49^2 \geq 1 \). Introducing two independent variables in the elliptical discriminant function, however, did not significantly decrease the number of misclassified sites as compared with the magnitude. Therefore, the magnitude of the current density can be used as the indicator of direct excitation.

The transverse-to-longitudinal current density ratio for excitation ranged from 0.90 to 1.04 for the three bivariate combinations analyzed. The approximation to a unity ratio follows from the method of calculation of current density as a product of conductivity tensor and potential gradient. Since the longitudinal-to-transverse ratio of the potential gradient was approximately 1/3, its multiplication by a conductivity ratio of 3.02 produced almost equal transverse and longitudinal current density thresholds. The actual measurement of the conductivity in different layers of the heart along and across fibers might improve the results, but this would require the application of the three- or four-electrode technique to many sites along and across fibers in the myocardium. The use of other conductivity values yielding \( \alpha_l/\alpha_r \) ratios of 2.5, 2.8, 3.2, and 3.5 (holding conductivity magnitude constant) for the calculation of current density thresholds decreases the accuracy of classification for the bivariate discriminant functions in each case without producing large changes in the magnitude threshold value. This implies that \( \alpha_l/\alpha_r \) is approximately 3 as previously reported.

The magnitude of energy was also evaluated as a threshold for excitation. The use of energy to define the directly excited and not directly excited populations for 3-msec pulses yielded 12.8\% total misclassification for the threshold energy value 9.7 \( \mu \)J/cm\(^2\). Potential gradient and current density contain errors of calculation that magnify with the formation of the dot product to obtain the energy. This may explain the larger misclassification errors for energy as compared with the most accurate classification methods for potential gradient and current density. Energy, however, may simply be a less specific method of classifying directly excited sites than current density or potential gradient.

Strength-duration curves. Potential gradient and current density are not the only factors that determine whether excitation occurs. The length of time during which the electric field is applied is also important. Strength-duration curves were constructed to determine the effect of pulse duration on the excitation thresholds (Figure 6). For potential gradient and current density, increases in the pulse duration beyond 3–3.5 msec did not increase the area directly excited (Figures 7 and 8) nor significantly change the excitation thresholds (Figure 6). Pulse durations shorter than 3 msec required larger potential gradients and current densities to directly excite the tissue as shown by the strength-duration curves. Both data sets were closely approximated by hyperbolic functions, although there appeared to be more rapid approaches to stable rheobases than could be fit by a hyperbolic function. The shape of these curves is similar to experimental data based on more traditional measurements of stimulus strength such as total delivered current.

Since energy is a function of stimulus duration as well as stimulus strength, increases in the pulse duration yield increases in the energy. Because the area directly excited did not increase for pulse durations longer than 3–3.5 msec, the energy threshold increased linearly for pulse durations longer than 3–3.5 msec (Figure 6C). The energy threshold for the longest pulse duration examined, 20 msec, was 76 \( \mu \)J/cm\(^2\) and was 30.5 \( \mu \)J/cm\(^2\) for the shortest pulse duration, 0.2 msec. The baseline minimum is approximately 0.8–2 msec, enclosing the predicted chronaxie values, 1.14–1.35 msec, from the three threshold-duration equations.

Anodal versus cathodal excitation. Controversy has long existed over the mechanism of excitation by extracellular stimulation with hyperpolarizing anodal pulses and revolves around the existence of "virtual cathodes" and break excitation. The hypoth-
esis that anodal excitation is on the "break" of the pulse while cathodal excitation is on the "make" was put forward in the 1950s. The theory that the removal of hyperpolarization is the cause of anodal excitation was challenged by Dekker who demonstrated that both make and break excitations occur for either polarity of stimulation and reported a complex relation between anodal and cathodal make and break excitations depending on the phase of the cardiac cycle. Dekker concluded that anodal excitation during diastole occurred on the make of the pulse but possessed a "utilization time" of 4-12 msec, that is, a longer latency than cathodal excitation. His conclusions were based on stimulation at twice threshold levels. Our data from stimulation at twice anodal diastolic threshold, but not for 5 mA and greater, agree with Dekker's conclusions demonstrating anodal excitation occurring before the break of the pulse but with a longer latency than cathodal stimulation (Figures 7C and 7D). The utilization times recorded in this study for twice threshold pacing ranged from 3 to 11 msec. When the current was increased so that the border of the directly excited region was distant from the stimulation site, this relation no longer held true. At stimulus currents of 5-70 mA, the activation times were not significantly different for anodal versus cathodal stimulation (p = 0.25, Figures 7E-7L). Also, no difference in the region directly excited for 5-70 mA anodal and cathodal stimuli or in the threshold potential gradients (p = 0.39) was observed. The presence of threshold defibrillation levels independent of electrode polarity also suggests an equal region directly excited by the anode and cathode.

The explanation of these results can be found in theoretical models that take into account the existence of microscopic conductivity changes in cardiac muscle. One-dimensional periodic core-conductor models reveal the presence of two components of the transmembrane potential: the aperiodic component that is equivalent to the transmembrane potential of the classic continuous fiber and the periodic oscillations whose period equals the cell length and whose amplitude is dependent upon the potential gradient established by the stimulus and upon the local changes in conductivity. Extrapolating these results to three dimensions suggests that direct excitation of myocardium distant from the site of stimulation is caused by the periodic component of the transmembrane potential. Because of these oscillations, the transmembrane potential more than a few cells away from the stimulus electrode has different polarities on opposite ends of the cardiac cell, thus depolarizing one end and hyperpolarizing the other. The depolarized end of the cell is the one closer to the stimulus electrode for cathodal stimulation and is the end farther from the stimulus electrode for anodal stimulation. For these stimuli (≥5 mA), the periodic component of the transmembrane potential in some regions distant from the stimulating electrode causes one end of the cell to be depolarized beyond the threshold so that the regions are directly excited. Because of the small dimensions of the cells, the differences in stimulation thresholds and regions directly excited for cathodal versus anodal stimulation are negligible for stimuli greater than 5 mA.

In contrast, the latency and the diastolic threshold for pacing, during which stimulus strengths much less than 5 mA are delivered, differ for anodal and cathodal stimulation. The traditional explanation of the observed differences is based on analysis of only the aperiodic component of the transmembrane potential, which causes depolarization of the cells in the immediate vicinity of the electrode for cathodal pacing, and hyperpolarization of these cells for anodal pacing. It has been postulated, therefore, that the mechanism of anodal activation is different from that of cathodal activation and that a hyperpolarizing current can activate the membrane either by an accommodation process or by break excitation. These hypotheses are not supported by experimental evidence for stimulation in electrical diastole; first, intracellular recordings have shown the presence of depolarizing current during anodal stimulation, and second, activation has been found to not be possible when the membrane is hyperpolarized by intracellular rather than by extracellular stimulation.

An alternative hypothesis to explain the differences between cathodal and anodal threshold stimulation takes into account the periodic component of the transmembrane potential arising from the discrete structure of the myocardium. According to this explanation, the cells immediately adjacent to the anode cannot activate because of the hyperpolarization caused by the aperiodic term of the transmembrane potential; instead, cells slightly farther away are activated because the amplitude of the aperiodic term is smaller, and the periodic oscillatory term causes the end of the cell distant from the anode to depolarize. Since for anodal pacing the aperiodic term counteracts depolarization instead of assisting it, the threshold is higher than for cathodal pacing. According to this explanation, stimulation with a cathodal electrode occurs when the stimulus strength is sufficiently strong that the additive effects of the aperiodic and oscillatory terms raise the transmembrane potential of the cells immediately around the electrode to threshold. The stimulation threshold is higher for an anode because the stimulus field must be sufficiently strong so that the depolarizing portion of the oscillatory term can overcome the opposing hyperpolarizing effect of the aperiodic term slightly distant from the anodal electrode and depolarize a portion of the membrane to above threshold. The increased latency associated with anodal stimulation is caused by slow conduction away from the site directly excited by the stimulus field since a major portion of the membrane of the neighboring cells is still hyperpolarized.
This hypothesis regarding the mechanism of extracellular stimulation by anodal and cathodal sources is based on the model of potential distribution in the periodic cardiac muscle. The available model is limited to the steady-state case with no time-dependent phenomena included, and therefore, only qualitative comparison is possible. Nevertheless, the experimental findings discussed above compared with the results of simulation revealed an excellent qualitative and possibly quantitative agreement.

**Classification of Directly Excited Sites**

This study would have been stronger if direct excitation had been determined by transmembrane recordings. During electrical diastole, the rise in transmembrane potential in the presence of an almost instantaneously applied extracellular potential presumably occurs within 1 msec and generates a propagated activation wavefront. If tissue under a bipole was directly excited but exhibited a long latency, the simultaneous or nearly simultaneous change in potential under the two separate poles should not produce the characteristic waveforms seen with bipolar recordings of a propagating wavefront. We therefore believe that sites classified as not directly excited are accurately classified.

The classification of directly excited sites is more likely to contain errors than classification of sites not directly excited. Assuming that activation is initiated by the make of the stimulus with no latency, the activation wavefront for a 3-msec pulse traveled for a time of approximately 5 msec (3-msec pulse plus 2-msec gain switching artifact) before detection was possible. For longitudinal and transverse conduction velocities of 0.63 and 0.32 m/sec, respectively, this corresponds to 3.2 and 1.6 mm, respectively, that the wavefront could travel before being detected. Sites were classified as directly excited only if no trailing edge of the activation complex was detectable immediately after the end of the stimulus. As most activation complexes are greater than 4 msec, this helped to minimize the inaccurate classification of directly excited sites for 3-msec pulse durations. Because the major component of the stimulus artifact occurs on its break, activations could be detected as early as 3 msec after the make of the stimulus after very short (0.2 and 0.4 msec) or very long (20 and 40 msec) pulse durations (Figure 8). The conduction velocity within the 3–6-msec period after the make of the stimulus for these pulse durations did not exhibit areas of rapid velocity on the subendocardium or elsewhere in the myocardium that would have increased the possibility of misclassification errors for the 3-msec pulses. Because activations could not be detected until 3–6 msec after the start of the pulse for 3-msec stimuli, however, some sites thought to be directly excited may not have been. For example, several sites with activation times of 3 and 4 msec for a 20-msec stimulus (Figure 8) are classified as directly excited or missing for the 3-msec stimulus (Figure 2). Small differences exist in the activation patterns after these two equal current stimuli, however, that make comparisons difficult. These possible misclassification errors for 3-msec stimuli would result in a small systematic error yielding slightly smaller field strength values at the directly excited boundary than actually exist. This would not, however, alter our basic conclusions concerning excitation threshold relations.

The misclassification errors listed in Table 1 and the range of overlap of the directly excited and not directly excited populations in Figure 5 reveal that the threshold values represent a region of overlap within which direct excitation is difficult to predict. For example, the range of overlap for the magnitude of the current density was 2.74 to 4.68 mA/cm²; that is, no site with Jₐ less than 2.74 mA/cm² was directly excited, and all sites with Jₑ greater than 4.68 mA/cm² were directly excited. This range of overlap may represent computational errors of the potential gradients, current densities, and energies, misclassification errors of directly and not directly excited sites, a range of excitability for different dogs or within individual dogs, or a combination of the above factors. Another possible reason for the misclassification errors may be that a given extracellular potential gradient or current density does not always cause the same change in transmembrane potential. Simulation with a bidomain model indicates that the threshold values for stimulation could be expected to exist elsewhere in the ventricles, although further experimentation is needed to verify this point. For stimulation during the relatively refractory period, the relation between the threshold values may not, however, hold true, and the threshold values for excitation would certainly be expected to increase. The construction of strength-interval curves with similar methods would be necessary to answer these questions. In addition, alteration of the electrophysiological properties of the myocardium by hypoxia, electrolyte abnormalities, changes in autonomic tone, or other abnormalities could be expected to result in different threshold values.

**Stability and Reproducibility of Recordings**

A second possible limitation of the study is that not only could the large number of recording electrodes alter the electric field and damage the myocardium to change the cellular response to the field, but the stimulus current may have, itself, damaged...
the cells. To examine these possibilities, control stimuli were delivered not only to assess changes in the stimulus potentials, potential gradients, and activation times but also to investigate the effects of high constant current shocks on these variables.

A linear decline in the stimulus potential occurred over time, and stable potential gradients and activation patterns were present for the 2-mA control stimuli. In addition, the stimulus potentials, potential gradients, and activation times did not change immediately before and after constant current shocks of 60 and 70 mA. These results, along with similar results from a previous study on the effects of plunge electrode insertion on stimulus potentials, potential gradients, and conduction velocity, validate the use of transmural plunge electrodes to study activation patterns and potential gradients in the canine myocardium. Plunge electrode spacing of 5 mm in healthy tissue does not appear to affect the activation patterns or potential gradients over time, and repeated high-current stimulation (≤70 mA) from a point source, although it may damage immediately adjacent tissue, appears not to damage nearby myocardium sufficiently to alter the stimulus potentials, potential gradients, or activation sequences.

**Use of the Term “Threshold”**

There are several possible limitations to our use of the term “threshold” for extracellular field parameters. The threshold values were determined retrospectively from the data and thus should also be verified prospectively in a second set of experiments. In addition, the stimulus current, and not the extracellular field, was the variable that was systematically changed in this study, although changes in the stimulus current certainly resulted in changes in the extracellular field.

Excitation is a complex temporal and spatial phenomenon that ultimately depends upon the inward sodium current and resulting change in transmembrane potential. Thus, the fundamental excitation threshold is that of the sodium current and change in transmembrane potential, not that of the extracellular field. Nonetheless, the recent development of a mathematical relation relating changes in the transmembrane potential to the application of extracellular fields leads us to believe that the excitation threshold expressed in terms of the extracellular field is an important step closer to defining the fundamental excitation threshold than are previously used methods such as total delivered current.

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**Appendix**

**Finite Element Method for Calculation of Potentials and Potential Gradients**

**Calculation of Potentials.** The problem of determining the potential field based on experimental data can be stated as follows:

\[
-\nabla(\sigma\nabla\phi) = f(x, y, z)
\]

(6)

This elliptic equation should be solved in the cuboid domain \( \Omega \) with the Dirichlet boundary conditions, that is, taking the potential of the boundary nodes as given. Potential is denoted by \( \phi \), and \( \sigma \) is the anisotropic conductivity tensor. For unipolar stimulation within the cube \( f(x,y,z)=p \cdot \delta(x-x_s, y-y_s, z-z_s) \), where a point source of strength \( p \) is placed at \((x_s, y_s, z_s)\), and where \( \delta \) is Dirac’s function.

Because of the curvature of the heart, the presence of cavities, and, ultimately, the changes of fiber orientation within the domain, the use of numerical methods is required to obtain the solution to Equation 6. The finite element method was chosen since it permits the modeling of the complicated pattern of anisotropy. The variational formulation of Equation 6 is

\[
\Pi(\phi) = \frac{1}{2} \int_\Omega (\nabla\phi)^T \sigma(\nabla\phi) \, dV + \int_\Omega f(x,y,z)\phi \, dV
\]

(7)

The finite element equations arise when the energy \( \Pi(\phi) \) is minimized with respect to potential \( \phi \). With the region in question divided into tetrahedral elements (Figure 9B) and with potential varying linearly within each element, the element matrix is

\[
K_e = v \cdot B^T R^T \sigma^p R B
\]

(8)

where \( v \) is the volume of the element, \( B \) is the gradient-potential coefficient matrix (i.e., \( \nabla\phi = B \cdot \phi \)), \( R \) is the transformation matrix used to rotate the global coordinate system to the local fiber orientation, and \( \sigma^p \) is the conductivity tensor for the principle axes of anisotropy.

The element matrices given by Equation 8 can be assembled into the system matrix, yielding the set of system equations

\[
K_s \Phi = \Phi^c
\]

(9)

where \( K_s \) is the system matrix (unconstrained), and \( \Phi^c \) is the vector containing point sources.

Applying the Dirichlet boundary conditions \( \Phi^b \) leads to the partitioning of the system matrix and to the following set of constrained system equations:

\[
K_c \Phi_c = \Phi^b - K_d \Phi_d
\]

(10)

that are solved for the unknown potentials \( \Phi_c \). The potential at internal nodes found from Equation 10 can then be compared with the corresponding "hidden" potentials obtained from experiments or from simulated data to estimate the root mean square error of the finite element solution. For a source located on the boundary of the region, a root mean square error of less than 2% and a correlation
coefficient of 0.999 were obtained when comparing the finite element potentials with the exact (i.e., simulated) values.

Calculation of potential gradients. Knowing the potential throughout the subdivided cube, the potential gradients in the \( x \), \( y \), and \( z \) directions can be calculated also with the finite element method but with the domain divided into bricks instead of tetrahedra. The reason for this change is that the bilinear shape function used for bricks gives a better approximation of gradients than the linear one used for tetrahedra. Within each eight-node brick element, the potential is interpolated by the following shape function:

\[
\phi(x, y, z) = c_0 + c_1 x + c_2 y + c_3 z + c_4 xy + c_5 yz + c_6 xz + c_7 xyz
\]

where \( x, y, z \) are the coordinates of a point within the element. The coefficients \( \vec{c} = (c_0, c_1, \ldots, c_7) \) can be calculated from the following equation:

\[
\vec{c} = V^{-1} \cdot \vec{\phi}
\]

where \( \vec{\phi} \) is the vector of potentials at the nodes of the brick element, and \( V \) is the Vandermonde matrix, which depends upon nodal coordinates:

\[
V = \begin{bmatrix}
1 & x_1 & y_1 & z_1 & x_1 y_1 & x_1 z_1 & x_1 y_1 z_1 \\
1 & x_2 & y_2 & z_2 & x_2 y_2 & x_2 z_2 & x_2 y_2 z_2 \\
1 & x_3 & y_3 & z_3 & x_3 y_3 & x_3 z_3 & x_3 y_3 z_3 \\
1 & x_4 & y_4 & z_4 & x_4 y_4 & x_4 z_4 & x_4 y_4 z_4 \\
1 & x_5 & y_5 & z_5 & x_5 y_5 & x_5 z_5 & x_5 y_5 z_5 \\
1 & x_6 & y_6 & z_6 & x_6 y_6 & x_6 z_6 & x_6 y_6 z_6 \\
1 & x_7 & y_7 & z_7 & x_7 y_7 & x_7 z_7 & x_7 y_7 z_7 \\
1 & x_8 & y_8 & z_8 & x_8 y_8 & x_8 z_8 & x_8 y_8 z_8
\end{bmatrix}
\]

combining Equations 11, 12, and 13, the shape function of Equation 11 assumes the form

\[
\phi(x, y, z) = [1 \ x \ y \ z \ xy \ yz \ xz \ xyz] \cdot V^{-1} \cdot \vec{\phi}
\]

The gradients can be obtained by differentiating Equation 14 with respect to \( x \), \( y \), and \( z \):

\[
\begin{align*}
\vec{g}_x &= \begin{bmatrix} 1 & 0 & 0 & 0 & y & 0 & z & yz \end{bmatrix} \cdot V^{-1} \cdot \vec{\phi} \\
\vec{g}_y &= \begin{bmatrix} 0 & 1 & 0 & 0 & x & 0 & xz \end{bmatrix} \cdot V^{-1} \cdot \vec{\phi} \\
\vec{g}_z &= \begin{bmatrix} 0 & 0 & 1 & 0 & y & x & xy \end{bmatrix} \cdot V^{-1} \cdot \vec{\phi}
\end{align*}
\]

The value of gradient components \( g_x \), \( g_y \), and \( g_z \) at each node of the element are calculated by substituting the \( x \), \( y \), and \( z \) coordinates of that point into Equation 15. The magnitude of the gradient is determined by

\[
g_m = \sqrt{g_x^2 + g_y^2 + g_z^2}
\]

The gradients that are important from the point of view of electrophysiology are the two transverse gradients perpendicular to the fiber axis, and the longitudinal gradient parallel to it. In the experiment, \( g_x \) is assumed to be always transverse, and the fibers are assumed to lie in the \( y-z \) plane forming angle \( \gamma \) with the \( y \)-axis (Figure 9A). To obtain the transverse and longitudinal gradients, the global
coordinate system (x, y, and z) is transformed into the local one (x, t, and l), in which the first two axes (x and t) point across fibers and the last one (l) is parallel to them. The relation between these two coordinate systems is

\[
x = x \\
y = t \sin y + l \cos y \\
z = -t \cos y + l \sin y
\]

(17)

Therefore, the gradients are related by the Jacobian of transformation Equation 17

\[
\begin{bmatrix}
\frac{\partial g_x}{\partial x} & \frac{\partial g_x}{\partial t} & \frac{\partial g_x}{\partial l} \\
\frac{\partial g_y}{\partial x} & \frac{\partial g_y}{\partial t} & \frac{\partial g_y}{\partial l} \\
\frac{\partial g_z}{\partial x} & \frac{\partial g_z}{\partial t} & \frac{\partial g_z}{\partial l}
\end{bmatrix}
\begin{bmatrix}
g_x \\
g_y \\
g_z
\end{bmatrix}
\]

(18)

The magnitude of the transverse gradient \(g_T\) can be obtained from

\[
g_T = \sqrt{g_x^2 + g_y^2}
\]

(19)

Accuracy analysis. The gradients computed with the technique described above are usually distorted by the presence of discretization error. The finite element method used to determine the gradients provides the means to assess this error. The value of the gradient at a particular point can be obtained from any of up to eight brick elements adjacent to this point (Figure 9C). These values differ among themselves, and their dispersion correlates with the error present in the solution. The average of the gradients in all elements surrounding the point is taken as the gradient at this point, and the degree of dispersion is analyzed to determine whether this gradient can be used for further analysis. The selection process, which takes into account the absolute and relative values of the dispersions and the distance from the source, eliminates almost all gradients with more than 10% error (Figure 3). The root mean square errors of the \(g_x\) and \(g_T\) components after the selection process are 6.3% and 2.2%, respectively. The error in \(g_x\) is slightly higher because of the round-off errors introduced by the transformation Equation 18.

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