Computer-based model of epidural motor cortex stimulation: Effects of electrode position and geometry on activation of cortical neurons

Amorn Wongsarnpigoon, Warren M. Grill *

Department of Biomedical Engineering, Duke University, Durham, NC 27708-0281, USA

Abstract

Objective: The aim of this study was to determine the effects of electrode placement, geometry, and polarity during epidural cortical stimulation (ECS) on thresholds for direct activation of cortical neurons.

Methods: We used a computational model of epidural electrical stimulation of the motor cortex coupled to compartmental models of cortical neurons.

Results: Thresholds varied with stimulation polarity and neuron position, and neurons deep within the sulci had much larger thresholds than those on the crowns or lips of the gyri. Axons were more excitable than cell bodies or dendrites. Delivering stimulation with the lead placed above or perpendicular to the sulci resulted in substantial stimulation of the gyri adjacent to the target gyrus. Electrode diameter and inter-electrode spacing influenced thresholds and affected the spread of activation in the cortex.

Conclusions: Electrode placement, geometry, and polarity during ECS influence excitation properties of cortical neurons substantially.

Significance: Epidural leads have varying geometries, and in clinical studies of ECS the placement of the lead has been inconsistent. These results provide an improved understanding of the effects of electrode placement, geometry, and polarity on the outcome of ECS and can facilitate the rational implantation and programming of ECS systems.

Keywords:
Finite element method
Motor cortex stimulation
Pyramidal cell

1. Introduction

Electrical stimulation of the cortex is a developing therapy for the treatment of neurological disorders including pain (Anderson et al., 2009; Lefaucheur et al., 2009; Nguyen et al., 1998; Rasche et al., 2006; Sakas et al., 2010; Tsubokawa et al., 1991; Velasco et al., 2009; Yamamoto et al., 2007); movement disorders (Katayama et al., 2002; Kleiner-Fisman et al., 2003), such as akinesia (Tani et al., 2007), dystonia (Pagni et al., 2008; Romito et al., 2007), tremor (Nguyen et al., 1998), myoclonus (Franzini et al., 2003) and Parkinson's disease (Drouot et al., 2004; Gutierrez et al., 2009; Pagni et al., 2008); tinnitus (De Ridder et al., 2007); depression (Nahas et al., 2009); aphasia (Cherney et al., 2010); and as an adjunct to stroke rehabilitation (Adkins et al., 2006; Brown et al., 2003; Kleim et al., 2003; Levy et al., 2008; Plautz et al., 2003; Teskey et al., 2003). Cortical stimulation can be achieved through transcranial direct current stimulation (tDCS; through the scalp and skull), epidural cortical stimulation (ECS; electrode placed below the skull and above the dura mater) and subdural stimulation (electrode placed below the dura mater) and subdural stimulation (electrode placed below the dura). ECS enables specific regions of the cortex to be targeted more effectively than tDCS and is less invasive than subdural stimulation. ECS may be a viable alternative to deep brain stimulation (DBS), which can cause behavioral side effects (Bejani et al., 1999; Houeto et al., 2002) and requires a complex and highly invasive surgical implant.
The mechanisms by which ECS has its therapeutic effects are unclear, and this lack of understanding will limit the full development of this promising treatment. The distribution of electric field and the spread of current during ECS cannot be easily predicted because the cortex and the surrounding anatomy have irregular geometries and inhomogeneous and anisotropic electrical properties. Also, because cortical neurons vary in shape, size, location, and orientation, it is not clear how they are affected by the electric field and current. In addition, cortical neurons are highly interconnected with neurons located in other cortical areas, subcortical structures, and the spinal cord. Previously, we constructed a three-dimensional finite element model of ECS and analyzed how current flow and electric fields were influenced by changes in the anatomy in and around the precentral gyrus (Nguyen et al., 1998). The different electrode placements may have stimulated different regions of the cortex, thus affecting the efficacy of ECS. As well, the surgical (epidural) leads that are available to clinicians have varying geometries, and it is unclear how these differences influence the outcome of ECS. Therefore, we investigated the effects of varying electrode positions, geometries, and polarities on neuronal activation produced by ECS. This improved understanding can aid in the selection and placement of epidural leads, as well as the design of ECS systems.

2. Methods

We developed computational models of epidural cortical stimulation to determine the effects of the position, polarity, and geometry of the epidural electrode(s) on activation of neurons in the cortex.

2.1. Extruded slab model of precentral gyrus

Details of the computational model of ECS were described previously (Wongsarnpigoon and Grill, 2008). Briefly, we constructed a three-dimensional extruded slab model of the precentral gyrus (the location of the motor cortex and the target of ECS for treatment of pain, movement disorders, and stroke rehabilitation), two adjacent sulci, and two neighboring gyri (Fig. 1). Different layers represented the cortex and surrounding anatomy, including the skull, dura mater, cerebrospinal fluid (CSF), gray matter, and white matter. The thickness of the gray matter (2.5 mm) was reduced in the present model to match more closely experimental measurements (Defelipe et al., 2002). The fibers in the white matter are oriented primarily perpendicular to the skull, and the conductivity of the white matter was anisotropic with a greater conductivity in the axial direction. The remaining anatomical layers had isotropic conductivities. The model included an epidural lead consisting of two disc electrodes (platinum iridium foil) embedded in a thin rectangular substrate (silicone elastomer) (Fig. 1c).

The model was implemented in COMSOL Multiphysics (version 3.4; Burlington, MA), and the baseline model contained approximately 197,000 tetrahedral elements. A finer mesh (smaller elements) was used to represent the lead and the region directly beneath the lead to provide more precise solutions, and a coarser mesh (larger elements) was used near the boundaries of the model, thereby decreasing computation time. The model was solved using the conjugate gradient method (Hestenes and Stiefel, 1952) with preconditioning (incomplete Cholesky factorization), and the total computation time was ~2 min. The output of the model was the spatial distribution of electric potentials in the cortex. Neither reducing the mesh size (i.e., increase number of elements by ~325,000) nor doubling the volume of the model had a substantial effect on the electric potential in the gray matter and white matter beneath the epidural lead. The electric potentials from the models with reduced mesh size and doubled volume changed by an average of 2.8% and 3.3%, respectively, from those obtained from the baseline model.

2.2. Compartmental models of cortical neurons

The electric potentials calculated with the ECS model were coupled to compartmental models of cortical neurons to determine thresholds for excitation. The neuronal models were implemented in NEURON (Hines and Carnevale, 1997) and solved using backward Euler integration with a time step of 0.01 ms. The geometries of existing models of layer 3 (L3) and layer 5 (L5) pyramidal cells (PCs) from cat visual cortex (Mainen and Sejnowski, 1996) were modified to accommodate the dimensions of human motor cortex (Table 1), but the electrical properties of model neurons were unchanged from the original models. Briefly, fast, inactivating voltage-dependent Na+ channels were present in all parts of the neurons, with a higher density in the axon hillock and initial segment and lower density in the soma and dendrites; fast voltage- and Ca2+-dependent K+ channels were located in all segments except the dendrites; and slow voltage- and Ca2+-dependent K+ and voltage-dependent high-threshold Ca2+ channels were located in the soma and dendrites. The dendritic trees in both neurons were

![Fig. 1](image-url) Three-dimensional (3D) extruded slab model of epidural cortical stimulation (ECS) of motor cortex. Cross-section of the model (a) was extruded to produce the 3D model (b). The epidural lead (c) was placed over the crown of the precentral gyrus in the baseline model.
lengthened by 60% so that dendrites reached layer 1. The axons were oriented perpendicular to the cortical surface and lengthened to terminate in layer 5/6 for L3 PCs (Kaneko et al., 2000) and to extend into the white matter for L5 PCs. A thalamocortical axon (TCA) was also modeled, consisting of 200 nodes connected by myelinated internodal segments with the myelin assumed to be a perfect insulator. The electrical properties of the TCA were identical to those of the axons of the PCs, and the terminals of all axons were nodes with "sealed ends" (i.e., current flowed in or out of terminals through the membrane of the last node).

### Table 1
Dimensions of compartmental models of cortical neurons.

<table>
<thead>
<tr>
<th>Model</th>
<th>Soma diameter (μm)</th>
<th>Node diameter (μm)</th>
<th>Myelin diameter (μm)</th>
<th>Axon length (mm)</th>
<th>Number of nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Layer 3 pyramidal cell</td>
<td>29.8</td>
<td>0.74</td>
<td>1</td>
<td>1.313</td>
<td>13</td>
</tr>
<tr>
<td>Layer 5 pyramidal cell</td>
<td>25</td>
<td>1.11</td>
<td>1.48</td>
<td>10.1</td>
<td>100</td>
</tr>
<tr>
<td>Thalamocortical axon</td>
<td>–</td>
<td>0.61</td>
<td>0.81</td>
<td>20.2</td>
<td>200</td>
</tr>
</tbody>
</table>

2.3. Extracellular stimulation of cortical neurons in model of ECS

The neuronal models were distributed uniformly within a region of the cortex beneath the epidural lead (Fig. 2). This region spanned 15 mm along the length of the precentral gyrus (z-axis), with the stimulating electrode in the middle, and along this dimension, neurons were distributed within slices of the cortex spaced 0.625 mm apart. Within each slice, neurons were positioned from the center of the crown of the precentral gyrus, down the bank along the central sulcus, back up the opposite bank located on the postcentral gyrus, and ending on the opposite crown on the postcentral gyrus (Fig. 2e and f). In total, there were 2650 of each of the three cell types represented in the ECS model. The somas of the L3 and L5 PCs were distributed at random (uniform distribution) depths within their corresponding layers, located 1700–1900 μm and 500–700 μm, respectively, above the boundary between the white matter and gray matter (DeFelipe et al., 2002) (Fig. 2a and b). TCAs terminated in L3 (1700–1900 μm) (Sloper, 1973), and the location of the terminals were also randomized. The axons of L5 PCs and TCAs located on the lips and banks of the gyrus approached the white matter perpendicular to the white matter–gray matter boundary, but curved towards the axial (y-axis) direction. (e) In the x–y plane, neurons were distributed within the cortex from the center of the crown of the precentral gyrus (C), around the lip (L), down the bank on the precentral gyrus (B), around the bottom of the sulcus (BS), up the opposite bank on the postcentral gyrus (OB), around the opposite lip on the postcentral gyrus (OL) and ending on the opposite crown on the postcentral gyrus (OC). Along the z-axis, the region within which neurons were distributed spanned 15 mm, and neurons were spaced by 0.625 mm. (f) Sample of L3 PCs distributed within 3D model. Model was split open along the central sulcus to show cells on both banks. Neurons were not modeled explicitly in the ECS model, but rather, the electric potentials calculated from the ECS model were used as extracellular sources for stimulation of the neurons.
simulate extracellular stimulation. The potentials were applied for 100 μs, simulating 100 μs monophasic pulses, and because the motor cortex model was linear with respect to electric potential, the amplitude and polarity of the pulse was controlled by scaling the extracellular potentials. Anodic and cathodic thresholds were determined individually for each of the 7950 model neurons. Parameters of the model were varied to determine the sensitivity of thresholds of cortical neurons to lead placement and geometry, and the ECS model with the original lead parameters will be referred to as the baseline model.

3. Results

We constructed a 3D extruded slab model of the motor cortex and calculated the electric potentials within the cortex during epidural electrical stimulation. These potentials were applied to compartmental models of L3 and L5 PCs and TCAs, which were distributed throughout the cortex. We analyzed the effects of varying the geometry and positioning of the epidural lead on threshold amplitudes for direct activation of the modeled neurons.

3.1. Validation of ECS model coupled to neuronal models

We first determined how well the model of ECS coupled to a L5 PC placed in the center of the crown of the precentral gyrus directly beneath the stimulating electrode reproduced experimental data from studies of cortical stimulation. Radman et al. (2009) simulated slices of rat motor cortex with uniform electric fields and observed that the transmembrane voltage of L5 PCs scaled linearly with the strength of the electric field. The polarization length ($\lambda$), defined as the ratio of the change in transmembrane voltage (mV) to the magnitude of the electric field (mV/mm), was calculated for each cell, and $\lambda$ was between -0.03 mm and 0.49 mm. We modeled this study by applying a constant voltage to the surface of the cortex (i.e., crowns of the gyri, but not the lips or banks), insulating the sides of the model, and setting the bottom of the model to ground. As in Radman et al., the transmembrane voltage of the soma scaled linearly with the strength of the electric field, and the calculated polarization length ($\lambda = 0.09$ mm) fell within the experimental range.

Gorman (1966) delivered subdural stimulation to cat motor cortex, and thresholds for direct activation of L5 PCs were 0.25 and 0.35 mA for pulse durations between 0.1 ms and 0.2 ms. Similarly, Jankowska et al. (1975b) delivered subdural stimulation to monkey motor cortex, and thresholds for direct activation of L5 PCs with 0.2 ms and 0.5 ms pulses were between 0.3 and 0.5 mA. In our model, we moved the electrode from above the dura mater (1.3 mm above cortex) to directly on the cortex, and thresholds for excitation of the L5 PC were 0.95, 0.55, and 0.31 mA, respectively, for 0.1, 0.2, and 0.5 ms anodic pulses, matching well the experimental studies.

Jankowska et al. (1975a) delivered intracortical microstimulation (ICMS) to the deep layers of monkey and cat motor cortex, and thresholds were < 30 μA with pulse durations of 0.2 and 0.5 ms. Similarly, Stoney et al. (1968) delivered ICMS to cat pericruciate cortex, and thresholds for pulse duration of 0.2 ms were < 20 μA. We modeled ICMS with a point current source located in layer 6 (2.4 mm below cortical surface), and thresholds were 20.2 and 13.6 μA for pulse durations of 0.2 and 0.5 ms, respectively, which fit well with the experimental data.

In addition, we used our model to replicate a clinical study of ECS over the motor cortex to treat neuropathic pain. In this study, focal muscular contractions were evoked at amplitudes between 4 and 10 mA with 210 μs pulses (Rasche et al., 2006). We simulated monopolar and bipolar stimulation with 210 μs pulses in the baseline model and measured anodic and cathodic thresholds for all L3 PCs, L5 PCs and TCAs distributed within the region of the cortex beneath the epidural lead (Fig. 2). For all neuron types, the minimum thresholds for monopolar anodic and bipolar stimulation were between 2.4 and 8.2 mA, while minimum thresholds for monopolar cathodic stimulation were between 2.4 and 33.5 mA. Although it is unclear how many and which types of neurons were activated to generate the muscle contraction in Rasche et al., model cortical neurons were activated at amplitudes within the range of amplitudes determined clinically. Collectively, the similarity of excitation properties observed in the model and measured experimentally across a range of geometries demonstrate the validity of our coupled ECS-neuron model.

3.2. Epidural stimulation of cortical neurons in baseline model

Excitation thresholds of model neurons varied with location within the cortex and stimulus polarity. Thresholds were generally lowest beneath the stimulating electrode on the crown or lip of the precentral gyrus (Fig. 3). However, for cathodic stimulation of L3 PCs, thresholds were approximately 25% lower on the superficial parts of the bank of the precentral gyrus than on the crown (Fig. 3f). On the banks deep in the sulcus and on the lip and crown of the postcentral gyrus, thresholds for all neurons were generally much larger than on the crown and lip of the precentral gyrus. On the crown of the precentral gyrus, anodic thresholds were lower than cathodic thresholds for L3 and L5 PCs, while for TCAs cathodic thresholds were lower.

Axons were more excitable than cell bodies and dendrites, and the sites of action potential initiation depended on the type and location of the neuron, as well as the polarity of stimulation (Fig. 4). For L3 and L5 PCs in the crown of the precentral gyrus, cathodic stimulation activated the neurons at the axon initial segment. Anodic stimulation, on the other hand, initiated action potentials at the axon terminals of L3 PCs and at the axon nodes closest to the white matter-gray matter boundary for L5 PCs. In TCAs in the crown of the precentral gyrus, anodic stimulation initiated action potentials at the white matter-gray matter boundary, while cathodic stimulation activated axons at the terminals in the cortex.

Excitation thresholds varied greatly compared to the baseline model when the electrical conductivity of the entire model was made homogeneous and isotropic. Similar results have been documented for models of DBS (Butson et al., 2007; Chaturvedi et al., 2010), demonstrating the importance of modeling carefully the inhomogeneity and anisotropy in the electrical conductivity of the brain and surrounding anatomy.

Axon diameters in the cortex vary greatly, and during ECS, thresholds for excitation of cortical neurons are inversely related to axon diameter (Manola et al., 2007). However, it is unclear if axon diameter influences the patterns and spatial distributions of thresholds, and we tested the effects of doubling the diameter of TCAs in the baseline model. Although thresholds decreased by an average of ~31% for anodic stimulation and ~36% for cathodic stimulation, the spatial distributions of threshold did not change qualitatively compared to distributions using the original axon diameter.

3.3. Analysis of electrode placement

The location and orientation of the epidural lead were varied since there is no consensus on how to best position the electrode for ECS. When the electrode was moved from above the center of the crown of the precentral gyrus towards the central sulcus, thresholds for monopolar stimulation increased on the crown of the precentral gyrus and decreased on the postcentral gyrus. The
location of the neurons with the lowest thresholds remained approximately beneath the stimulating electrode. As a result, when the electrode was placed above the central sulcus, thresholds for excitation of neurons in the postcentral gyrus were approximately equal to those in the precentral gyrus (Fig. 5). Thresholds of cells and axons on the banks deep within the central sulcus remained substantially greater than on the lips and crown of the gyri.

When the epidural lead was oriented perpendicular—rather than parallel—to the precentral gyrus, neurons in the adjacent gyri were activated at substantially lower amplitudes. Two configurations were analyzed: one electrode placed above the postcentral gyrus and the other in the same location as in the baseline model (Fig. 6a–d), or the electrodes “straddling” the precentral gyrus (Fig. 6e–g). In both configurations, we tested bipolar stimulation as well as stimulation with both electrodes set to the same polarity and amplitude (equipolar).

In the first configuration, bipolar and equipolar stimulation exhibited substantially lower thresholds for neurons of all types in the postcentral gyrus than in the baseline model, and in some cases thresholds were lower than for neurons in the precentral gyrus (Fig. 6a–d). However, the electrode above the postcentral gyrus did not have a substantial effect on thresholds for neurons in the crown of the precentral gyrus, which were approximately the same as for monopolar stimulation. Thresholds for equipolar stimulation in the crown were about twice as large as in the baseline model, and because half of the current was delivered by each electrode, the electrode over the precentral gyrus delivered approximately the same amplitude at threshold during monopolar and equipolar stimulation. For neurons on the precentral gyrus closer to the precentral sulcus, bipolar stimulation mostly increased thresholds compared to the baseline model, while equipolar stimulation reduced thresholds.

In the second electrode configuration with the electrode straddling the precentral gyrus, thresholds for neurons in the crown of the precentral gyrus increased relative to the baseline model for both bipolar and equipolar stimulation. Also, the lowest thresholds were no longer found for neurons in the crown, but rather, neurons on the lips of the gyri exhibited the lowest thresholds. Because a
greater area of the electrodes was above the adjacent gyri than the precentral gyrus, the thresholds to excite neurons in the adjacent gyri were approximately equal to or even less than those to excite neurons in the precentral gyrus.

3.4. Analysis of electrode and substrate geometry

The geometry of the epidural lead, including the inter-electrode spacing (IES), the diameter of the electrodes, and the width of the substrate, was varied as these parameters vary among different types of epidural leads. Bipolar and equipolar stimulation thresholds varied with IES. For all cell types, bipolar stimulation using the baseline IES (15 mm) did not substantially change thresholds in neurons beneath the stimulating electrode compared to monopolar stimulation (Δ[threshold] < 18%), but thresholds increased by an average of 42% in the rest of the cortex (Fig. 7). Equipolar stimulation increased thresholds (total current from both electrodes) compared to monopolar stimulation nearly everywhere: thresholds increased by 70–115% beneath the stimulating electrode, and the median increase in threshold was 51% across the entire population of cells. When IES was decreased from 15 mm to 5 mm, thresholds increased further for bipolar stimulation both beneath the electrode (10–140%) and even more for all cells in the cortex (median increase ≈ 130%); consequently, stimulation was more focused on the region beneath the electrodes (Fig. 7). On the other hand, thresholds for equipolar stimulation with decreased IES were reduced (4–35% beneath the electrode; median decrease ≈ 24% across population), and this geometry created a larger, more uniform area of stimulation. Thresholds for neurons on the crown directly between the two electrodes were greater than thresholds for neurons directly beneath either of the two electrodes for both bipolar (T = Thresholdbetween/Thresholdbeneath > 1.9) and equipolar (T > 2.85) stimulation with the baseline IES (Fig. 7h). When IES was decreased differences in thresholds between the neurons directly between the two electrodes and the neurons beneath the electrodes were reduced compared to the baseline model for both bipolar (T_{IES=15 \text{mm}} - T_{IES=5 \text{mm}} = ΔT > 4.8) and equipolar (ΔT > 1.9) stimulation (Fig. 7h). Furthermore, during equipolar anodic stimulation thresholds were lower between the electrodes than beneath the electrodes (0.89 < T < 0.99).

The diameter of the electrodes had a moderate impact on thresholds and influenced spatial selectivity for all neuron types. When the electrode diameter was increased, thresholds generally increased in the precentral gyrus beneath the electrode.Doubling the diameter increased thresholds by 11–59% across all neuron types, while halving the diameter decreased thresholds by up to 21%. Changes in electrode diameter also affected spatial selectivity. The minimum thresholds for anodic stimulation of L3 and L5 PCs and for cathodic stimulation of TCAs were directly related to electrode diameter (Fig. 8a). As well, the initial slopes of the input–output curves (number of activated neurons vs. stimulus amplitude) were directly related to electrode diameter (Fig. 8b). However, as stimulus amplitude increased, the input–output curves converged. Thus, larger electrode diameters decreased the spatial selectivity for neurons beneath the electrode but had little effect farther from the electrode.

Although substrate width (i.e., dimension in x-axis) affected thresholds in most parts of the cortex, thresholds remained relatively unchanged beneath the electrode, where thresholds were still lowest. In this region, doubling the width of the substrate reduced thresholds by <15% while halving the width increased thresholds by <23% compared to the baseline model. Substrate width changed thresholds mostly around the edge of the substrate, and this effect was greatest on the lips and crown of the postcentral gyrus. Still, thresholds in the postcentral gyrus remained more than ~10 times greater than in the precentral gyrus, indicating that the crown and lips of the precentral gyrus were still the primary regions of activation during ECS.

4. Discussion

We used a 3D extruded slab model of epidural cortical stimulation (ECS) coupled to compartmental models of cortical neurons to quantify the patterns and spatial extent of neural activation with different electrode geometries, polarities, and positions during ECS. Neurons were distributed in a region of the cortex beneath the epidural electrode spanning the precentral and postcentral gyri, and thresholds were calculated individually for stimulation of each neuron. In the baseline model, thresholds and the sites of action potential initiation varied with both polarity of stimulation...
and location in the cortex. Placing the electrode over a sulcus or rotating the lead increased thresholds in the precentral gyrus and reduced thresholds in the adjacent gyrus. Decreasing the inter-electrode spacing (IES) affected the spread of stimulation, resulting in increased thresholds in the cortex during bipolar stimulation and decreased thresholds during equipolar stimulation. Increasing the diameter of the electrodes also increased threshold amplitudes but decreased spatial selectivity, while changing the width of the substrate had only minor effects on threshold. In all cases, thresholds were much greater for activation of neurons on the banks of the gyri deep in the sulcus than on more superficial parts of the gyri (i.e., crown and lip).

4.1. Limitations

The neuronal models in this study—layer 5 (L5) and layer 3 (L3) pyramidal cells (PCs) and thalamocortical axons (TCAs)—represent only a fraction of the myriad neurons and neural elements found in the cortex. PCs represent 75–80% of the neurons in the cortex (Markram et al., 2004) and can be found not only in L3 and L5, but also in L6 (Amaral, 2000). The dendritic morphologies of the model PCs were based on cells from cat visual cortex (Mainen and Sejnowski, 1996), and although the basic geometry of PCs across species is fairly stereotypical (conical soma, descending axon, apical and basal dendrites), the specific morphologies of PCs vary among species (DeFelipe et al., 2002). It is unclear to what extent these variations influence the excitation properties of PCs to cortical stimulation.

The remaining 20–25% of the neurons in the cortex consist of local interneurons (Markram et al., 2004). Whereas the morphologies of PCs are fairly homogeneous, local interneurons are highly diverse. As a result, it is unlikely that the responses of a few local interneurons to ECS can be generalized. To explore how thresholds of interneurons in the cortex varied with neuronal geometry, we constructed a compartmental model of a nonspecific cortical interneuron, consisting of a 20-μm diameter soma and a 1 mm long myelinated axon, the approximate width of a cortical column, since the axons of cortical interneurons typically arborize within a single cortical column (Markram et al., 2004). Four different dendritic morphologies were modeled: no dendrite; a single straight dendrite (length = 0.5 mm) pointing in the opposite direction of the axon; the same dendrite but pointing at a right angle to the axon; and a dendrite pointing away from the axon with two segments branching off of the end of the main trunk. These neurons were positioned in the baseline model in the same region of the cortex as described previously (Fig. 2) at a depth of 1.25 mm below the cortical surface. As with the other cell types in the baseline model, thresholds in the crown and lip of the precentral gyrus were lower than in other parts of the cortex and varied with the position of the neuron and polarity of stimulation. However, thresholds varied greatly with dendritic morphology. For example, thresholds on the crown of the precentral gyrus were 61% lower on average for neurons with the branched dendrite than the other dendritic morphologies. In addition, minimum thresholds in the cortex differed by as much as 3400% (2.5–85.6 mA for cathodic stimulation of interneurons with no dendrites) as the orientation of the axon with
respect to the cortical surface was varied, illustrating the substantial impact of the orientation of the interneuron on thresholds for excitation of interneurons. This analysis of local interneurons demonstrated the difficulty in generalizing the results from a relatively small number of neurons to all interneurons due to the diversity in geometries. Thus, a wide array of more detailed models of interneurons is necessary to understand more completely the effects of ECS on interneurons.

The terminals of all axons were nodes with "sealed ends" (i.e., current flowed in or out of terminals through membrane). Terminal conditions can have substantial impact on the transmembrane voltage response near axon terminals and depends on whether the terminal is sealed or unsealed, as well as the electrical and geometrical properties of the unsealed end (Rubinstein, 1993). The effects of the terminal conditions on thresholds for excitation were examined with TCAs in the baseline model. First, the terminals were unsealed, and the ends were assigned the same electrical properties as the nodal membrane. Thresholds for excitation of unsealed TCAs changed by <0.1% compared to sealed TCAs. Next, the area of the terminals was doubled, and thresholds changed by an average of 3% across all neurons. Finally, the area of the terminals was restored to its original value, and the terminals were assigned passive electrical conductivities (i.e., conductance was independent of time and transmembrane voltage). On the bank of the precentral gyrus, anodic thresholds increased by \( \frac{1}{24} \times 30\% \) while cathodic thresholds were not substantially different compared to sealed TCAs. Everywhere else in the cortex, cathodic thresholds increased by \( \frac{1}{24} \times 30\% \) and anodic thresholds were not substantially different compared to sealed TCAs. For all terminal conditions, the spatial distributions of thresholds were qualitatively similar to distributions with sealed TCAs. Because axon terminals were highly excitable, further study is needed to fully understand the effects of ECS on interneurons.
needed of the precise geometrical and electrical properties of the terminals.

We modeled populations of independent and non-communicating neurons, and we only measured thresholds for direct stimulation. During cathodic surface stimulation (i.e., electrode directly on cortex), thresholds for indirect activation, via stimulation of presynaptic axons by ECS and subsequent excitatory post-synaptic potentials (EPSPs), are lower than for direct activation (Gorman, 1966; Hern et al., 1962; Phillips and Porter, 1962). As well, synaptic inputs could have affected our results through modulation of excitability. For example, postsynaptic potentials can polarize a neuron and change the threshold for direct activation. Conversely, the direct effects of ECS can also influence excitability, affecting how a neuron responds to synaptic inputs. Specifically, subthreshold stimulation of a neuron changes the conductance of voltage-gated sodium channels (Grill and Mortimer, 1995), and subthreshold depolarization enables EPSPs to be generated at NMDA receptors (Nowak et al., 1984). None of these effects were considered in the present model, but given the large thresholds for direct activation of cortical neurons, our results imply that indirect effects contribute to the therapeutic effects of ECS. Because both indirect and direct activation can excite neuronal circuits distant from the site of action potential initiation, the biological effects induced by ECS may not be localized to the site of action potential initiation.

Despite these limitations, the model reproduced experimental data quite well. The model data fit well with experimental measurements of thresholds for not only ECS but also intracortical microstimulation, subdural cortical stimulation, and uniform electric field polarization. As well, our results agreed with experimental measures of the effect of stimulation polarity on direct activation of L5 PCs. Specifically, subdural cortical stimulation directly activated L5 PCs at lower amplitudes with monopolar anodic stimulation than with monopolar cathodic stimulation (Gorman, 1966; Hern et al., 1962; Holsheimer et al., 2007; Katayama et al., 1988; Phillips and Porter, 1962). Further, in one of these studies (Phillips and Porter, 1962), the electrode location producing the lowest threshold for anodic stimulation of PCs was over the lip of the precentral gyrus on the central sulcus, while the location of lowest threshold for cathodic stimulation was more towards the crown of the gyrus, and the lowest cathodic threshold was less than the lowest anodic threshold. Changes in thresholds with electrode position and stimulus polarity determined with the model (Fig. 5) agree with these experimental data. For some of the L5 PCs on the lip of the precentral gyrus, the electrode location producing the lowest threshold for anodic stimulation was over the

![Fig. 7. Influence of inter-electrode spacing (IES) on thresholds. Thresholds for L5 PCs with baseline IES for (a) bipolar and (b) equipolar anodic stimulation, respectively. Equipolar cathodic stimulation is not shown because thresholds were greater than 100 mA. The plots are representative of distributions of thresholds for L3 PCs and TCAs. Thresholds were < 13 mA within the white contour line in (a). Thresholds with IES = 5 mm for (c) bipolar, (d) equipolar anodic, and (e) equipolar cathodic stimulation. (f) Comparisons of thresholds for different polarities and IES for neurons located directly under one of the electrodes. For bipolar stimulation, bars in the “+” and “-” group refer to neurons directly under the anode and cathode, respectively. For equipolar stimulation, “+” refers to equipolar anodic stimulation and “-” refers to equipolar cathodic stimulation. Thinner bars indicate smaller IES. (g) Influence of polarity and IES on average change in thresholds across all neurons in the cortex compared to baseline. (h) Effects of stimulation polarity and IES on the ratio of thresholds for neurons directly between the two electrodes and directly beneath the electrodes (T).](image-url)
lip, while cathodic stimulation over the crown of the precentral gyrus activated the same neurons at lower amplitudes. Thus, even without considering the effects of synaptic inputs or modeling every type of cortical neuron, the present study is still useful for understanding the effects of electrode placement and geometry on the effects of ECS.

4.2. Comparison with previous modeling studies

Two previous studies analyzed the effects of ECS on cortical neurons using methods different than those of the present study (Manola et al., 2005, 2007). In the previous studies, electric potentials calculated from a computational model of the human motor cortex were coupled to compartmental models of cortical fibers (perpendicular and parallel to cortical surface) and cortical neurons with simplified dendritic trees. Four fibers and three neurons were modeled, and they were located only on the precentral gyrus. On the other hand, the present model included 7950 cortical neurons and fibers with accurate morphologies and membrane properties, and these neurons were distributed across a larger region of the cortex, including the postcentral gyrus. Also, in the previous studies, the geometry of the epidural lead was modeled after the Medtronic Resume electrode, which has different dimensions than the Northstar Neuroscience lead modeled in the present study (Table 2). Although both studies analyzed the effects of stimulation polarity and electrode location on thresholds for excitation of cortical neurons, the present study also considered the effects of electrode geometry.

Despite differences in methodology, the results of the previous studies were mostly consistent with the results of the present study. Excitation of L5 PCs in the baseline model agreed with results from the previous studies for monopolar stimulation directly above the center of the crown of the precentral gyrus: anodic thresholds were lower than cathodic thresholds in the crown, and cathodic thresholds were lower than anodic thresholds for L5 PCs on the bank of the precentral gyrus. Also, both studies predicted similar sites of action potential initiation, in particular, the nodes near the boundary between the gray matter and white matter. In addition, the previous studies demonstrated that during bipolar stimulation, thresholds for excitation of neurons beneath the electrodes were substantially influenced by the superposition of electric fields generated by the anode and cathode with small IES (7 mm) but not with larger IES (10 mm), and these results agreed with the present study.

4.3. Sites of action potential initiation

The sites of action potential initiation revealed how the geometry of the cortex and the neurons affected thresholds. Axons were more excitable than cell bodies and dendrites, and the orientation and geometry of the axons substantially influenced thresholds and the sites of action potential initiation. In the baseline model, several neurons in different parts of the cortex were activated at the white matter–gray matter boundary, and this low threshold point was caused by the discontinuity from the unequal conductivities of the gray and white matter. These results agree with previous studies of neuronal activation in regions of inhomogeneous electrical conductivity (Grill, 1999). In a computational model of ECS, pyra-

Table 2
Dimensions and geometries of epidural leads.

<table>
<thead>
<tr>
<th>Make (model)</th>
<th>Electrode configuration (rows x columns)</th>
<th>Electrode diameter (mm)</th>
<th>Inter-electrode spacing (mm)</th>
<th>Substrate dimensions (L x W; mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northstar Neuroscience</td>
<td>1 x 2</td>
<td>3.75</td>
<td>15</td>
<td>40 x 14</td>
</tr>
<tr>
<td>(c) 2 x 3</td>
<td></td>
<td>3</td>
<td>9 (within row)</td>
<td>30 x 30</td>
</tr>
<tr>
<td>Medtronic (Resume II)</td>
<td>1 x 4</td>
<td>4</td>
<td>10</td>
<td>44 x 8</td>
</tr>
<tr>
<td>(Medtronic)</td>
<td>2 x 4 (offset rows)</td>
<td>4 x 2.5 (rectangular)</td>
<td>7 (within row)</td>
<td>45 x 10</td>
</tr>
<tr>
<td>St. Jude Medical (Lamitrode 44)</td>
<td>3 (between row)</td>
<td></td>
<td>3 (between row)</td>
<td></td>
</tr>
<tr>
<td>Electrocorticography [ECoG]</td>
<td>Varies</td>
<td>-5</td>
<td>~10</td>
<td>Varies</td>
</tr>
</tbody>
</table>

a Source: Levy et al. (2008).
c Source: Kleiner-Fisman et al. (2003).
midal neurons were activated at nodes in the proximity of the transition of the white matter–gray matter boundary (Manola et al., 2007) and in a computational model of transcranial magnetic stimulation (TMS), axons were activated at the white matter–gray matter boundary (Miranda et al., 2007).

Whether such an abrupt transition in electrical conductivity as represented in the present model actually exists between the white matter and gray matter is unclear, and a more gradual transition may shift the site of action potential initiation. To test the effect of a gradual transition in electrical conductivity at the boundary, the baseline model was altered to include a 0.5-mm transition layer between the gray and white matter. Within this layer, the conductivity changed linearly with distance from that of the gray matter to that of the white matter, resulting in an increase in thresholds of ~33% compared to the baseline model for neurons beneath the electrode. Even with this smoother transition in conductivity, action potentials were still initiated near or within the transition layer. These results suggest that neurons are particularly excitable at the white matter–gray matter boundary and possibly at other regions of inhomogeneous electrical conductivity (e.g., cerebral infarcts).

The terminals of axons were often the site of action potential initiation in L3 PCs and TCAs, depending on the direction the axon was pointing and the stimulus polarity. In the crown of the precentral gyrus, action potentials were initiated at axon terminals of L3 PCs during anodic stimulation and of TCAs during cathodic stimulation. In other words, the axons pointing away from the electrode and those pointing towards the electrode were activated at their terminals by stimuli of opposite polarity. However, the lower thresholds of L3 PCs along the banks demonstrate the greater excitability of terminating axons and illustrate the importance of neural geometry. This observation also explains why thresholds for anodic stimulation of L3 PCs on the bank of the precentral gyrus were larger than on the bank of the postcentral gyrus, despite the closer proximity of the precentral gyrus to the electrode. While the axons of the L3 PCs on the bank of the precentral gyrus pointed towards the electrode, those on the bank of the postcentral gyrus pointed away from the electrode. Also, thresholds for L3 PCs were lower in the bottom of the sulcus than on the surrounding banks of the gyri (Fig. 5c and d), demonstrating that the orientation of the neuron can have greater influence on threshold than the location of the neuron. These results agree with previous studies showing that the axon terminals of cortical neurons are highly excitable and can be activated at lower stimulation amplitudes than nearby neural elements (Dostrovsky et al., 2000; Gustafsson and Jankowska, 1976; Maccabee et al., 1993; McIntyre and Grill, 2002; Miranda et al., 2007; Nair et al., 2008; Salvador et al., 2010). Further, our results are consistent with previous computational modeling studies demonstrating the sensitivity of thresholds for activation of axon terminals to the orientation of the axon and its proximity to the electrode (Rattay, 1999, 2008; Rubinstein, 1993).

Although a large proportion of human TCAs terminate in L3 as modeled in the present study, TCAs terminate in all layers of the cortex (Sloper, 1973). To determine the effects of the layer in which TCAs terminate on thresholds for excitation, we ran the baseline model again with TCAs terminating in L5. On average, thresholds increased very little (2–3%) compared to TCAs terminating in L3 for both anodic and cathodic stimulation. However, beneath the electrode anodic thresholds increased by ~13% while cathodic thresholds increased by ~60% compared to TCAs terminating in L3. The difference was a result of the site of action potential initiation. Action potentials were initiated at the white matter–gray matter boundary during anodic stimulation, and this site did not change when the terminal was moved to L5. However, action potentials were initiated at the terminals during cathodic stimulation, and these sites were farther away from the electrode compared to baseline. As a result, the location of the terminal had a greater effect on cathodic thresholds than anodic thresholds beneath the electrode.

Action potentials were also initiated at axon bends and axon initial segments, and these locations on the axon have been identified as sites of action potential initiation in previous studies of cortical stimulation. Cathodal stimulation delivered to the surface of monkey motor cortex directly activated corticospinal axons at the initial segment (Amassian et al., 1990), as observed in the present model. As well, axon bends were highly excitable during TMS (Amassian et al., 1992; Maccabee et al., 1993; Miranda et al., 2007; Salvador et al., 2010). In summary, cortical neurons can be activated at different points along their axons, and the site of action potential initiation depends on axonal geometry, stimulation polarity, and the position of the neuron relative to the electrode and regions of inhomogeneous electrical conductivity.

4.4. Clinical relevance

The results of this study facilitate the rational implantation and programming of ECS systems. Clinically, bipolar stimulation is typically used (Anderson et al., 2009; Canavero and Paolotti, 2000; Canavero et al., 2002; Cherney et al., 2010; Franzini et al., 2003; Katayama et al., 2002; Lefaucheur et al., 2009; Nguyen et al., 1998; Rasche et al., 2006; Sakas et al., 2010; Tani et al., 2007), with the rationale that the proximity of the anode and cathode focuses stimulation to a specific area of the cortex and limits the spread of activation to the rest of the cortex. Indeed, our simulations revealed that bipolar stimulation increased thresholds compared to monopolar stimulation for neurons beyond the stimulating electrode, while thresholds were lowest beneath the electrodes. Although current passes through the region of the cortex between the electrodes as it travels from the anode to the cathode, thresholds for excitation of neurons directly between the two electrodes were greater than beneath the electrodes. This was also the case when the electrodes “straddled” the precentral gyrus, and thresholds were lowest beneath the electrodes, not in the crown of the precentral gyrus between the electrodes. In addition, during both bipolar and equipolar stimulation, the two electrodes stimulate two distinct populations of neurons (e.g., Manola et al., 2005, Figs. 4 and 7), and it is unclear if and how activation of one population affects the other. For these reasons, the most prudent method of stimulation may be monopolar or equipolar stimulation over the target. However, clinically available implantable pulse generators (IPGs) for ECS do not permit complete control of electrode montage (i.e., monopolar, bipolar, equipolar). For example, the Medtronic Synergy does not permit monopolar stimulation (Holsheimer et al., 2007), and Northstar Neuroscience’s Renova system supplied the same amplitude and polarity to entire rows of electrodes (Brown et al., 2006). As suggested by Holsheimer et al. (2007), IPGs should be designed to allow greater flexibility in electrode montage.

During implantation of the epidural lead, clinicians must decide how to place the electrode(s) with respect to the cortical target. For ECS of motor cortex for the treatment of pain, intra-operative motor evoked potentials (MEPs) can be used to identify optimal electrode locations (Holsheimer et al., 2007). However, it is unclear if MEPs can be used for other neurological disorders. Electrode location had a substantial impact on the region of the cortex where cortical neurons were activated at the lowest thresholds. To minimize interactions between neurons under the electrodes during bipolar or equipolar stimulation, one of the electrodes can be placed on an adjacent gyrus, as is often done clinically (Anderson et al., 2009; Brown et al., 2006; Lefaucheur et al., 2009; Nguyen et al., 1998; Velasco et al., 2009). However, this configuration led
to substantially lower thresholds in the adjacent gyrus compared to stimulation with the lead oriented over and parallel to the pre-central gyrus, and this could lead to side effects in clinical ECS. For example, although ECS is typically delivered to the pre-central gyrus for the treatment of pain (Rasche et al., 2006), stimulation of the adjacent post-central gyrus can exacerbate pain (Tsukabara et al., 1993). Thus, unless ECS over the adjacent gyrus is known to be innocuous, stimulation should be delivered only over the targeted gyrus.

Placing the electrode above the central sulcus failed to stimulate selectively neurons deep in the sulcus, and thresholds in the post-central gyrus decreased substantially. Selective stimulation of neurons located deep within a sulcus appears exceedingly difficult with ECS and may require more invasive methods of cortical stimulation. Thresholds for neurons located on the banks of the gyri deep within the central sulcus had larger thresholds than neurons on the crowns or lips for all electrode placements, polarities, and geometries. The hand area of the motor cortex lays deep within the central sulcus (Yousry et al., 1997), and this area is a common target of ECS (Brown et al., 2006; Levy et al., 2008; Pagni et al., 2008). However, our results indicate that these neurons cannot be directly activated without co-activation of neurons on the crowns and lips of the pre-central and post-central gyri. Subdural stimulation or intracortical microstimulation may enable greater localization of stimulation to neurons deep in the sulcus. Another option may be intra-sulcular stimulation, where an electrode is placed beneath the dura mater within a sulcus (Hosomi et al., 2008). Although these invasive methods may provide greater localization, the importance of localization is not well understood. Stimulation of a wide area of cortex may be more beneficial than targeting a small area of the cortex for certain disorders; certainly TMS and tDCS deliver less focal stimulation than ECS but are effective treatments nonetheless for pain, movement disorders, and psychiatric disorders (Canavero, 2009). Furthermore, cortical stimulation was delivered concurrently with motor rehabilitation in rats after cerebral ischemia, and a distributed electrode configuration was more effective than a single focal electrode configuration at enhancing motor performance (Boychuk et al., 2011).

Because the geometries of clinical surgical leads used for ECS made by different companies are not uniform (Table 2), understanding how electrode and lead geometry impacts the outcome of ECS is important for delivering efficient and effective treatment. Thresholds beneath the electrode were directly related to electrode diameter, and accordingly, the amplitude required to produce therapeutic effects during ECS will likely be directly related to electrode diameter, and the range of IES used in the present study (5–15 mm) was within the range of IES of clinically available epidural leads (3–18 mm; Table 2). The effects of IES on distributions of threshold are likely dependent on the thickness of the CSF beneath the electrode, which influences the distance between the electrodes and the cortex as well as the degree of current shunting through the CSF (Manola et al., 2005; Wongssarpignon and Grill, 2008). IES may also affect the ability to perform “current steering”, a technique where stimulation is delivered through multiple independent sources to direct the flow of current and focus stimulation on a specific region between the electrodes. Current steering can be used in cochlear implants (Berenstein et al., 2008; Bonham and Litvak, 2008; Landsberger and Srinivasan, 2009), peripheral nerve stimulation (Veraart et al., 1993), spinal cord stimulation (Alo and Holzheimer, 2002), and deep brain stimulation (Butson and McIntyre, 2008). In ECS, current steering may be effective for targeting regions of the cortex located between electrodes without moving the epidermal lead. With the baseline IES, thresholds were lowest beneath the electrodes and not between the electrodes for both bipolar and equipotential stimulation. On the other hand, reducing IES altered the spatial distribution of thresholds between the electrodes (Fig. 7), and thresholds were lowest for equipotential anodic stimulation directly between the electrodes, indicating that the fields generated by the electrodes interacted to a greater degree. These results suggest that the ability to steer current during ECS is influenced by IES.

Acknowledgments

The authors would like to thank Brad Fowler and Bill Rowe for useful technical discussion, and John Pormann and the staff of the Duke Scalable Computing Support Center. This work was supported in part by Northstar Neuroscience, Inc. and in part by a Graduate Fellowship sponsored by the Medtronic Foundation.

References


Butson CR, Cooper SE, Henderson JM, McIntyre CC. Patient-specific analysis of the volume of tissue activated during deep brain stimulation. Neuroimage 2007;34:661–70.


