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Role of Soft-Tissue Heterogeneity in Computational Models of Deep Brain Stimulation

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Abstract

Background—Bioelectric field models of deep brain stimulation (DBS) are commonly utilized in research and industrial applications. However, the wide range of different representations used for the human head in these models may be responsible for substantial variance in the stimulation predictions.

Objective—Determine the relative error of ignoring cerebral vasculature and soft-tissue heterogeneity outside of the brain in computational models of DBS.

Methods—We used a detailed atlas of the human head, coupled to magnetic resonance imaging data, to construct a range of subthalamic DBS volume conductor models. We incrementally simplified the most detailed base model, and quantified changes in the stimulation thresholds for direct activation of corticofugal axons.

Results—Ignoring cerebral vasculature altered predictions of stimulation thresholds by < 10 %, whereas ignoring soft-tissue heterogeneity outside of the brain altered predictions between –44 % and 174 %.

Conclusion(s)—Heterogeneity in the soft tissues of the head, if unaccounted for, introduces a degree of uncertainty in predicting electrical stimulation of neural elements that is not negligible and thereby warrants consideration in future modeling studies.

Keywords

deep brain stimulation; electric field; heterogeneity; vasculature; soft tissues

Introduction

Magnetic resonance image (MRI)-based bioelectric field models of the human head show promise for optimizing deep brain stimulation (DBS) therapies [1]. These models typically

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Conflict of Interest Statement

CCM is a paid consultant for Boston Scientific Neuromodulation, and is a shareholder in the following companies: Surgical Information Sciences, Inc.; Autonomic Technologies, Inc.; Cardionomic, Inc.; Enspire DBS, Inc.; Neuros Medical, Inc.

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use finite element methods to solve for the electric field generated during DBS and are coupled to cable models of axons to quantify the neural response to stimulation. However, a wide range of different model representations for the human head are currently used in both academic and industrial research. We hypothesized that these volume conductor differences are responsible for substantial variance in model predictions.

Recent studies have identified the degree of heterogeneity and anisotropy that is required to accurately model the electric field in the human head [2], while others have highlighted the importance of accurately representing boundary conditions in models of DBS [3, 4]. Therefore, the goal of this study was to integrate the latest advancements in anatomical and electrical DBS modeling to identify the role of cerebral vasculature and soft-tissue heterogeneity outside the brain on the neural response to stimulation. We used a highly detailed multimodal image-based anatomical model of a human head and neck, or MIDA, which was recently made available by the FDA [5], as a template for constructing a range of subthalamic DBS models. The degree of model detail ranged from complex to simple and enabled us to quantify errors in predicting the neural response to DBS that are associated with ignoring cerebral vasculature and soft-tissue heterogeneity outside the brain.

Material and Methods

The methodology in this study was adopted from our previous work [2] with specific integration of MIDA atlas volumes [5].

Image processing

All images, unless specified otherwise, were processed using the FMRIB software library (FSL) v5.1 [6]. MIDA contains locations of 116 anatomical structures [5]. Our base case, MIDA₁₂, was constructed by combining the 116 structures into 12 electrically equivalent classifications: dura, grey matter, white matter, CSF, muscle, tendon, bone, fat, dry skin, intervertebral disks, blood, and air. Subsequently, these 12 regions were combined in different ways to form four simplified anatomical representations: MIDA₁₁, MIDA₇, MIDA₆, and MIDA₁ (figure 1a). MIDA₁₁ was derived from MIDA₁₂ by substituting the voxels of blood with the mode type of tissue across the 26 nearest neighbors, with replacement. If the mode was blood, the voxel of blood was replaced by the majority constituent, which was grey matter and muscle inside and outside the brain, respectively. MIDA₇ and MIDA₆ were derived from MIDA₁₂ and MIDA₁₁, respectively, by constructing a partial skull that enclosed the brain and combining all other regions outside the skull into a lumped soft-tissue region. We constructed the partial skull by dilating the brain mask and subtracting the dilated and original masks so that the resultant shell was contained within but not outside the portion of the skull that surrounded the brain. We constructed MIDA₁ by treating the entire head as a homogeneous, isotropic conductive medium, minus the encapsulation sheath (see below).

The MR images used to construct MIDA are not publically available. Therefore, we co-registered MIDA to the MNI 152 standard space using a 12-parameter affine transformation. The inverse transformation was used to map a probabilistic atlas of a subthalamic nucleus (STN) [7] from MNI space to MIDA; we thresholded the atlas so that the volume of the STN

was $\sim 150 \text{ mm}^3$ [8]. We also used a 12-parameter affine transformation to co-register MIDA to the diffusion-weighted (DW) MR image of the healthy subject from FSL's course data. The DW image, which underwent eddy-current and susceptibility corrections, was used to help define anisotropy within the brain.

Bioelectric field models

We constructed five bioelectric field models corresponding to the five different anatomical representations that we derived from MIDA. We used Seg3D [9] to construct tessellated surfaces that bounded the brain, skull, and soft-tissue volumes of MIDA_{7/6}. Next, we modeled the Medtronic 3389 DBS electrode array; the electrode array was placed within the right STN (figure 1b) and enclosed by a 0.5 mm thick layer of encapsulation tissue [10, 11]. Finally, we used COMSOL Multiphysics v5.1 (COMSOL Inc., Burlington, MA) to construct tetrahedral meshes within the aforementioned volumes. The union of all three meshes was the tetrahedral mesh used for all five head models.

For each head model, the corresponding anatomical representation was used to help define a conductivity tensor (Σ) for all elements comprising the tetrahedral mesh. Anatomical representations originally derived from MIDA had voxels that were $0.5 \text{ mm} \times 0.5 \text{ mm} \times 0.5 \text{ mm}$, but due to memory constraints in defining the tensor field, we down-sampled the images to $1 \text{ mm} \times 2 \text{ mm} \times 2 \text{ mm}$. Σ s within the parenchyma and CSF of the brain were modeled as anisotropic. The eigenvectors of these Σ s were derived from the fitted diffusion tensors of the DW MR image, and the load preservation approach from [2] was used to calculate eigenvalues of Σ given an isotropic conductivity (σ) and eigenvalues of the diffusion tensors. Σ s in all other regions, including the encapsulation tissue, were isotropic. That is, $\Sigma = \sigma \mathbf{I}$, where $\mathbf{I}$ is the identity matrix. The σ s for each tissue type were the measured conductivities from [12] at 1 kHz. The exceptions were the encapsulation, dura and air, which had a σ of 0.13 S/m [13], 0.03 S/m [14], and 1×10^{-12} S/m, respectively. The σ of the homogeneous isotropic regions in MIDA₇, MIDA₆, and MIDA₁ were chosen so that the electrical load of contact 2 matched that of MIDA₁₂ (precision $< 0.1 \%$). The electrical load was the access resistance of the electrode plus the dynamic load of the electrode-tissue interface (see below) for a 70 μs stimulus pulse, thereby matching the calculation of Medtronic IPGs.

We used the finite element method to solve Laplace's equation for monopolar and bipolar electrode configurations. In the monopolar case, electrode 2 was the cathode, and the outer boundary of the head was insulated, except at the base of the neck, which was set to ground. In the bipolar case, electrodes 2 and 3 were the cathode and anode, respectively, and the entire head was insulated.

We approximated the spatiotemporal distribution of potentials by scaling the spatial distribution of potentials at time equals zero with the solution of an equivalent circuit representation of the model [2]. The surface area of each contact is $\sim 5.98 \text{ mm}^2$. Assuming each electrode had a specific double-layer capacitance (c_{dl}) and specific Faradaic resistance (r_f) of 30 $\mu\text{F}/\text{cm}^2$ and 150 Ωcm^2 , respectively [15], the equivalent C_{dl} and R_f were 1.8 μF and 2.5 k Ω , respectively.

Axonal models

Trajectories of 1000 descending corticofugal (DCF) axons (figure 1b) that coursed through the internal capsule were taken from a tractographic atlas [16] available in Lead DBS [17]. The tracts were originally defined in MNI space, so we mapped them to MIDA space using the inverse of the affine transformation described in Image Processing. Each streamline was used to represent the trajectory of a multi-compartment cable axon model. The NEURON (v7.3) simulation environment [18] was used to implement cable models of myelinated axons. The axons models were $3\mu\text{m}$ in diameter and modified from [19]. The stimulus waveform was a 130 Hz train of asymmetric rectangular pulses. Each pulse consisted of a short $60\mu\text{s}$ cathodic phase, an interphase delay of $80\mu\text{s}$, and a secondary $\sim 367\mu\text{s}$ passive discharge phase (figure 1c), matching the temporal dynamics of Medtronic IPGs.

Results

Electrical loads predicted in the base case, MIDA_{12} , were $1.26\text{ k}\Omega$ and $1.61\text{ k}\Omega$ in the monopolar and bipolar stimulation cases, respectively, which are representative of clinical measurements [20, 21]. Stimulation thresholds for evoking a muscle twitch in subthalamic DBS are typically around 5 V [22]. MIDA_{12} predicted that between $\sim 0\%$ and 45% of DCF axons were activated with monopolar stimulation at 5 V and 10 V , respectively, also consistent with a previous study [23].

Altering heterogeneity across the different models had a marked effect on how the potentials decayed throughout space, thereby affecting not only their magnitude but also their shape (figure 2b). These field-shaping effects led to both under- and overestimation of stimulation thresholds in MIDA_{11} , MIDA_7 , and MIDA_6 compared to MIDA_{12} , whereas all thresholds were overestimated in MIDA_1 .

The error analysis on the stimulation thresholds was focused on axons whose stimulation amplitudes were $\sim 10\text{ V}$ in MIDA_{12} . Errors in the monopolar case ranged from $-0.2 - +7.8\%$, $-44 - +174\%$, and $-92 - +637\%$ in MIDA_{11} , MIDA_7 , and MIDA_1 , respectively, when the load was matched. The median absolute error in these three cases was 1.3% , 12% , and 378% , respectively. Errors were markedly less in the bipolar case compared to the monopolar case (figure 2d); compared to altering the electrode configuration, errors were less sensitive to a change in fiber diameter and even less sensitive to changes in pulse width (figure 2e).

Discussion and Conclusions

The goal of this study was to determine if the cerebral vasculature and heterogeneity in the soft tissues outside of the brain could be ignored in computational models of DBS. Replacement of blood vessels with other tissues had a negligible effect on model predictions. However, combination of all the soft tissues into a single homogeneous and isotropic medium, as is commonly done in DBS models, had a non-negligible effect that should not be ignored, especially if attempting to generate patient-specific predictions on associations between neural activation and stimulation parameter settings.

We found that simply matching the electrical load of the volume conductor across differing levels of model complexity did not guarantee accurate results. Therefore, matching the predicted electrical load in the model to an electrical load measured clinically cannot compensate for a lack of anatomical detail in the patient's head model. Nonetheless, we propose that matching electrical loads can still be useful. There is, for example, a fair amount of uncertainty in the parameters defining the glial scar. Post-mortem studies in humans and cats have established ranges for the thickness and conductivity of the glial scar that surrounds the DBS lead [10, 13, 24], but the exact geometry and conductivity of the scar are likely to vary across patients, and over time. Errors in $MIDA_1$ were the largest, more specifically, when σ was a typical value (i.e., 0.2 S/m) used when modeling a homogeneous, isotropic brain; but errors were reduced by choosing σ so that the electrical loads of $MIDA_1$ and $MIDA_{12}$ were matched. Thus, parameterizing the glial scar so that the predicted and measured electrical loads match will likely reduce errors in model predictions.

Current standards for anatomical complexity in computational models of DBS lie somewhere between $MIDA_6$ [25] and $MIDA_1$ [26]. Constructing a patient-specific DBS model, analogous to $MIDA_{12}$ is not readily achievable because it takes a team of trained experts and years of time to generate the anatomical segmentations found in MIDA [5], so a compromise is needed. Prior works [23, 27], as well as this one, show that models like $MIDA_1$ largely misestimate the extent of activation compared to models that incorporate heterogeneity and anisotropy in the brain. Further, image-processing tools, such as FSL, are freely available. Therefore, we propose that models like $MIDA_{11}$ and $MIDA_6$ are recommended for research teams focused on constructing accurate models of clinical DBS. We have found that a model like $MIDA_{11}$ can be approximated by warping the non-brain region of MIDA to that of a *de novo* patient; but if a reasonable warping is not possible, models like $MIDA_6$ are still a better alternative than simplified models, like $MIDA_1$.

Models like $MIDA_{11}$ and $MIDA_6$, however, are not without their limitations. In this work, all models were based on MIDA, which was used as a proxy for ground truth; but like any atlas, it is imperfect and subject to its own limitations, such as segmentation errors and subject-specific anatomical anomalies. Additionally, uncertainty in the electrical parameters of the model will continue to be a source of variance in model predictions. Given such limitations, the next step of development should be to experimentally test the predictions of $MIDA_{11}$ level models on a patient-specific basis to evaluate their accuracy.

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Figure 1.

Models of subthalamic DBS. (a) Computational models were derived from five electrical representations of MIDA [5] (sagittal views). MIDA₁₂ is MIDA combined into 12 electrically equivalent classifications. MIDA₁₁ is MIDA₁₂ but without blood (see *Image Processing*). MIDA₇ and MIDA₆ were derived from MIDA₁₂ and MIDA₁₁, respectively, by combining six regions and portions of the skull into a single soft-tissue (ST) region. MIDA₁ was constructed by treating the entire head, as a homogeneous and isotropic medium. (b) The Medtronic 3339 lead was implanted in the subthalamic nucleus (STN) and used to stimulate descending corticofugal (DCF) axons. A 0.5 mm thick encapsulation sheath surrounded the lead. The applied potentials reflect monopolar cathodic stimulation at an amplitude of -1 V. (c) The voltage drop across the electrical load of the head over time.

Figure 2.

Errors from simplifying MIDA₁₂. (a) Stimulation thresholds (V_{th}) of corticofugal axons in MIDA₁₂ (log₁₀ scale). MP = monopolar, BP = bipolar. (b) Left: the potentials (Φ) and second difference of the potentials ($\delta^2\Phi$) across the nodes of Ranvier during monopolar stimulation for an axon with a minimum electrode-to-axon distance (r_{ea}) of 4.4 mm. Right: the ratio (log₂ scale) of the maximum $\delta^2\Phi$ of MIDA₁₁ (*top-right*), MIDA₇ (*middle-right*), or MIDA₁ (*bottom-right*) to that of MIDA₁₂. (c) The relative errors in V_{th} , on an axon by axon basis, versus r_{ea} . The conductivities of the lumped regions in MIDA₇, MIDA₆, and one version of MIDA₁ (*left*) were chosen so that the electrical load of contact 1 matched that of MIDA₁₂. Dashed red line = median absolute error. (d) The same as c except for bipolar stimulation. (e) Sensitivity of errors to changes in pulse width and fiber diameter for MIDA₆ vs. MIDA₁₂.