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Analyzing the Tradeoff between Electrical Complexity and Accuracy in Patient-Specific Computational Models of Deep Brain Stimulation

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Abstract

Objective—Deep brain stimulation (DBS) is an adjunctive therapy that is effective in treating movement disorders and shows promise for treating psychiatric disorders. Computational models of DBS have begun to be utilized as tools to optimize the therapy. Despite advancements in the anatomical accuracy of these models, there is still uncertainty as to what level of electrical complexity is adequate for modeling the electrical field in the brain and the subsequent neural response to the stimulation.

Approach—We used magnetic resonance images to create an image-based computational model of subthalamic DBS. The complexity of the volume conductor model was increased by incrementally including heterogeneity, anisotropy, and dielectric dispersion in the electrical properties of the brain. We quantified changes in the load of the electrode, the electric potentials, and stimulation thresholds of descending corticofugal (DCF) axon models.

Main Results—Incorporation of heterogeneity altered the electric potentials and subsequent stimulation thresholds, but to a lesser degree than incorporation of anisotropy. Additionally, the results were sensitive to the choice of method for defining anisotropy, with stimulation thresholds of DCF axons changing by as much as 190 %. Current approaches for defining anisotropy underestimated the expected load of the stimulation electrode, which led to underestimation of the extent of stimulation, and more accurate predictions of the electrode load were achieved with alternative approaches for defining anisotropy. The effects of dielectric dispersion were small compared to the effects of heterogeneity and anisotropy.

Significance—The results of this study help delineate the level of detail that is required to accurately model electric fields in the brain.

Keywords

deep brain stimulation; anisotropy; dielectric dispersion; patient-specific

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1. Introduction

Deep brain stimulation (DBS) is a promising alternative to traditional pharmacology for treating neurological disorders. DBS is highly effective in treating movement disorders (e.g., Parkinson's disease and essential tremor) and shows promise for treating psychiatric disorders (e.g., obsessive compulsive disorder and depression). The fundamental purpose of DBS is to modulate pathological network activity in the brain via delivery of ~100 Hz rectangular electrical pulses (McIntyre and Hahn, 2010).

Bioelectric field models of the human head have substantially advanced over the past decade and are now being utilized to optimize clinical DBS therapies. For example, models of subthalamic DBS have helped to retrospectively identify potential therapeutic white matter targets for Parkinson's disease (Butson et al., 2011, Maks et al., 2009) and prospectively select stimulation parameters that were more energy efficient and less disruptive to cognitive-motor abilities than settings defined with traditional clinical practice (Frankemolle et al., 2010). These types of models rely on magnetic resonance (MR) images to tailor anatomical aspects of DBS models to each patient's head. However, despite advancements in anatomical accuracy, there is still uncertainty as to what level of electrical complexity is adequate for modeling the electrical field in the brain.

Accurate modeling of DBS requires incorporation of heterogeneity and anisotropy in the brain (Åström et al., 2012, Chaturvedi et al., 2010), which is not surprising given that grey matter, white matter, and cerebral spinal fluid (CSF) have markedly different electrical properties (Geddes and Baker, 1966, Latikka et al., 2001). There is, however, currently no consensus on how anisotropy should be represented in a model. For example, CSF and grey matter are traditionally regarded as isotropic (Gabriel et al., 1996a), and white matter is regarded as anisotropic (Nicholson and Freeman, 1975, Ranck Jr and BeMent, 1965) with prolate conductivity tensors (Nicholson, 1965). Because the tortuous microstructure in grey matter is not always symmetric, and because many white matter regions have multiple fiber bundles that cross in different directions, these traditional assumptions can oversimplify the situation.

The advent of diffusion-weighted (DW) MR imaging (Basser et al., 1994) provided an alternative approach for representing anisotropy and inhomogeneity in DBS models (McIntyre et al., 2004). The DW image contains information about macroscopic diffusion, which is used to define a diffusion tensor for each voxel, and a cross-property relationship (CPR) is then used to construct conductivity tensors from the diffusion tensors (Tuch et al., 2001). This cross-property approach is useful because it incorporates information about the microstructure of the brain and allows anisotropy to be represented in all brain regions. However, the limitations of using the Tuch CPR have yet to be explored within the specific context of DBS models.

The electrical properties of the brain also exhibit frequency-dependence. As frequency decreases below 0.1 GHz, the conductivity of brain matter decreases, and its permittivity increases (Gabriel et al., 1996c). This frequency-dependence, or dielectric dispersion, occurs because neural membranes charge more at lower frequencies and charge redistributes

between the intracellular and extracellular spaces (Foster and Schwan, 1989). Ignoring dielectric dispersion in simplified models of pulsatile brain stimulation leads to appreciable differences in the model predictions (Bossetti et al., 2008, Butson and McIntyre, 2005, Grant and Lowery, 2010), and these effects have yet to be explored in more detailed models of DBS.

The goal of this study was to determine how differences in the complexity of DBS models impact predictions of axonal stimulation in the human brain. We considered three levels of increasing complexity. To begin, the brain was treated as homogeneous and isotropic. Heterogeneity was incorporated by splitting the brain into CSF, grey matter, and white matter; and then four different approaches were used to define anisotropy in these brain regions. Lastly, we incorporated dielectric dispersion. Previous works on modeling DBS have assessed the effects of heterogeneity and anisotropy on model predictions, albeit in anatomically simplified models. This work is the first to compare different approaches to implementing anisotropy in a heterogeneous brain and subsequently assess the importance of dielectric dispersion in a heterogeneous and anisotropic brain. The results of this study will help define the level of detail that is necessary for accurate modeling of DBS in future studies.

2. Methods

2.1. Brain image acquisition and processing

The patient modeled in this study was scanned one week prior to their DBS surgery using a 3 Tesla Siemens Magnetom TIM Trio scanner (Siemens Medical Solutions USA; Malvern, PA, USA). Magnetic resonance (MR) images were acquired using a 12-channel head matrix coil with a maximum gradient magnetic field strength of 40 mT/m. T1-weighted MR (T1w) images were acquired using an MPRAGE sequence: field of view = 224 mm × 256 mm × 176 mm, relaxation time = 2600 ms, echo time = 3.02 ms, fractional anisotropy = 8°, and GRAPPA factor = 2.

Diffusion-weighted MR images were acquired using a diffusion-weighted single-shot spin-echo sequence with the following parameters: a b-value of 1000 s/mm², voxel resolution = 2 mm × 2 mm × 2 mm, 64 slices with 128 phase encoding steps and 128 frequency encoding steps, and 64 non-collinear directions with two averages. All DW images underwent eddy current and susceptibility corrections.

Co-registrations were conducted using the FMRIB software library (FSL) v5.0 (Greve and Fischl, 2009, Jenkinson et al., 2002, Jenkinson and Smith, 2001). The FMRIB Linear Image Registration Tool (FLIRT) was used to co-register the T2w and DW images to the T1w image, the reference image space in this study. All registrations were conducted using a rigid six-parameter affine transformation with three translations and three rotations.

We used the Brain Extraction Tool (BET) (Jenkinson et al., 2002, Jenkinson and Smith, 2001) to segment the patient's MR images into three regions (figure 1a). The T2w MR image was used to define the brain and the part of the skull that surrounded the brain, and the T1w MR image was used to define a lumped soft-tissue region. The brain region in the

T1w MRI was then further subdivided into CSF, grey matter, and white matter (figure 1b) using FMRIB's Automated Segmentation Tool (FAST) (Zhang et al., 2001). Subcortical structures, including the thalamus, pallidum, caudate, putamen, and brainstem were segmented using FMRIB's Integrated Registration and Segmentation Tool (FIRST) (Patenaude et al., 2011); and we used FreeSurfer (Fischl, 2012) to segment the cortex into different cortical regions.

Localization of an electrode array within the subthalamic nucleus (STN) was conducted using Human Cicerone software (Miocinovic et al., 2007), as this software allowed us to simultaneously visualize the virtual implanted array within the STN and surrounding nuclei. First, we used a nine-parameter affine transformation with 3 translations, 3 rotations, and 3 scaling factors to warp the patient's thalamus, pallidum, caudate, and putamen to the same subcortical structures in MNI space (see the Harvard-Oxford structural atlas in FSL). Then, the inverse transform was used to map a probabilistic volume of the STN in MNI space (Forstmann et al., 2012) to the patient's T1w space.

2.2. Bioelectric field model

A computational model of electrical conduction (figure 2) was constructed with the MRI data following a five step process. First, we constructed surfaces meshes that delineated the different head regions. BET was used to construct triangular meshes that defined the outer surface of the brain, the inner and outer surfaces of the skull, and the outer surface of a lumped soft-tissue region. We used MeshLab (meshlab.sourceforge.net) to apply a sequence of filters to the surface meshes: (i) Quadratic Edge Collapse Decimation was used to reduce the number of faces by 50 %; (ii) Laplacian smooth with surface preservation was used to smooth the decimated mesh; (iii) i and ii were repeated until the mesh consisted of 800–1000 faces; and, (iv) 4–8 Subdivision was used to convert the triangular mesh into a quadrilateral mesh.

The second step used the surface meshes to construct volumes representing the brain, skull, and lumped soft-tissue region. We used the non-uniform rational basis spline (NURB) toolbox written by D.M. Spink in MATLAB (v2014b, MathWorks, Natick, MA) to convert the quadrilateral meshes to NURBs. The NURBs were then used to define closed volumes in COMSOL Multiphysics v5.1 (COMSOL Inc., Burlington, MA).

The third step constructed a model of the Medtronic 3387 electrode array. The model array consisted of four cylindrical electrodes, numbered from 0 to 3, starting from the contact closest to the tip of the shaft. Electrodes were 1.5 mm in height, 0.635 mm in radius, and had an edge-to-edge inter-electrode spacing of 1.5 mm. Inactive annular electrodes, with an outer radius of 0.635 mm, had a thickness of 0.15 mm. The model array was placed in the right STN. We positioned the array so that contacts 0 and 2 were near the ventral and dorsal boundaries of the STN, respectively, and the shaft was oriented so that it was reflective of surgical trajectories typically used in subthalamic DBS for Parkinson's disease (figure 2d).

The fourth step defined the electrical properties of the different head regions (table 1). Unless specified otherwise, the conductivity of the brain, including the CSF, was modeled as heterogeneous and anisotropic (see section 2.2.1), while the conductivities of all other

tissues regions were modeled as homogeneous and isotropic. For time-variant analyses, all tissue regions, including the grey and white matter, had a permittivity (ϵ) that was homogeneous and isotropic. The dependence of the electrical properties on frequency, or dielectric dispersion, in all tissue regions except the CSF was modeled using the Cole-Cole relaxation equations defined in (Gabriel et al., 1996b). The CSF was purely conductive (i.e., $\epsilon = 0$), and its conductivity was independent of frequency (Baumann et al., 1997).

The fifth and final step constructed a tetrahedral volume mesh in the model head and used the finite element method (FEM) to solve Laplace's equation.

$$\nabla \cdot ([\Sigma \{\omega, x, y, z\} + j\omega\epsilon \{\omega\}] \cdot \nabla \Phi) = 0 \quad (1)$$

In equation 1, Σ is a conductivity tensor that depends on the angular frequency, ω , and position; and j is the imaginary unit. Note, we used Σ to differentiate a tensor conductance from a scalar conductance, σ , which is the degenerate form an isotropic Σ .

The electrode-tissue interface (ETI) and dura and arachnoid maters were modeled using thin boundaries subject to continuity:

$$\hat{n} \cdot \sigma^* \cdot \nabla \Phi = (\sigma_b + j\omega\epsilon_b) \cdot h^{-1} \cdot (\Phi_1 - \Phi_2), \quad (2)$$

where h is the thickness of the boundary, Φ_1 and Φ_2 are the potentials on either side of the boundary, and b denotes a property of the boundary. The Faradaic resistance ($r_f = h/\sigma_b$) and double-layer capacitance ($c_{dl} = \epsilon_b/h$) of the ETI were chosen to be $150 \Omega\text{cm}^2$ and $30 \mu\text{F}/\text{cm}^2$, respectively (Wei and Grill, 2009). We lumped the dura and arachnoid maters into a purely resistive ($\epsilon_b = 0$) boundary with a conductivity of 0.03 S/m (Struijk et al., 1993a). The h of the lumped dura and arachnoid layer was 2.3 mm , which was the median distance between the surface meshes that defined the outer brain and inner skull. A fixed potential of 1 V was imposed on the active contact, and no current was allowed to pass through the outer surface of the head, except at the inferior boundary of the head (i.e., the neck), which had a fixed potential of 0 V .

The FEM was solved using a Fourier-based approach (Butson and McIntyre, 2005). We solved equation 1 at 1025 frequencies uniformly spaced between 0 and 51.2 kHz . Then we calculated the discrete Fourier transform (DFT) coefficients of the applied voltage waveform versus time at the aforementioned frequencies, scaled the solutions by the corresponding DFT coefficients, and use the inverse DFT to obtain the spatiotemporal distribution of potentials in the head volume. The model was solved using $406,335$ third-order elements (~ 1.9 million degrees of freedom). Refinement of the volume mesh changed the interpolated potentials and subsequent stimulation thresholds by $< 1 \%$ with respect to the same values prior to refinement.

2.3. Construction of conductivity tensor fields in the brain

We considered four approaches for defining anisotropy in the brain, two of which are currently used (Section 4.1.1), and two of which are novel to this study (Section 4.1.2). In all approaches, tensors were reconstructed from their eigen-decomposition:

$$\Sigma = V \text{diag}(\sigma_1, \sigma_2, \sigma_3) V^T, \quad (3)$$

where V is the orthogonal matrix of orthonormal eigenvectors; σ_1 , σ_2 , and σ_3 are the eigenvalues of Σ ; and T is the transpose operator. The methodology for defining the eigenvectors and eigenvalues for each tensor is described in the following sections, and a more detailed discussion of the motivation and assumptions underlying each approach is discussed in Section 4.1.

2.3.1. Classical approach—Cortex and CSF have conductivities that are insensitive to direction (Yedlin et al., 1974), unlike white matter regions in the brain and spine, whose conductivities depend on direction (Nicholson and Freeman, 1975, Ranck Jr and BeMent, 1965). For example, the conductivity along a fiber tract, such as the internal capsule, is approximately nine times greater than the conductivities transverse to the tract (Nicholson, 1965). Therefore, a common approach for defining anisotropy, which we call the classical approach, treats grey matter and CSF as isotropic, and white matter as anisotropic with a prolate Σ (figure 3a).

All eigenvalues of tensors in CSF were equal to 1.45 S/m (Baumann et al., 1997), and all eigenvalues of tensors in grey matter were equal to 0.23 S/m (Gabriel et al., 2009). For white matter, the eigenvalues of Σ were calculated based on a volume constraint,

$$\frac{4}{3}\pi\sigma_{\text{iso}}^3 = \frac{4}{3}\pi\sigma_1\sigma_2\sigma_3, \quad (4)$$

where the left-hand side is the volume of a spherical isotropic tensor whose degenerate form is an effective scalar conductivity (σ_{iso}), and the right-hand side is the volume of an ellipsoidal anisotropic tensor that corresponds to Σ .

Equation 4 was parameterized in terms of two ratios: $w_{12} = \sigma_1/\sigma_2$ and $w_{13} = \sigma_1/\sigma_3$.

$$\sigma_1 = \sigma_{\text{iso}} w_{12}^{1/3} w_{13}^{1/3} \quad (5)$$

$$\sigma_2 = \sigma_{\text{iso}} w_{12}^{-2/3} w_{13}^{1/3} \quad (6)$$

$$\sigma_3 = \sigma_{iso} w_{12}^{1/3} w_{13}^{-2/3} \quad (7)$$

We used $\sigma_{iso} = 0.14$ S/m (Güllmar et al., 2010), and $w_{12} = w_{13} = 9$ (Nicholson, 1965).

V was the identity matrix for CSF and grey matter; and for white matter, the columns of V were the eigenvectors of the diffusion tensor (D) fitted to each voxel in the DW MR image.

2.3.2. Tuch cross-property relationship—A CPR, originally described by Tuch et al. (Tuch et al., 2001), is often used to relate the statistical moments of the tissue microstructure in diffusion to that of conduction via a least squares solution. This approach, which we referred to as the Tuch CPR approach, takes the following form:

$$\sigma_\lambda = \frac{\sigma_e}{d_e} \left[d_\lambda^2 \frac{d_i}{3d_e^2} + d_\lambda \left(\frac{d_i}{3d_e} + 1 \right) - \frac{2d_i}{3} \right] + O(d_i^2), \quad (8)$$

where σ_λ and d_λ are the eigenvalues of Σ and D , respectively; σ_e is a microscopic extracellular conductivity; d_e is a microscopic extracellular diffusivity; and d_i is a microscopic intracellular diffusivity. We used $\sigma_e = 1.52$ S/m, $d_e = 2.04 \mu\text{m}^2/\text{ms}$, and $d_i = 0.12 \mu\text{m}^2/\text{ms}$ (Tuch et al., 2001).

A D was defined for each voxel in the DW image using the FMRIB Diffusion Toolbox (FDT), and then equation 8 was used to calculate the eigenvalues of Σ . We assumed D and Σ shared the same eigenvectors (Basser et al., 1994), and Σ was re-constructed using equation 3.

2.3.3. Volume conservation and load preservation—We considered two additional approaches, which were novel to this study. The first approach, referred to as the volume-conservation (VC) approach, is a heuristic that is a more generalized form of the volume constraint from Section 2.3.1. The VC approach incorporated *in vivo* measurements but made no assumptions about the eccentricity of Σ . First, we used the ratio of the eigenvalues of D to define the ratio of the eigenvalues of Σ . That is, $w_{12} = d_1/d_2 = \sigma_1/\sigma_2$ and $w_{13} = d_1/d_3 = \sigma_1/\sigma_3$. Next, *in vivo* measurements were used to define a σ_{iso} for CSF (Baumann et al., 1997), white matter (Güllmar et al., 2010), and grey matter (Gabriel et al., 2009). And finally, equation 4 was used to calculate the eigenvalues of Σ .

The other new approach was referred to as the load-preservation (LP) approach. Like the above, the LP approach incorporated *in vivo* measurements and made no assumptions about the eccentricity of Σ . However, instead of conserving the tensor volume of the *in vivo* measurement, we chose Σ so that the electrical load of an infinite conductive medium was the same in both the isotropic and anisotropic cases. Assuming that the ratio of the eigenvalues in both D and Σ were the same, we defined the following:

$$\sigma_1 = \sigma_{iso} \theta(w_{12}, w_{13}) \quad (9)$$

$$\sigma_2 = \sigma_{\text{iso}} \theta(w_{12}, w_{13}) w_{12}^{-1} \quad (10)$$

$$\sigma_3 = \sigma_{\text{iso}} \theta(w_{12}, w_{13}) w_{13}^{-1}, \quad (11)$$

where θ is a scalar function of w_{12} and w_{13} (figure 3c).

θ was calculated numerically by constructing an FEM model of a spherical shell with an inner and outer radius of 1 mm and 100 mm, respectively. The inner and outer surface of the model were set to 1 V and 0 V, respectively; and we used a binary search algorithm (tolerance < 1 %) to find a Σ that yielded the same current as the spherical shell with a conductivity of σ_{iso} .

We used a nonlinear analytic expression to approximate the continuous form of θ .

$$\theta^* = \frac{v_1 w_{12}^m}{u_1^m + w_{12}^m} \frac{v_2 w_{13}^n}{u_2^n + w_{13}^n} \quad (12)$$

The root mean square relative error between θ^* and θ was minimized (< 1 %) with the following parameter values: $v_1 = 2.15$, $u_1 = 1.21$, $m = 8.00 \times 10^{-1}$, $v_2 = 1.85$, $u_2 = 1.12$, and $n = 8.00 \times 10^{-1}$.

2.4. Tractography

We used the combination of probabilistic tractography and a post-processing algorithm to define the trajectories of descending corticofugal (DCF) axons. To begin, we used the FMRIB bedpost tool to estimate diffusion parameters in each voxel of the DW image (Behrens et al., 2014), and subsequently, the FMRIB probabilistic tracking tool (probtrackx) was used to construct streamlines that connected the right motor cortex to the brainstem (figure 2a). 1000 streamlines were generated from each voxel within the mask defining the brainstem, and we kept only streamlines that met certain criteria: The waypoint and termination criterions were that the streamlines passed through and terminated in the brainstem, and the exclusion criterion was that the streamlines could not pass through the basal ganglia structures, CSF, or left hemisphere.

The output from probabilistic tractography was a volume density of the number of streamlines that passed through each voxel in space, known as a connectivity distribution. We fit a weighted smoothing spline to the connectivity distribution, using the density of streamlines at each point in space as the weights, and we used 100 ellipses along the length of smoothing spline to define the boundaries of the DCF axons (figure 4). Sets of random points were uniformly distributed in each of the 100 ellipses, and the points were connected so that the axons maintained their topographical organization across all ellipses. The details of the post-processing steps are outlined in the Appendix.

2.5. Cable models of axons

The NEURON (v7.3) simulation environment (Carnevale and Hines, 1997) was used to implement cable models of myelinated axons. We began with a validated model of a mammalian motor axon (McIntyre et al., 2002) and adjusted its geometry to reflect better the geometry of axons found in the brain. Axons of cortical neurons have a fiber diameter (i.e., axon diameter + myelin thickness) that ranges from 1–10 μm (Yagishita et al., 1994), the majority of which are predicted to be between 1 and 4 μm ; and probability distributions of fiber diameters in some major fiber bundles in the brain are maximal between ~ 2 and 4 μm (Assaf et al., 2008, Barazany et al., 2009). Thus, we chose a fiber diameter of 3 μm for our model DCF axons.

Empirical relationships between fiber diameter and other geometrical properties of the axon have been well-studied (Berthold et al., 1983, Nilsson and Berthold, 1988, Rydmark, 1981, Rydmark and Berthold, 1983). We used 4th order polynomials to reproduce the empirical relationships summarized in (McIntyre et al., 2002); and, in turn, the polynomials were used to extrapolate all other geometrical parameters except the internodal length and length of the paranodal segment. For the diameter chosen, we assumed the relationship between fiber diameter and internodal length was linear (Jacobs, 1988), and the length of the paranodal segment was 4 % of the internodal length (Rydmark and Berthold, 1983). The geometry of the axon model is summarized in the Appendix.

2.6. Theoretical analyses

We used our DBS model to assess how incorporation of heterogeneity and anisotropy affected predictions on neural excitation. In the base case, all tissue regions were isotropic and homogeneous. Heterogeneity was incorporated by splitting the brain into grey matter, white matter, and CSF. We then used four different approaches to incorporate anisotropy in the brain (see section 2.3).

We also assessed the impact of dielectric dispersion on model predictions. The parametric models developed by (Gabriel et al., 1996b) were used to define $\Sigma(\omega)$ and $\epsilon(\omega)$ for grey matter (see Appendix), white matter, skull, and the lumped soft-tissue region. Since the muscles and tendons occupy a majority of the soft-tissue volume, we used the parametric relationships for muscle to define the electrical properties of the lumped soft tissue region.

We factored the FEM solution into a spatial and temporal component to reduce storage requirements and allow for variable time integration over any length of time (see Appendix).

$$\Phi(x, y, z, t) \cong \Phi(x, y, z, t=0)y(t) \quad (13)$$

y is the solution of an equivalent four-element circuit consisting of a parallel combination of a double-layer capacitance (C_{dl}) and Faradaic resistance (R_f) that represents the ETI in series with a parallel combination of an access resistance (R_a) and access capacitance (C_a) that represents the tissue. The relationship between applied waveform (x) and y satisfied the following ordinary differential equation:

$$C_{dl}x' + R_f^{-1}x = (C_{dl} + C_a)y' + (R_f^{-1} + R_a^{-1})y \quad (14)$$

C_{dl} was calculated by multiplying c_{dl} times the area of the electrode, which equaled 1.8 μF ; and R_f was calculated by dividing r_f by the area of the electrode, which equaled 2.5 k Ω . R_a and C_a were numerically calculated using the FEM solution. Note: C_a was only non-zero when dielectric dispersion was included.

The interpolated potentials were used to stimulate model DCF axons with a 130 Hz train of biphasic asymmetric waveforms (figure 2c). Asymmetric pulses had a short 100 μs cathodic phase followed by a long 900 μs anodic phase. It should be noted that waveforms used in clinical stimulators also include a short interphase interval between the anodic and cathodic stimulation phases (Butson and McIntyre, 2007) that depends on the stimulation parameters; and depending on the type of stimulator used, the charge-balancing phase may be active (i.e., voltage- or current-regulated) or passive. We elected to use an idealized waveform for this theoretical work, but when using a computational model for clinical research, one should tailor the waveform to the clinical stimulator.

Because equation 1 is linear, the solution at any given amplitude was calculated by multiplying the solution at 1 V with a scalar, and a bisection algorithm (error tolerance < 1 %) was used to quantify the stimulation thresholds of three independently sampled populations of 100 DCF axons. An axon was defined as active when at least one action potential reached both of its ends.

The various model cases were compared by quantifying differences in the load of the electrode, the generated potentials, and the stimulation thresholds of model DCF axons. The load of the electrode was the combination of the loads of the tissue and ETI at 70 μs . This definition is consistent with how the load is measured in Medtronic's implantable pulsed stimulators. The distributions of stimulation thresholds were compared using a two-sample Kolmogorov-Smirnov statistical test ($\alpha = 0.05$), and we used the median or median absolute difference to quantify differences between the different model cases.

3. Results

We used MR images to create an image-based computational model of subthalamic DBS. The electrical properties of the skull and lumped soft tissue were isotropic and homogeneous, and we evaluated how heterogeneity and anisotropy in the electrical properties of the brain impacted model predictions. Subsequently, we allowed the electrical properties of the different head regions to vary with frequency, and we quantified the impact of dielectric dispersion on model predictions.

3.1. The effect of heterogeneity and anisotropy on model predictions

In the most simplified version of the head model, the base case, the soft-tissue region, skull, and brain were all isotropic and homogeneous. We incorporated heterogeneity by splitting the brain into CSF, white matter, and grey matter; and each region was assigned its own σ_{iso} .

Compared to the base case, adding heterogeneity changed the distribution of potentials used to stimulate DCF axons by 24 %, where the metric for change was the median absolute difference (MAD). A MAD of 24 % in the potentials corresponded to a MAD of 22 % in the stimulation threshold voltages (V_{th}) of the DCF axons (table 2).

Next, we included anisotropy, which led to marked changes in the model predictions (figure 5). Between the anisotropic, heterogeneous cases and the isotropic, heterogeneous case; the MAD in the potentials varied between 1.9 and 37 %, which corresponded to an MAD of between 48 and 190 % in the V_{th} of the DCF axons (table 2). More specifically, changes in model predictions were greater for the Tuch CPR approach than the classical, VC, and LP approaches. These results indicated that the modeled predictions were more sensitive to incorporation of anisotropy in the brain than incorporation of heterogeneity in the brain.

Changes in the potentials and V_{th} could be explained by changes in the electrical load of contact 0. In the base case, the load was 0.82 k Ω . The load increased to 0.98 k Ω when the brain was treated as heterogeneous and isotropic, and the distribution of V_{th} of the DCF axons was statistically different than that of the base case. The median V_{th} of the heterogeneous, isotropic case decreased with respect to that of the base case (figure 5a).

Subsequently, inclusion of anisotropy decreased the load of contact 0. Compared to the heterogeneous, isotropic case, the load decreased by more than 100 Ω when anisotropy was defined using either the classic or Tuch CPR approaches. Of particular note was the precipitous drop in the load that occurred when using the Tuch CPR, where the load decreased from 0.98 k Ω to 0.68 k Ω . This precipitous drop in the load caused the potentials to decay more rapidly with increasing distance (figure 5b), and the median V_{th} of the DCF axons increased with respect to the heterogeneous, isotropic case (figure 5a). With the alternative approaches, the changes in the load were more modest. Despite modest changes in the load, the median V_{th} differed by > 1.5 V with respect to the heterogeneous, isotropic case. All four heterogeneous, anisotropic cases had distributions of V_{th} that were statistically different than that of the heterogeneous, isotropic case.

The model predictions were also markedly different amongst the four anisotropic cases (figure 6). For example, the MAD in the V_{th} of DCF axons was > 30 % between all approaches except the VC and LP approaches. These appreciable differences suggest that the assumptions underlying implementations of anisotropy require further careful consideration.

3.2. The effect of dielectric dispersion on model predictions

We fit equation 14 to waveforms of the potential versus time at the junction between the ETI and tissue. All fits yielded C_a of ~ 2 nF, which was more than two orders of magnitude smaller than C_{dl} , so polarization in the tissues was negligible. To determine an effective waveform of the potentials over time, we subtracted the impedance of the ETI from the impedance of contact 0, constructed a transfer function, and fit a three-element Randles circuit to the output waveform from the inverse DFT (figure 7b). The load was 1.07 k Ω . Although the inclusion of dielectric dispersion increased the effective load of contact 0, there was little effect on the stimulation thresholds. For example, the MAD in the stimulation thresholds of DCF axons was < 1 % between the heterogeneous, anisotropic case

with tensors defined using the LP approach and the same case with dielectric dispersion included (table 2).

4. Discussion

The fundamental goal of this study was to determine the impact of representing various levels of detail in electrical models of brain stimulation. The study was focused on clinical DBS, so we assessed the tradeoff between complexity and accuracy by quantifying changes in model predictions with increasing level of complexity. Incorporation of heterogeneity altered the calculated electric potentials and subsequent stimulation thresholds, but to a lesser degree than incorporation of anisotropy. The largest changes in model predictions were observed when anisotropy was incorporated, and additionally, the results were sensitive to the choice of method for implementing anisotropy. Incorporation of dielectric dispersion led to a more accurate prediction of the spatiotemporal variation in the potentials, which altered the load; however, the effect of dielectric dispersion on the stimulation thresholds was small compared to effects of heterogeneity and anisotropy.

4.1. Modeling anisotropy in the brain

4.1.1. Current approaches—The classical approach has been used for decades to define anisotropy in electrical models of nervous tissue (Holsheimer, 2002, Struijk et al., 1993b, Struijk et al., 1992, Veltink et al., 1989) and is still being used today (Hernández-Labrado et al., 2011, Lee et al., 2012). The classical approach makes three assumptions, one of which is that all CSF regions are isotropic. This assumption seems reasonable, considering CSF electrically resembles a saline solution. However, the issue is that not all voxels in an MR image classified as CSF contain only CSF. Take, for example, voxels at the boundaries between the ventricles and brain, or the cortex and the dura. These pseudo voxels of CSF contain portions of brain parenchyma, blood vessels, or choroid plexus; and ignoring anisotropies that result from partial-volumes effects can lead to significant errors in model predictions (Hyde et al., 2012).

The classical approach also assumes that all grey matter regions are isotropic, although grey matter is comprised of cell bodies, neuropil, myelinated axons, and blood vessels. On macroscopic length scales, if the volume of tissue is relatively large, and the barriers that impede transport are, on average, randomly orientated, then transport phenomenon like diffusion can appear isotropic (Pierpaoli et al., 1996). Counteracting this effect, however, are partial-volume effects that are increasingly prevalent at larger length scales. As microscopic length scales are approached, asymmetries in the microstructure emerge, and as a result, grey matter begins to appear anisotropic (Komlosh et al., 2007). Therefore, some degree of anisotropy is expected in grey matter regions.

Lastly, the classical approach assumes that all white matter is anisotropic with prolate Σ s. This assumption is based on measurements taken within the internal capsule (Nicholson, 1965) and dorsal column of the spinal cord (Ranck Jr and BeMent, 1965), where a majority of the axons follow the same trajectory. Σ s are also expected to be prolate in fascicles within peripheral nerves and major fiber bundles within the brain, such as the corpus callosum and

pyramids. However, in brain regions like the pons or centrum semiovale, where multiple fiber crossings are present, Σ s are likely to be oblate ($\sigma_1 < \sigma_2 = \sigma_3$) or scalene ($\sigma_1 > \sigma_2 > \sigma_3$).

More recent works have used the Tuch CPR to define anisotropy in the brain (Åström et al., 2012, Butson et al., 2007, Chaturvedi et al., 2010, Schmidt et al., 2013). The Tuch CPR approach makes no assumptions about the degree of anisotropy in the CSF or brain parenchyma, but its limitations have not been assessed. We found that when the Tuch CPR approach was used, the load of the stimulation electrode was substantially less than what was expected. For example, in the STN, the load of a single contact on the Model 3387 array is expected to be between 1 k Ω and 1.5 k Ω (Cheung et al., 2013). Although measurements taken *in vivo* with implantable pulse generators can be quite variable, changing over time, between contacts, and with the applied amplitude; they provide reasonable upper and lower bounds for which predicted model loads should fall within. When the brain was modeled as heterogeneous, the load of contact 0 was 0.98 k Ω , and when equation 8 was used to incorporate anisotropy, the load decreased to 0.68 k Ω . This decrease in the load led to a more rapid decay in the potentials with increasing distance from the electrode, and the median voltage required to stimulation DCF axons increased by more than twofold compared to the heterogeneous case (figure 5a).

The precipitous drop in the load that occurred when using the Tuch CPR can be explained by examining its output (figure 8a). The effective isotropic conductivity of grey matter is expected to be between 0.1 S/m and 0.3 S/m (Gabriel et al., 1996c, Latikka et al., 2001). Although many grey matter regions were anisotropic, greater than 99 % of the conductivities estimated by the Tuch CPR were well beyond the upper limit of the expected range (figure 8b). The same issue was also observed in white matter but not CSF.

The Tuch CPR assumes that the intracellular space is electrically shielded at frequencies <1 kHz. This assumption is reasonable, considering redistribution of charge between the intracellular and extracellular spaces of nervous tissue, although evident at frequencies as small as 10 Hz, is substantially more pronounced at frequencies >1 MHz (Gabriel et al., 1996c). Hence, the microscopic intracellular conductivity was set to 0, and the Tuch CPR was parameterized using only σ_e , d_e , and d_f . Making this simplification has two repercussions. One, because redistribution of charge is ignored at all frequencies, the Tuch CPR cannot incorporate dielectric dispersion, which is an important factor for accurate modeling of bioelectric fields (see section 4.2). And two, because the Tuch CPR is strongly weighted by $\sigma_e = 1.52$ S/m, a value close to the conductivity of CSF (Baumann et al., 1997), it is able to predict the conductivity of CSF but at the expense of overestimating the conductivities of grey and white matter.

4.1.2. Alternate approaches—As discussed above, the typical approaches for defining anisotropy in the brain have significant shortcomings. Overestimating the conductivity of the brain parenchyma leads to substantial increases in the predicted stimulation thresholds, which was more an artifact of overestimation than a true effect of accounting for anisotropy in the brain. Therefore, we set out to define alternative approaches that address the drawbacks of the typical methods.

The VC approach is a general form of the classic approach, as it was derived from the volume constraint (equation 4) used in the classic approach; but unlike its predecessor, the VC approach makes no assumptions about the degree of anisotropy in the brain tissues. There are, however, disadvantages to using the VC approach. Without additional constraints, equation 4 is an undetermined system because there are three unknowns (i.e., σ_1 , σ_2 , and σ_3) and only one equation. Therefore, equation 4 must be constrained, which we did by assuming that the ratios of the eigenvalues in Σ (i.e., w_{12} and w_{13}) were the same as those in the corresponding measured D . In other words, we assumed D and Σ had the same fractional anisotropy, which is not necessarily true. Another disadvantage is that the volume constraint equates the geometric mean of the eigenvalues of Σ to an effective scalar conductivity, σ_{iso} , so the VC approach is a heuristic rather than a formulation based on first principles.

The LP approach, like the VC approach, begins with a scalar conductivity, σ_{iso} . σ_{iso} reflects a degenerate tensor and contains no information about the macroscopic anisotropy or heterogeneity of the tissue, but implicit in this value is information about the load of the tissue. For example, in an *in vivo* experiment, one typically measures a lumped load or impedance, and a model fit is used to resolve the geometric-independent electrical properties. Even in instances where the tissue is anisotropic, the model fit is made tractable by assuming isotropy, and only effective scalar values are reported (Gabriel et al., 1996c, Latikka et al., 2001). Knowing the geometry of the source and tissue medium, as well as the effective load, one can re-solve the inverse problem to determine which Σ , if any, reproduces the load of the source. (Note: Σ can be complex-valued.) This was the motivation for the LP approach.

What differentiates the LP approach from the VC approach is the use of principles of electrical conduction, rather than a heuristic, to numerically determine a scalar relationship between σ_{iso} and the eigenvalues of Σ (equations 9–11). Recall, equations 9–11 were dependent on a scalar mapping function, θ . We calculated θ with $\sigma_{\text{iso}} = 1$ S/m and the eigenvectors of Σ oriented in the x, y, and z directions. However, θ was the same regardless of the value of σ_{iso} and the orientation of Σ . This was expected. The potentials of a point source in an infinite homogeneous and anisotropic medium are proportional to $|\Sigma|$, the determinate of Σ , so the load of the medium is also proportional to $|\Sigma|$ (Li and Uren, 1998). Because Σ is symmetric, $|V| = 1$, and by the distributive property of determinates, $|\Sigma| = \sigma_1 \sigma_2 \sigma_3$ (see equation 3). If two tensors have the same load, this will remain true regardless of their orientation or a scaling factor.

The LP approach also assumes D and Σ have the same fractional anisotropy. As demonstrated by Tuch et al. (Tuch et al., 2001), the CPR between D and Σ is highly linear, as the first-order coefficient of equation 8 is more than 100 and 9 times greater than the second-order coefficient and y-intercept, respectively. Although the assumption of equal fractional anisotropy is not necessarily true, it is likely a reasonable simplification.

Because the classic and Tuch CPR approaches are not able to reproduce loads that have been measured in STN DBS, and because conservation of the volume of a tensor is not derived from any principles of electrical conduction, we recommend the LP approach be used for defining anisotropy. However, further validation of this method is required. Given a cohort

of subjects whose loads were measured across multiple contacts and electrode configurations, one can test the predictive power of this method by comparing the theoretical and measured loads. However, more direct methods of validation that measure potentials and/or current-density distributions are currently not possible in humans.

Course metrics, such as the lumped load of a conducting volume, cannot resolve heterogeneity in the electrical properties of the volume. Therefore, the LP approach should only be regarded as a temporary solution until more advanced techniques for probing conduction at the millimeter scale and below are developed. One emerging imaging technique that holds promise for measuring current density distributions on the millimeter scale is magnetic resonance electrical impedance tomography (MREIT) (Seo et al., 2005), which is now being used to image human tissues (Kim et al., 2009). Just as DW images can be used to define D on the length scale of millimeters, MREIT images could be used to define Σ .

4.2. Accounting for the effect of dielectric dispersion in DBS

Previous theoretical studies have analyzed the effect of dielectric dispersion on the electric potentials generated by DBS. Bossetti et al. (Bossetti et al., 2008) constructed a simplified model of a point source current in an infinite medium and observed that for pulse widths used in DBS, the permittivity of the tissue could be ignored if an appropriate conductivity was chosen. Grant and Lowery (Grant and Lowery, 2010) corroborated these results in a more complex model consisting of the Model 3387 array inside of a homogeneous, isotropic brain with surrounding concentric spherical shells representing the outer tissue layers. Our investigation extends upon these works by examining whether the effect of dielectric dispersion is the same or different in an anatomically-detailed head model with a brain that is heterogeneous and anisotropic.

Polarization in the brain was negligible compared to polarization at the ETI, as C_a was more than two orders of magnitude less than C_{dl} . This result was expected considering a majority of the power in typical DBS pulse trains is concentrated between 1 and 10 kHz (figure 7a), and within this frequency band, the complex conductivity in grey and white matter is approximately real-valued (i.e., $\omega\epsilon/\sigma$ is $\ll 1$) (Gabriel et al., 1996c). Therefore, despite an increase in model complexity, the results were still in agreement with previous work (Bossetti et al., 2008, Grant and Lowery, 2010).

With a forward Fourier FEM approach, we calculated an equivalent load of 1.07 k Ω , which fell within the range of loads measured clinically in subthalamic DBS (Cheung et al., 2013). Although the effect of dielectric dispersion on the stimulation thresholds was negligible in the computational model of DBS, the same may not be true for other DBS applications and electrical stimulation therapies. The issue is incorporation of dielectric dispersion requires a considerable amount of computational resources and time. For example, calculating the spatiotemporal distribution of potentials required solving the FEM model at 1025 frequencies. It took approximately 30 minutes to solve the model once on a 8 $\times$ Intel(R) Core (TM) i7-4790K computer (at 4.0 GHz), and the total solution time was ~ 21 days. Use of multithreading reduced the total solution time to ~ 7 days, and we predict this time can be

reduced to a couple of hours or less by using a compute cluster to solve the model at all frequencies simultaneously.

4.3 Model limitations

There are a number of limitations that should be addressed. First, we ignored the pia mater. The BET in FSL extracts the inner surface of the skull, and at this surface, we represented the dura and arachnoid maters with a Robin boundary condition (equation 2). The surface between the cortex and CSF was not explicitly modeled (see below), so a Robin boundary condition for the pia was not included. It is possible that the presence of the pia mater may be required for accurate modeling of the electric field near the surface of the brain, but because ignoring the dura and arachnoid maters did not alter the stimulation thresholds of DCF axons by $> 1\%$ (results not shown), we predict that incorporation of the pia will have a negligible effect on our results.

Another limitation was that grey matter, white matter, and CSF were not modeled as three separate sets of volumes. Rather, we modeled the brain as one volume, used data from the MR images to construct a heterogeneous and anisotropic tensor field in scaled voxel space, and used nearest-neighbor interpolation to define the tensor field on the nodes of the unstructured FEM mesh. This approach obviates the need for a very fine mesh that respects all the boundaries between different types of brain regions; but if the mesh is too coarse, then errors result from misestimation of the true boundaries. Global refinement of the mesh in the brain altered the stimulation thresholds of DCF axons by $< 0.1\%$. Therefore, the resolution of the mesh was fine enough to approximate the boundaries between the CSF, grey matter, and white matter.

Our patient-specific head model accounted for heterogeneity, anisotropy, and dielectric dispersion in the brain tissue and CSF, but there are a number of details that we did not address. One detail we ignored was partial-volume effects within the brain voxels. Voxels were classified as CSF, white matter, or grey matter based on the tissue type that was predicted to fill the largest volume fraction within each cubic region; but accurate modeling of the electric field may require that one account for the presence of the minority constituents, especially at boundaries between the different tissue regions. In addition, we also ignored anisotropy and heterogeneity within the skull and lumped soft tissue region. Accurate source localization in modeled electroencephalograms requires that one account for anisotropy in the skull (Marin et al., 1998). Therefore, further investigation on the tradeoff between accuracy in calculating the electric field within the brain and model complexity is warranted.

5. Conclusion

The results demonstrated that accurate modeling of the electric field in the brain required incorporation of heterogeneity, anisotropy, and dielectric dispersion. Of particular importance was the finding that current approaches for incorporating anisotropy underestimated the extent of stimulation, and this is predicted to be more a factor of the limitations of these approaches, rather than the addition of directional dependence in the conductivity. It is for this reason that we recommend an alternative approach for

incorporating anisotropy (i.e., the LP approach) that makes no assumptions about the degree of anisotropy, utilizes *in vivo* measurements, and is based on fundamental principles of electrical conduction.

The heterogeneous temporal variation in the potential field across space can be modeled by incorporating frequency-dependence in the electrical properties of the tissues. This dispersion of time constants affected the predicted load of the electrode but had negligible effects on the predicted stimulation thresholds. Therefore, it is reasonable to ignore the effects of dielectric dispersion in computational models of STN DBS, but the same conclusion does not necessarily apply to other target locations or electrical stimulation therapies. Altogether, these results will help define a “gold standard” for accurate modeling of DBS in future studies.

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Appendix

Additional Methods

Construction of streamlines

The connectivity distribution resulting from probabilistic tractography (Section 2.4 and figure 2a) was processed so that smooth topographically-organized streamlines could be reconstructed (figure 4). First, we fit a weighted smoothing spline to the connectivity distribution. The spline was fit to the centers of non-zero voxels in the the connectivity distribution, and the weights were the respective density of streamlines in each non-zero voxel. Next, we divided the fitted spline into 100 segments and defined elliptical boundaries at each segment. An oblique plane was defined at the beginning of each segment whose normal vector was collinear with the tangent vector of the fitted spline. Points 2 mm from each respective plane were projected onto the planes, and a best-fit circumscribing ellipse was used to define the boundary of the fiber tract at each segment. Finally, sets of 300 random points were uniformly distributed in each of the 100 ellipses, and the points were connected so that the axons were maximally smooth. Maximal smoothness was achieved by connecting the axons so that the sum of all distances traveled by axons between segments was minimized.

It should be noted that these post-processing steps are not intended as a general supplement to probabilistic tractography. Rather, the purpose of the post-processing was to reconstruct streamlines that were topographically organized and smooth, which general probabilistic tractography algorithms do not guarantee. Our *ad hoc* algorithm was adequate because the connectivity distribution was unimodal in the vicinity of the STN. However, for more complex multimodal connectivity distributions that contain bifurcations and/or fiber

crossing, preserving topographical organization and imparting global smoothness requires a more rigorous formulation (Zhang et al., 2013).

Construction of frequency-dependent tensor fields

The file containing the contents of $\Sigma(\omega, x, y, z)$ for a given ω required ~ 87 MB of storage. Rather than construct and store 1025 tensors, we proposed a tensor field with the following form:

$$\Sigma(\omega, x, y, z) = \sum_{i=1}^n \Sigma_i^*(x, y, z) U_i(x, y, z) \sigma_i(\omega) \quad (\text{A.1})$$

where, Σ_i^* is Σ when $\sigma_{\text{iso}} = 1$ S/m (e.g., see equations 5–7) in a given region, U_i is one in the region of interest and zero elsewhere, $\sigma_i(\omega)$ is the relationship between σ_{iso} and ω , and n is the number of regions.

The brain was comprised of grey matter, white matter, and CSF; so $n = 3$. The advantage of a piecewise linear form was that instead of saving 1025 matrices, we could reconstruct Σ for any given ω using only three matrices and three vectors, substantially reducing storage requirements. The scalar field, $e(\omega, x, y, z)$, in the brain was also constructed using a form similar to equation A.1.

Justification for a separable solution

The potentials generated within a conductive volume decay at approximately the same rate and can be described using a single time constant if the current density distribution in the bulk medium is uniform. This explains why equation 13 is a suitable approximation for equation 1 when the brain is treated as homogeneous and isotropic (Howell et al., 2014). However, when heterogeneity and anisotropy are included, the current density distribution in the brain tissue is no longer uniform, as indicated by amorphous isopotential contours (figure 1c), and use of equation 13 becomes questionable.

A nonuniform current density distribution gives rise to a potential field whose rate of decay varies with position (Oldham, 2004), which was observed in the heterogeneous, anisotropic model (figure A1a). Anisotropy was defined using the LP approach, and the model DCF axons were stimulated using the solution of equation 1 or its approximation, equation 13, where the effective waveform, $y(t)$, was determined *post hoc* (figure 7). The MAD in the stimulation thresholds was < 1 % between these two cases – noting that $y(t)$ was similar to the average waveform 10 mm from the stimulation electrode (figure A1b). Therefore, despite the variation in the rate of decay of the potentials with position, equation 13 was a suitable approximation for the solution of equation 1. Although use of equation 13 was justified in our model, one must test the validity of equation 13 before generalizing its use for any given model.

Figure A1. The potentials decay at a variable rate when heterogeneity and anisotropy are present in the brain tissue. (a) The distribution of time constants (τ s) at which the potentials reached $1-e^{-1}$ of their starting value were determined by fitting the solution of equation 14 to waveforms of the potentials versus time at each location in space. u_1 and u_2 denote displacements from the center of contact 0 (red) in an orthogonal plane that divided the 3387 lead in two halves. Anisotropy was defined using the load preservation approach. (b) The waveforms of the potentials versus time are normalized by their maximum value and compared against the average spatial waveform.

Geometry of Modeled Axons

The geometry of the descending corticofugal axons is summarized in table A.1.

Table A1

Geometry of Descending Corticofugal Axons^a

Parameter ^b	Description	Unit(s)	Value
D	Fiber diameter	μm	3
INL	Intermodal length (NoR-NoR separation)	μm	300
L_{NoR}	Length of NoR	μm	1
D_{NoR}	Diameter of NoR	μm	1.21
w_{NoR}	Periaxonal width of NoR	m	2×10^{-3}
L_{MYSA}	Length of MYSA	μm	3
D_{MYSA}	Diameter of MYSA	μm	1.21
w_{MYSA}	Periaxonal width of MYSA	μm	2×10^{-3}
L_{FLUT}	Length of FLUT	μm	12
D_{FLUT}	Diameter of FLUT	μm	1.73

Parameter ^b	Description	Unit(s)	Value
w _{FLUT}	Periaxonal width of FLUT	μm	4×10 ⁻³
L _{STIN}	Length of STIN	μm	89.67
D _{STIN}	Diameter of STIN	μm	1.73
w _{STIN}	Periaxonal width of STIN	μm	4×10 ⁻³
n _l	Number of myelin lamella	unitless	51
n _{NoR}	Number of NoR	unitless	1
n _{MYSA}	Number of MYSA elements per segment ^c	unitless	2
n _{FLUT}	Number of FLUT elements per segment ^c	unitless	2
n _{STIN}	Number of STIN elements per segment ^c	unitless	3

^aThe electrical parameters of the axon model are summarized in (McIntyre et al., 2002).

^bNoR = Node of Ranvier, MYSA = myelin attachment segment, FLUT = paranodal main segment, STIN = internodal segment

^cOne segment has the following pattern: NoR-MYSA-FLUT-STIN-STIN-STIN-FLUT-MYSA...

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Figure 1.

Image-based computational model of electrical conduction in a human head. (a) T1- and T2-weighted MR images were used to segment a brain region (*red*), a skull region (*green*), and a region of lumped soft tissues (*blue*). (b) The brain region was further segmented into cerebral spinal fluid (CSF, *blue*), grey matter (*red*), and white matter (*yellow*). (d) Equipotential contours surrounding contact 0 of the Model 3387 electrode array when placed in the subthalamic nucleus (STN).

Figure 2.

Electrical stimulation of descending corticofugal (DCF) axons. (a) A connectivity distribution (*blue*) was used to predict the trajectories of DCF axons. Streamlines connected the brain stem (*yellow*) to the right motor cortex (*green*) and did not intersect the CSF, basal ganglia structures, or left hemisphere (*red*). Axes reflect radiological convention. (b) Contact 0 in a monopolar cathodic configuration was used to stimulate model axons at a stimulation amplitude of -2.5 V. (c) The stimulus waveform was a train of asymmetric rectangular pulses with a short cathodic $100\ \mu\text{s}$ phase followed by a long $900\ \mu\text{s}$ anodic phase at 130 Hz

(*inset*). (d) The red streamlines denote model DCF axons that were activated by stimulation through contact 0. STN = subthalamic nucleus.

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Figure 3.

Implementations of anisotropy in the brain. (a) An anisotropic conductivity tensor (Σ) can be decomposed into three conductivities (i.e., σ_1 , σ_2 , and σ_3) in three orthogonal directions (v_1 , v_2 , and v_3). It is common to treat tensors in white matter as prolate and tensors in cerebral spinal fluid (CSF) and grey matter as approximately degenerate. More recent approaches make no assumptions about the shape of the tensors and model Σ as a general ellipsoid. (b) We used a spherical shell with an inner and outer radius of 1 mm and 100 mm, respectively, to approximate a homogeneous, infinite conductive medium. The anisotropic tensor (Σ) was parameterized by its largest eigenvalue (σ_I), the ratio of σ_I to σ_2 (w_{I2}), and the ratio of σ_I to σ_3 (w_{I3}). The eigenvalues of the isotropic tensor (σ_{iso}) were all 1 S/m. We used a numerical approach to determine a scalar mapping (θ) between σ_{iso} and Σ (see equations 9–11). (c) θ could be approximated with a nonlinear analytic function (see equation 12).

Figure 4.

Reconstructing smooth streamlines within a volume of interest. Probabilistic tractography yields a connectivity distribution (*black*), which is volume density of the number of streamlines that pass through each voxel in space. A weighted smoothing spline (*red*) was fitted to the centers of the non-zero voxels in the connectivity distribution, and bounding ellipses (*green*) were used to define the boundaries of an elliptical fiber bundle.

Figure 5.

The effect of heterogeneity and anisotropy on model predictions of neural excitation. (a) Distributions of the stimulation threshold voltages (V_{th}) of DCF axons located 3 mm from the electrode surface. Outliers (red plus signs) are > 1.5 times the interquartile range from the ends of the boxes. The different anisotropic, heterogeneous cases are summarized in section 2.3. CPR = cross-property relationship (Tuch et al., 2001). Note: analyses in this work were conducted on the entire population of DCF axons. We show only a subset of the DCF axons in panel a because it demonstrates that axons greater than 3 mm from the electrode are unlikely to be activated at the stimulation amplitudes used in clinical practice (1–10 V). (b) The potentials in the brain with increasing x displacement from the surface of contact 0.

Figure 6.

Four methods for defining anisotropy in the brain. (a) Tensor fields within grey and white matter across the four different cases (see section 2.3): Tuch cross-property relationship (CPR), classical, volume conservation (VC), and load preservation (LP). The right subthalamic nucleus is shown in pink. Note: tensors in the cerebral spinal fluid were ignored because they were > 10 times the size of tensors in the brain parenchyma. The scale bar for tensors is on the bottom right corner. Tuch CPR inset: tensors were scaled by a factor of 0.5 to limit overlap. (b) Differences in model predictions between the four different cases. $\Phi =$

potential field, DCF = descending corticofugal, V_{th} = voltage-regulated stimulation threshold.

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Figure 7.

Equivalent electrical load when dielectric dispersion was included. (a) The voltage-regulated waveform applied to the stimulation electrode (*top*), the magnitude of the discrete Fourier transform (DFT) of x (*middle*), and the magnitude of the transfer function for the voltage drop across the tissue (*bottom*). (b) The inverse DFT yielded an equivalent waveform of the voltage drop across the tissue over time (V_a), and a fitted three-element Randles circuit was used to calculate the lumped access resistance (R_a) of the tissue. C_{dl} = lumped double-layer capacitance, R_f = lumped Faradaic resistance, and C_a = the lumped (access) capacitance of the tissue. C_a was ignored because it had a negligible effect on the filtered waveform.

Figure 8.

The Tuch cross-property relationship overestimates the conductivity of brain tissues. (a) Mapping diffusion tensor eigenvalues to conductivity tensor eigenvalues using equation 8. Fitted parameters were varied according to the ranges (mean plus/minus one standard deviation) given in (Tuch et al., 2001). Mean diffusivities in brain parenchyma vary between 0.5 and 1.0 $\mu\text{m}^2/\text{ms}$ (Yu et al., 2006) (b) A diffusion tensor field was fit to the DW image, and equation 8 was used to calculate the eigenvalues (σ_1 , σ_2 , and σ_3) of the conductivity tensor field within the brain. The histograms summarize the distribution of σ_1 (red), σ_2 (blue), and σ_3 (green) in the cerebral spinal fluid (CSF, *top*), grey matter (*middle*), and white matter (*bottom*). Examples of measured isotropic conductivities for CSF and grey matter are 1.45 S/m (Baumann et al., 1997) and 0.23 S/m (Gabriel et al., 2009), respectively. 0.61 S/m and 0.067 S/m are examples of longitudinal and transverse conductivities, respectively, that have been measured in white matter (Ranck Jr and BeMent, 1965).

Table 1

Electrical Properties of Different Tissues with Increasing Model Complexity

Tissue/Category	isotropic	anisotropic ^{1,2}	dielectric dispersion ^{3,4}	
	σ (S/m)	σ (S/m)	σ (S/m)	ϵ_r
CSF	1.5	TF	N/A	N/A
Grey matter	0.23	TF	TF(ω) ³	f(ω) ³
White matter	0.14	TF	TF(ω) ³	f(ω) ³
Glial scar	0.13	N/A	N/A	N/A
Dura and arachnoid ⁵	3.0×10^{-2}	N/A	N/A	N/A
Skull ⁶	2.0×10^{-2}	N/A	f(ω) ³	f(ω) ³
Soft tissues ⁷	0.33	N/A	f(ω) ³	f(ω) ³

¹ Only regions within the brain (including CSF) were treated as anisotropic.

² section 2.3 and table 2 summarize how tensors in the brain regions were constructed.

³ The model was solved using a Fourier approach. The dependence of Σ/σ and ϵ_r on angular frequency, f(ω), for brain parenchyma, skull, and soft tissues are from (Gabriel et al., 1996b).

⁴ The electrode-tissue interface was modeled as a thin layer (equation 2) with a Faradaic resistance and double-layer capacitance of $150 \Omega\text{cm}^2$ and $30 \mu\text{F}/\text{cm}^2$, respectively (Wei and Grill, 2009).

⁵ The dura and arachnoid mater were lumped in a thin layer (equation 2) with a thickness of 2.3 mm.

⁶ Only the part of the skull that surrounded the brain (figure 1a) was considered.

⁷ The muscles, tendons, cervical vertebrae, fat, skin, intervertebral disks, blood, air, and portions of the skull within the soft tissues were lumped into a single conductive region.

Abbreviations: TF = tensor field, CSF = cerebral spinal fluid, σ = conductivity, ϵ_r = relative permittivity

Table 2

Changes in Model Predictions with Increasing Complexity in the Head Model

Tissue properties ¹	Metric ²		
	load (k Ω)	MAD Φ ³ (%)	MAD V_{th} ³ (%)
homogeneous, isotropic	0.82	N/A	N/A
heterogeneous, isotropic ³	0.98	24	22
heterogeneous, anisotropic (<i>Tuch CPR</i>) ⁴	0.68	37	190
heterogeneous, anisotropic (<i>classical</i>) ⁴	0.87	19	97
heterogeneous, anisotropic (<i>volume conservation</i>) ⁴	0.96	4.8	56
heterogeneous, anisotropic (<i>load preservation</i>) ⁴	1.01	1.9	48
heterogeneous, anisotropic (<i>load preservation</i>), dielectric dispersion ⁵	1.07	0.6	0.30

¹The different approaches (*italicized*) for defining anisotropy are summarized in section 2.3.

²The electrical load of contact 0 (Model 3387) in the subthalamic nucleus at $t = 70 \mu s$, the median absolute difference (MAD) in the electric potentials, and the MAD in the stimulation thresholds of corticospinal track axons.

³MAD is between the heterogeneous, isotropic case and the homogeneous, isotropic case.

⁴MAD is between the heterogeneous, anisotropic cases and the heterogeneous, isotropic case.

⁵MAD is between the heterogeneous, anisotropic case with *load preservation* and the same case with dielectric dispersion