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Theoretical Optimization of Stimulation Strategies for a Directionally Segmented Deep Brain Stimulation Electrode Array

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Abstract

Goal—Programming deep brain stimulation (DBS) systems currently involves a clinician manually sweeping through a range of stimulus parameter settings to identify the setting that delivers the most robust therapy for a patient. With the advent of DBS arrays with a higher number and density of electrodes, this trial and error process becomes unmanageable in a clinical setting. This study developed a computationally efficient, model-based algorithm to estimate an electrode configuration that will most strongly activate tissue within a volume of interest.

Methods—The cerebellar-receiving area of motor thalamus, the target for treating essential tremor with DBS, was rendered from imaging data and discretized into grid points aligned in approximate afferent and efferent axonal pathway orientations. A finite-element model (FEM) was constructed to simulate the volumetric tissue voltage during DBS. We leveraged the principle of voltage superposition to formulate a convex optimization-based approach to maximize activating function (AF) values at each grid point (via three different criteria), hence increasing the overall probability of action potential initiation and neuronal entrainment within the target volume.

Results—For both efferent and afferent pathways, this approach achieved global optima within several seconds. The optimal electrode configuration and resulting AF values differed across each optimization criteria and between axonal orientations.

Conclusion—This approach only required a set of FEM simulations equal to the number of DBS array electrodes, and could readily accommodate anisotropic-inhomogeneous tissue conductances or other axonal orientations.

Significance—The algorithm provides an efficient, flexible determination of optimal electrode configurations for programming DBS arrays.

Index Terms

Deep Brain Stimulation; DBS; Programming; Computational Models; Essential Tremor; Parkinson's Disease; Electrode Arrays; Optimization

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I. Introduction

Deep brain stimulation (DBS) is an effective surgical procedure for the treatment of a number of neurological and neuropsychiatric disorders, including medication-refractory Parkinson's disease (PD), essential tremor (ET), dystonia, and severe obsessive compulsive disorder [1]. The procedure involves the placement of a lead of electrodes into a precise brain region to modulate abnormal neuronal activity with various forms of pulsatile electrical stimulation. Successful treatment is characterized by both symptom suppression and lack of side-effects. Such success requires accurate lead placement as well as spatially targeted stimulation settings to avoid activating regions that elicit, for example, adverse motor [2], sensory [3], and cognitive [4] side-effects for the patient. Traditional designs of the DBS lead implant (for example, the Medtronic model 3387/3389) use four cylindrical electrodes to deliver current in an omnidirectional fashion around the lead. A major improvement to this existing design would be enabling one to direct or steer current both along and around the DBS lead. This feature would be especially useful in cases of off-target DBS implants [5], [6] and for small or complex-shaped brain targets, such as the pedunculopontine nucleus [7], [8] for treating freezing of gait in patients with PD.

Several designs for high-density DBS arrays (DBSAs) with circumferentially-segmented electrodes have been advanced in recent years through computational studies [5], [8], [9] and *in-vivo* studies in non-human primates (NHPs) [6] and humans [10], [11], [12]. Here, we modeled DBS leads with 32 oval shaped electrodes arranged in 8 rows of 4 electrodes each, radially separated by 90° [6], [5], [8]. The surface areas of the DBSA electrodes were a fraction of the size of cylindrical electrodes found on commercial leads and have potential for improving the spatial resolution of targeting modulation of neuronal activity within the brain to improve overall therapy.

The safety and efficacy of current shaping technology has recently been investigated clinically using leads with annular [12] and circumferentially-segmented [10], [11] designs. In the latter case, therapeutic current thresholds were 43% lower with a radially directed stimulation scheme compared to the omnidirectional scheme [10]. Further, the 'therapeutic window' (difference in current thresholds to produce a meaningful symptom suppression and to sustain a side-effect) was the widest when using radially directed stimulation [10], [11]. Current shaping along the length of the DBS lead in patients with ET has also been shown to better alleviate stimulation-induced dysarthria while preserving tremor control [12]. The challenge with such current shaping approaches, however, especially in the case of DBSAs, is the number of possible electrode configurations and size of the stimulation amplitude, frequency, and pulse width parameter space [5].

Optimal programming of a DBSA has potential to improve treatment benefit and expedite the programming process. The current framework for programming the stimulation settings of DBS leads with four annular electrodes typically begins with evaluation of each contact using monopolar stimulation at fixed frequencies and pulse widths [13], [14]. The setting that requires the lowest stimulation amplitude to maximize therapy and/or has the widest therapeutic window is set for chronic stimulation unless persistent adverse side-effects are observed, in which case bipolar or multipolar stimulation configurations may be explored by

combining the chosen contact with adjacent contact(s). The programming process can be time consuming [15], especially in cases when low-threshold side-effects appear. Furthermore, relying on direct patient feedback for programming may not be feasible for disorders in which the therapeutic benefits may not emerge for weeks to months after starting stimulation [16], [17]. The efficacy of this programming method is also influenced by other factors, such as the intuition and experience of the DBS programmer, as well as the time allotted to each patient [18]. To explore the vast parameter space of the DBSA using this manual method of programming would not be feasible, since each additional electrode would prolong programming time in a nonlinear fashion and also pose a steeper learning curve. In addition, this method of programming four-electrode leads may underutilize the full potential of the DBSA to deliver optimal stimulation through a combination of active electrodes [19], [20].

Alternative programming approaches have been proposed aimed at increasing the efficiency of the process. One such approach uses a probabilistic efficacy atlas derived from intraoperative microstimulation response data [21]. The atlas is nonlinearly warped onto the pre-operative magnetic resonance imaging (MRI) data (co-registered to post-operative CT) to guide programming. This approach requires substantial accumulation of intraoperative patient data which is not readily accessible to the larger neuromodulation community. In addition, individual brain anatomy can vary substantially [22] and an entirely empirical approach may not be adequate.

Another proposed method estimates the volume of tissue activated (VTA) [23], [24], [25] from a particular DBS setting by simulating an activating function [26] derived from a finite element model solution of the tissue voltages along the neuron membrane compartments during DBS. In this case, DBS lead positions within the nucleus or fiber tract are dictated by the co-registration of a patient's pre-operative magnetic resonance (MR) brain imaging with post-operative MR imaging or computed tomography scan data. The benefit of this approach is that it provides direct visualization of the neuronal pathways that are modulated for a given stimulation setting [27].

The second spatial derivative of the extracellular voltage potential, or activating function (AF), generated through the DBS lead is the driving force behind action potential initiation in neuronal processes [26] and can be used to predict the VTAs [28]. However, AF thresholds for neuronal activation depend on axon orientation and distance from the stimulation source [29]. An alternative approach is to apply the AF to compartment neuron models [30] in a target region, which can have detailed morphologies and biophysical parameters, and then find the stimulus amplitudes to initiate an action potential [28]. Such biophysical models, usually performed in the NEURON programming environment [31], can provide additional information about neuronal activation that AF alone may not describe, but this process can be time consuming and computationally intensive. In order to obtain the patient-specific stimulation strategy solutions, thousands of such simulations using different electrode configurations, axon orientations and locations must be run ahead of time, and the VTA solutions must be precompiled and stored [27]. Due to the resource-intensive and time consuming nature of this approach, it may not be readily accessible to the broader research and clinical community.

In this study, we propose an algorithm that leverages the superposition of the activating function, thus requiring only a set number (equal to the number of electrodes) of anatomical FEM simulations to be run. By combining this with the principles of convex optimization, we formulate an approach that maximizes the AF values in the volume of interest. We consider three separate optimization criteria that may be used with this approach. Overall, the methods presented here bypass the need to run extensive simulations of neuronal activation, providing an automated, computationally efficient way to patient-specific programming of a DBSA implant.

II. Methods

We constructed a computational model of motor thalamic DBS using current-controlled stimulation using non-human primate MRI data (Fig. 1). High frequency stimulation of the ventral intermediate nucleus of thalamus (Vim) in humans can suppress tremor, while persistent paresthesias is thought to emerge from activation of the adjacent sensory thalamic nucleus (ventral posterolateral nucleus of thalamus/VPL) [32]. In the non-human primate, the equivalent nuclei to Vim and VPL are the oral (VPLo) and caudal (VPLc) ventral posterior lateral nuclei of thalamus, respectively [33]. We reconstructed both VPLo and VPLc and modeled independent current-controlled stimulation through each DBSA electrode ($n=32$). Volumes were discretized into points arranged in a grid pattern, with anatomically realistic afferent and efferent fiber orientations. We show a theoretical maximum AF value for each grid point, which forms a theoretical maximum curve (Max Curve) that cannot be surpassed. We take advantage of the principle of voltage superposition to achieve AF values as close as possible to this Max Curve through the use of convex optimization algorithms (Fig. 2).

A. Reconstruction of Thalamic Nuclei and DBSA

High field magnetic resonance imaging (7T, Magnex Scientific) was performed on a female rhesus macaque monkey (*macaca mulatta*) under isoflurane anesthesia at the University of Minnesota's Center for Magnetic Resonance Research using a Siemens console. All procedures were approved by the University of Minnesota's Institutional Animal Care and Use Committee and complied with United States Public Health Service policy on the humane care and use of laboratory animals. A customized head coil was developed with 16-channel transmit and 16+6 receive channels, in which 4 coils mounted on top of the subject's head and 2 ear-loop coils were added to enhance signal detection from subcortical structures [34]. Susceptibility-weighted imaging (SWI) data was acquired with a 3D flow-compensated gradient echo sequence. SWI data was aligned to the anterior commissure (AC)-posterior commissure (PC) plane (Analyze 11.0, AnalyzeDirect) and resliced into serial coronal sections with 40 coronal images spanning the thalamus. Matching plates from a rhesus macaque brain atlas [35] were nonlinearly deformed [36], [37] to the coronal MR images, and the contours of VPLo and VPLc within each were extracted. These contours were imported into a B-spline modeling program (Rhinoceros) and arranged serially at an interval of 0.4 mm (voxel size) along the anterior-posterior direction. The contours were then lofted into 3D surfaces.

B. Finite Element Model of stimulation through the DBSA

The DBSA (NeuroNexus, Ann Arbor, Michigan) consisted of 8 rows of 4 elliptical electrodes (semi-major axis: 0.265 mm; semi-minor axis: 0.14 mm). The lead was 0.5 mm in diameter and 40 mm in length. The angular distance between adjacent electrodes in the same row was 90° and the distance between two adjacent rows of electrodes was 0.75 mm. A 0.1×40 mm (thickness $\times$ height), 0.18 S/m homogeneous encapsulation layer and a 100×100 mm (diameter $\times$ height), 0.3 S/m cylinder of homogeneous bulk tissue surrounded the lead [38], [39], [40]. The DBSA electrodes and insulation were assigned conductance values of 10^6 S/m and 10^{-12} S/m, respectively. The electrode surfaces were designated as boundary current sources and the walls of the bulk tissue cylinder were set to ground. The voltage distributions resulting from electrical stimulus perturbations were calculated via the finite element method solving Poisson's equation in COMSOL Multiphysics (v4.3b). Simulations of monopolar cathodic (-1 mA) stimulation were performed with each of the electrodes acting as the cathode ($n=32$).

C. Discretization of Thalamic Volumes

A 3D reconstruction of the DBSA geometry was created in Rhinoceros and placed within the VPLo close to its lateral border with VPLc such that the electrodes spanned the length of the VPLo. The trajectory of the lead was 77° above the horizontal plane and 10° from the sagittal plane [41] (Fig. 1). The electrodes were assigned indices from 1 to 32, such that the contacts facing posterior, medial, anterior, and lateral were labeled 1, 2, 3 and 4, respectively. This order of labeling was maintained in every row, with indices increasing along the vertical direction. The lead, VPLo, and VPLc were then rotated together such that the center of the first row of electrodes was consistent with the FEM model. The rotation matrix (T_{AF}) was stored for this change in a coordinate system from AC-PC to FEM model coordinates.

The afferent fiber orientations into VPLo and VPLc are about 45° from the intercommissural line in the coronal plane and 60° in the sagittal plane [42]. The efferent fiber orientation from VPLo and VPLc to cortex follows a ventral-medial to dorsal-lateral direction approximately 45° from the intercommissural plane in the coronal direction [43, 44]. At the scale of the grid spacing used in this study, the thalamus is generally considered to be an isotropic structure [40]. The surfaces of the DBSA, VPLo, and VPLc were generated in Rhinoceros and the vertices of these surfaces were imported into the Matlab programming environment (v2013b, MathWorks) using the AC-PC coordinate system. The vertices of thalamic volumes were rotated (rotation matrix T_j) such that either the afferent or efferent fiber directions were oriented in the z-direction. A 3D rectangular grid consisting of multiple layers spanning the z-direction was constructed for each volume. Each layer spanned the maximal extent of the volume in the x and y directions and consisted of 10,000 points (100×100) in total. An additional layer was added to either side of the existing grid for calculating AF values. These grid points were arranged in this way to represent axonal node compartments. The distance between layers of grid points was 0.5 mm in both the efferent and afferent directions, consistent with internodal distances of myelinated axons used in previous studies [19]. The coordinates of these grid points were transformed into AC-PC

space by multiplying T_f^{-1} (Fig. 3) and then were transformed into the FEM model space by multiplying T_{AF} . Data regarding the discretization process are listed in Table I.

D. Activating Function Values and Construction of the Max Curve

Using each FEM model solution stored previously, the activating function values for each grid point along the fiber direction was calculated using the following formula:

$$\frac{\partial^2 V}{\partial x^2} = \frac{V(x+\Delta x) - 2V(x) + V(x-\Delta x)}{\Delta x^2} \quad (1)$$

where x is a position along the direction of fibers, V is the voltage value as a function of position, and Δx is the internodal distance. The AF values for grid points within the layers at either end cannot be calculated and these points are therefore discarded. Points that overlap spatially with the DBSA are also discarded. The AF values for the remaining n points can be stored in a $32 \times n$ matrix C :

$$C = \begin{pmatrix} \nabla_{1,1}^2 & \cdots & \nabla_{1,n}^2 \\ \vdots & \ddots & \vdots \\ \nabla_{32,1}^2 & \cdots & \nabla_{32,n}^2 \end{pmatrix} \quad (2)$$

where the i^{th} row contains the AF values resulting from stimulation through the i^{th} electrode alone, delivering -1 mA monopolar cathodic current. Poisson's equation in electrostatics dictates that the tissue voltage distribution is related to the current by:

$$\nabla \cdot \sigma \nabla V = -I \quad (3)$$

where σ is the tissue conductance, and I is the current. From (3) it is possible to derive that

$\frac{\partial^2 V}{\partial x^2} \propto I$. Along with (1), it can be shown that the AF values resulting from multiple voltage sources can be linearly superimposed. To find the maximum possible AF value at a given grid point from any possible electrode configuration (subject to a 1 mA power constraint), we can consider the following thought experiment: suppose there are n different categories of items that can be manufactured, each with the same cost but different profit margins. For a given manufacturing budget, the highest profit achievable occurs when the entire budget goes into manufacturing the most profitable item. Likewise, it can be readily shown that the highest possible AF value achievable at each grid point is obtained when stimulating through a single electrode using the entire 1 mA of current. Therefore the maximum value in each column (j) of the C matrix is the theoretical maximum AF value possible for grid point j . The maximum AF values are sorted in ascending order and arranged into the Max Curve. Each grid point represents the center of a membrane compartment. Positive AF values are responsible for directly depolarizing the cell membrane and considered here as potential initiation sites for action potential generation [26]. Negative AF values represent direct hyperpolarization of the cell membrane and thus limit the likelihood of generating action potentials. The goal as defined in this study was to obtain the highest AF value possible at each grid point within VPLo. This corresponds to maximizing proximity to the Max Curve.

E. Convex Optimization

The volume activation problem can thus be framed conceptually as follows: “How do we bring as many of the grid points as close as possible to their corresponding maximum AF values on the Max Curve?” To formulate this problem mathematically, we applied the principle of superposition to denote the AF values due to a given electrode configuration:

$$AF_j = C_j^T I \quad (5)$$

where I is the 32×1 vector of currents through each electrode, and AF_j and C_j are the AF value and column of C corresponding to grid point j . Together, the AF values resulting from stimulation at each grid point can form another curve called the Actual Curve. At each grid point j , the difference between the maximum AF value and the actual AF value from stimulation with I is given by the following:

$$AF_{j,max} - AF_j = C_{j,max} - C_j^T I \quad (6)$$

Using (6) as a measure of discrepancy between the Max Curve and the Actual Curve, we can set the objective to minimize discrepancy. Specifically, we considered three different optimization criteria using three different measures of discrepancy between the two curves. For simplicity, we have used constraints in all three cases that the currents through any of the 32 electrodes be greater or equal to zero and that the sum of all currents through the electrodes be equal to 1mA. The latter constraint was arbitrarily defined and can be adjusted as necessary in the context of using total current amplitudes that do not express stimulation-evoked side effects. Using only the difference between the Max Curve and Actual Curve as a measure, the problem can be solved by linear programming (LP) as follows:

$$\begin{aligned} &\text{minimize: } \sum (C_{j,max} - C_j^T I) \\ &\text{subject to: } \sum I_k = 1 \text{ and } I_k \geq 0, \text{ for all } k \end{aligned}$$

Using the square of the difference between the two curves, the problem can be solved by quadratic programming (QP):

$$\begin{aligned} &\text{minimize: } \sum (C_{j,max} - C_j^T I)^2 \\ &\text{subject to: } \sum I_k = 1 \text{ and } I_k \geq 0, \text{ for all } k \end{aligned}$$

Finally, the maximum deviation (MD) between the two curves as a criterion to minimize is given by:

$$\begin{aligned} &\text{minimize: } \max_j (C_{j,max} - C_j^T I) \\ &\text{subject to: } \sum I_k = 1 \text{ and } I_k \geq 0, \text{ for all } k \end{aligned}$$

For linear programming, quadratic programming, and maximum deviation minimization via convex optimization, the problem is well-posed and has a unique, global minimum. Here, we considered all three of these criteria separately (LP, QP, and MD), and implemented the

optimization in MATLAB (v2013b) using the cvx package for solving convex optimization problems [45]. All computations and performance assessments were run on a PC with eight cores, 64-bit operating system, 24.0 GB RAM, and an Intel Core i7 processor at 3.40 GHz. To verify optima were reached, one million random electrode configurations were generated, and their corresponding discrepancy measures were obtained to construct noise histograms for each of the three methods.

F. Runtime and Sampling Robustness

We ran the algorithms on random subsets of grid points to assess (1) the algorithm's runtime with respect to number of grid points used, and (2) the robustness of electrode configuration solutions with respect to sampling. Each of the three optimization criteria (MD, QP, LP) was used on random subsets of the efferent VPLo grid points. The random subsets consisted of eight sampling levels: 1/2, 1/4, 1/8, 1/16, 1/32, 1/64, 1/128, and 1/256 of the total number of grid points within the volume. We obtained and ran 31 random subsets of grid points for each sampling level. The resulting electrode configurations were assessed based on the average height and angle of the active electrodes. The runtime was also measured. This yielded 31 measurements of height, angle, and runtime for each sampling level.

III. Results

A. Electrode Configurations

The optimal current output in the efferent and afferent cases is shown graphically in Figs. 4 and 5, respectively. In both cases, MD had the most active contacts, while LP had the least (contacts delivering 1 μ A or more current were considered active). The distribution of current amongst the active contacts was fairly uniform in the MD criterion solutions and less so in the QP criterion solutions. In the efferent case, the mean current output was 0.067 ± 0.037 mA per electrode (mean $\pm$ std) for the MD solution and 0.091 ± 0.104 mA per electrode for the QP solution. In the afferent case, the mean current output was 0.072 ± 0.043 mA per electrode for the MD solution and 0.2 ± 0.147 mA per electrode for the QP solution. In the efferent case, the active electrode contacts faced the anterior or posterior directions primarily. In the afferent case, most active electrodes faced medially or laterally. In the case of the LP solution, for both efferent and afferent cases, the entire 1 mA current was applied through only one contact, as expected from the previously mentioned thought experiment.

B. Activating Function Values

The algorithm AF solutions were based on grid points in VPLo and were optimized to achieve proximity to the VPLo Max Curve. The resulting AF values for both VPLo and VPLc are summarized in Table II and shown graphically in Fig. 6. Not surprisingly, higher AF values were concentrated near the active electrodes. In both the efferent and afferent cases, the MD, QP and LP solutions produced successively tighter concentrations of larger AF values along the length of the thalamic nuclei. The MD solution AF values exhibited the least amount of spread both spatially and numerically. The LP solution, on the other hand, exhibited the most spread, the largest mean, and the largest maximum AF values, but also produced the lowest AF values within VPLo. Fig. 7 illustrates the proximity of the actual AF values to the Max Curve for VPLo grid points. The LP solution had many points that

achieved their maximum value, though a relatively large variation in AF values was once again evident across grid points. In contrast, very few grid points from the MD and QP solutions achieved their maximum values, but there was relatively less variation in AF values compared to the results using the LP criterion.

C. Optimization Results

Fig. 8 shows three different measures comparing the performances of the MD, QP, and LP solutions to one million random (chance) electrode configurations. Stimulating electrode configurations *I* (three separate criteria solutions and 1 million random solutions) were used to calculate the model predicted actual AF values using (5). The results were arranged into the Actual Curve. The maximum deviation, sum of differences, and square of the sum of differences between the Actual Curve and the Max Curve were calculated. As expected, the MD solution achieved the lowest maximum deviation, the QP solution achieved lowest sum of square of deviations, and LP solution achieved the lowest sum of deviations. Furthermore, within each of these categories, the best-performing solution performed significantly better than chance. While no single optimization solution yielded better-than-chance results across all three measures, MD tended to perform better relative to chance in all categories. QP and LP showed better-than-chance performance for all except the maximum deviation category. The p-values for each category are listed in Table III.

D. Runtime and Sampling Robustness

In terms of runtime (Fig. 9: C,F,I), mean duration for 27,173 efferent VPLo grid points was 3.0 seconds for the MD solution, 3.4 seconds for the QP solution, and 0.2 seconds for the LP solution. Runtime scaled nonlinearly with respect to number of grid points, such that sampling half the grid points reduced runtime by more than half. Using subsets of the full grid points for the computation yielded active electrodes with similar mean height (Fig. 9: A, D, G) and mean angular direction (Fig. 9: B, E, H). However, smaller subsets yielded larger standard deviations of the active electrode heights and directions.

IV. Discussion

Current steering has shown promise for improved therapy in other electrical stimulation technologies such as cochlear implants [46], retinal prostheses [47], spinal cord stimulation [48], and nerve cuff electrodes [49]. With the introduction of higher density DBS arrays, current steering technology has the potential to significantly improve DBS therapy by shaping the electric field toward a target volume while avoiding regions that could induce adverse side effects [1]. In this study, we presented a computationally efficient, mathematically flexible optimization formulation to optimize and shape current delivery through a 32-channel DBSA in order to enhance the probability of neuronal activation within VPLo thalamus. This approach is readily extensible to other DBS lead designs and other DBS targets within the brain.

A. Predicting Neuronal Activation

Several computational methods have been used to predict neuronal activation. The first spatial derivative along the neuronal process has been shown to be appropriate for modeling

activation near the vicinity of the soma [50]. However, computational studies have also shown that the waveforms used in DBS applications are likely to elicit action potentials first in the axons [51], [52] based upon the second spatial derivative of the extracellular voltage along the axonal processes [26], [53]. Such calculations can be performed using spatially distributed multi-compartment neuron models [54] to obtain a VTA. However, this process is computationally intensive. A more efficient approach, as described in this study, is to use the AF values along the estimated direction of neuronal processes to predict the VTA. This method is widely used [6], [28], [55], [56] but still requires large amounts of simulations to be run and the results stored in order to account for different orientations and displacements of neuronal processes from the source(s) of stimulation [19]. Studies have pointed out the limitations to this approach [57] and a novel method for VTA prediction using artificial neural networks (ANN) has been proposed [58], although substantial amounts of simulations are still needed to generate different stimulation scenarios to train the ANN.

Our goal here was to increase the probability of neuronal activation instead of determining the exact activation profile using VTA prediction. We do this by maximizing AF values, taking advantage of well-established theories associating higher AF values with neuronal activation [26] [53]. It is not straightforward to set an exact threshold AF value due to the variation in reported values [6] [9], and the dependence on factors such as fiber orientation and distance of compartments to the active electrode(s) [29]. Nevertheless, the method presented here circumvents such limitations by determining a theoretical maximum AF value at each grid point (Max Curve) given a current input limit. These grid points represent neuronal compartments, each with the ability to initiate an action potential. The goal of our superposition and optimization-based framework is to achieve proximity between the stimulation-induced AF values and the Max Curve. This ultimately aims to increase the probability for action potential initiation or other forms of sub-threshold modulation.

While we used the Max Curve, the algorithm can be readily adapted to activation thresholds, such as a constant AF threshold used in some studies [6], [9], [28] or a nonlinear AF threshold fall-off with respect to distance from the stimulating electrode [29]. Here we selected the Max Curve as the target criteria to compare each grid point against its own theoretical maximum AF value. This avoids certain issues that constant AF thresholds may introduce, such as weighting the discrepancies due to grid points far from the electrodes too heavily. Furthermore, it is possible that certain AF values on the Max Curve are negative, which means that the hyperpolarizing effect would elicit an indirect depolarizing influence on the axons. These points can be omitted from the C matrix so that the algorithm can focus on the remaining points with positive AF values on the Max Curve. Here, we chose to keep these points in this study.

B. Algorithm and Performance

Finding the optimal stimulation strategy for high-density electrode arrays remains a challenge in various electrical stimulation technologies. Manipulation of the amounts of current delivered through each electrode has been shown to shape the spatial distribution of voltage potentials, their gradients [59], and ultimately the VTA [60].

Algorithms for automatic generation of stimulating electrode configurations require well-defined neuronal response measures and an understanding of the underlying mechanisms of action. In cochlear implant studies, the goal is to minimize current spread from activating multiple electrodes so as to reduce the effects of interfering stimulation. Studies have proposed using psychophysical measurements to find the optimal electrode configuration in order to selectively activate a particular neural site [61], [62]. In DBS, the goal has been viewed as one to maximize modulation of neuronal spike activity within a target brain region, while avoiding activation of pathways implicated in the manifestation of side effects. In terms of the former, one of the established approaches is to search through pre-compiled solutions to find the settings that give the most overlap between the VTA and the target volume [63]. For DBS arrays, this approach would require massively large computational resources to calculate this solution. The computational efficiency of our approach arises from circumventing VTA prediction, while maintaining simplicity in user inputs: the power constraint (1 mA in this study), the target volume, and fiber orientations (in order to discretize the volume into grid points aligned in that orientation).

From Table IV, the mean AF values differed depending on the orientation of the fibers. However, this difference was not significant. Within VPLo (Fig. 7/Table IV), the LP solution achieved the highest mean AF values, but also resulted in the largest spread of data (about 2.5–4 times larger than the MD solution, and 1.5–2.3 times larger than the QP solution). Meanwhile, the QP solution produced slightly larger mean AF values than the MD solution in both efferent and afferent cases, and only had a slightly larger spread.

Based on this analysis, the LP criterion would be selected if one was interested in optimizing for the average AF value in the region of interest. Indeed, the LP solution converges on a single electrode, which has the greatest influence on the AF mean value. The LP criterion is mathematically equivalent to maximizing the mean AF values across all grid points. As such, it is expected that some grid points from the LP solution will lie on the Max Curve (as shown in Fig. 7) since all the current is applied to a single electrode and thus certain grid points will achieve their maximum AF and lie on the Max Curve by definition. On the other hand, if one considers generating a more uniform activating function value of the region of interest, the QP and MD criteria would be more appropriate. It is important to note that each criterion is meant to be used independently. What remains is performing the electrophysiological investigation to ascertain which criterion yields the most robust therapeutic effect with DBS.

There are other considerations to factor into this calculation. For one, charge density limits of stimulation at a given electrode may impact the LP approach more than the other two curve fitting approaches, since the LP solution converges on a single electrode. Additionally, the QP and MD criteria require multiple electrodes with independent current controlled stimulators that are not yet widespread clinically.

The optimization approach with MD, QP, and LP criteria each outperformed one million random electrode configurations in their respective measures of proximity to the Max Curve (Fig. 8). However, no single criterion solution yielded better-than-chance performance for all three measures. Indeed, while the LP solution clearly achieved the best performance for

sum of deviations, it also had the worst performance for the other two measures. It is thus important to recognize that the efficiency and mathematical flexibility of these algorithms must be coupled with a clear goal of what are the desired criteria for the resulting AF values. These criteria may depend on patient-specific parameters (e.g. modulating a target uniformly or leveraging activation of a pathway that can have broad synaptic influence over the entire region [5].

The algorithm runtime for each of the MD, QP, and LP criteria was on the order of several seconds for the number of grid points used here, making it feasible for on-site patient-specific clinical use. Runtime scaled nonlinearly with respect to number of grid points (i.e. halving the number of grid points reduced runtime by more than half). However, this nonlinear relation was not very strong. Randomly sampling half the grid points yielded a similar average height and angle of active electrodes, indicating that the algorithm is robust to changes in grid point resolution. However, very small samples (corresponding to low grid point resolutions) resulted in chance electrode configurations, since the spatial extent of the samples was sparse relative to the spatial features of the electric field. The algorithm presented here also allows for fast computation of multiple stimulating electrode configurations using the same DBSA to target different neuronal subpopulations within a target region, as in the case of coordinated reset stimulation [64], [65] to desynchronize pathological oscillations.

C. Study Limitations and Future Work

This study applied the optimization concept using relatively simplistic models to create a controlled environment. One important limitation to this study is the simplicity of the tissue model and its underlying neuron morphologies. For example, the volumes of VPLo and VPLc were discretized in two fixed directions, and the grid points were arranged in serial layers. A more realistic way to discretize the volumes would be to populate them with grid points that are more morphologically realistic [5], [52], [66], [67], [43]. Second, while the activating function was computed with potentials constrained to the approximate axonal trajectories within thalamus, the voltage distribution itself was obtained under the assumption of a homogeneous and isotropic tissue medium. This approximation is reasonable at the grid point spacing considered here [40], though a more realistic model would incorporate conductance inhomogeneity as well as anisotropy through diffusion tensor imaging [68]. The changes would take place in the initial construction of the FEM (e.g. extracting anisotropic and inhomogeneous tissue conductivities from diffusion tensor imaging data), but would not impact the overall efficiency of the algorithm. As such, this framework enables one to readily adapt the model with changing implant environments (e.g. to model edema in acute implants vs. encapsulation in chronic implants). Third, we did not model the voltage drop or capacitance of the electrode-electrolyte interface. Such considerations are important [69], and the optimization algorithms developed in this study are amenable to the inclusion of such complexities as part of future iterations of the algorithm. Another important consideration is that the algorithm in its current form does not include minimization of the AF values in regions deemed to elicit side effects when stimulated, such as VPLc [5], [70], [71]. Such an algorithm, which optimizes both cathodic and anodic currents delivered through the DBSA, is part of a subsequent study.

Validation studies exploring these parameters are needed to clarify this relation between the AF criteria and both electrophysiological changes in the brain and behavioral outcomes in the subject. Studies in the fields of cochlear and retinal implants have demonstrated that current steering can create ‘virtual electrodes’ by differential distribution of current between physical electrodes to elicit percepts intermediate to those produced using monopolar configurations [46], [72]. In DBS, clinical validation studies have shown that stimulation strategies based on computational models can be superior to clinically derived strategies to limit cognitive deficiencies [23] and improve therapeutic outcomes [25].

Electrophysiological studies to validate the model predictions are important and have been limited to date. For one, it is important to consider the spatial distribution of the modulated neuronal firing patterns around the DBS lead [73] [74] and how this varies amongst algorithm-generated stimulus settings and the setting derived from a clinical exam. It is also important to validate the models at a circuit level [75] to compare the ability for a given set of settings to modulate neuronal activity throughout the affected network. Ultimately, it is important to directly measure behavioral outcomes, such as motor capsule side effects [63] and symptom reduction [10] [11], in a clinical setting to determine if the algorithm generated stimulation is more effective and efficient.

V. Conclusion

In this study, we have described an efficient computational algorithm for programming high-density DBSAs using convex optimization. The algorithm departs from the traditional approach of VTA prediction by solely aiming to achieve higher probabilities of neuronal activation within a target volume. The FEM-based nature of this approach allows it to readily accommodate any patient-specific, anisotropic/inhomogeneous data. A limited number of simulations (equal to the number of electrodes) are all that is needed to compute the optimization routine, which in itself requires seconds to compute. Together, this convex optimization-based framework for electrode configuration selection presents a novel approach for on-site patient-specific clinical application.

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Fig. 1. Three-dimensional thalamic nuclei reconstructions were generated from (A) NHP susceptibility-weighted imaging and (B) warped brain atlas overlays. (C) Sagittal and (D) coronal view of the reconstructed VPLo and VPLc with the implanted DBSA.

Fig. 2.

Procedural flowchart for this study. Three different optimization criteria (MD, QP, LP) were considered separately.

Fig. 3. Discretization of thalamic volumes. The top row (A,B) shows the discretization process for the efferent direction while the bottom row (C,D) shows the process in the afferent direction. Both the VPLo and VPLc are shown in coronal orientation. In either case, the left image shows grid points arranged in serial layers spanning either volumes. The red arrow indicates the orientation of the neuronal processes. The right image shows only those grid points that fall within the volume (red points). The internodal distance between successive layers of grid points are shown. (A) and (C): VPLo. (B) and (D): VPLc.

Fig. 4.

Algorithm-generated electrode configurations for the thalamic efferent pathway approximations. The left, middle, and right columns show outcomes from the MD, QP and LP optimization criteria, respectively. Active contacts ($> 1 \mu A$) in each case are shown in red (top row) with the precise amount of current calculated by the algorithm shown in indexed colors (second row). Axial views (third row) and oblique views (fourth row) of VPLo and VPLc are shown in the context of the DBSA with active contacts shown in red.

Fig. 5. Algorithm-generated electrode configurations for the thalamic afferent pathway approximations. Labeling is identical to that described for Figure 4.

Fig. 6.

Comparison of Max Curve (red) to solutions obtained by MD, QP, and LP for efferent (top) and afferent (bottom) data. Grid points in the region of interest are sorted based on their maximum achievable values. For each optimization criterion, the actual value at each grid point is plotted underneath its maximum possible value. Therefore, the closeness of the grid points to the Max Curve is a measure of optimization performance. (A–C) and (G–I): AF values at all grid points are presented in units of V/mm^2 . (D–F) and (J–L): Grid points with AF values less than $-0.01 \text{ V}/\text{mm}^2$ were omitted in these plots. The remaining AF values were made positive by adding 0.01 and the natural logarithm of the resulting values was computed.

Fig. 7.

AF values resulting from DBSA stimulation using algorithm-generated electrode configurations. (A–C): Efferent data, axial view of the AF values resulting from stimulation configurations generated using the MD, QP, and LP criteria, respectively. (D–F): Coronal view of the AF values shown in (a–c). (G–I): Afferent data, axial view of the AF values resulting from stimulation configurations generated using the MD, QP, and LP criteria, respectively. (J–L): Coronal view of the AF values shown in (g–i). For visualization purposes, all AF values greater than -0.01V/mm^2 were made positive by adding 0.01 and the natural logarithm of the resulting values was computed. The logarithm values were used as indexed colors. The color bar in this figure ranges from -6 to -3 in logarithm values. Points with values outside of this range were directly assigned the values of -6 or -3 . Points with AF values less than -0.01V/mm^2 were assigned logarithm values of -6 . Refer to Figure

1(D) for borders between VPLo and VPLc in the coronal view. Refer to Figure 4 or 5 for the border in the axial view.

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Fig. 8.

Performance comparison of MD, QP, and LP to one million random electrode configurations (gray normalized histogram), in efferent and afferent data. The three measures considered (Max Deviation, Sum of Squares, Sum) each indicate deviation from maximum possible activating function values. Thus, lower values correspond to better performance.

Fig. 9.

Comparison of runtime and sampling robustness for MD, QP, and LP. The original number of grid points for efferent data was 27,173. For each level of sampling ($1/2$, $1/4$, etc.) a random subset of the original points were selected. (A, D, G) Average height of active electrodes with respect to multiple sampled subsets. Standard deviation of height progressively increases as smaller subsets of original points are used. (B, E, H) Average angular direction of active electrodes. Similarly to average height, standard deviation increases toward random distribution. (C, F, I) Runtime and logarithm of runtime with respect to sampling.

TABLE I

Volume Discretization Data

Efferent Data		
	Total Grid Points	Number of Grid Points in C matrix
VPLo	17×10^4	27173
VPLc	17×10^4	34059
Afferent Data		
	Total Grid Points	Number of Grid Points in C matrix
VPLo	11×10^4	20836
VPLc	14×10^4	25010

Table II

Activating function Values

Efferent VPLo				
	Mean (V/mm ²)	Std (V/mm ²)	Max (V/mm ²)	Min (V/mm ²)
MD	7.763×10^{-4}	0.022	0.445	-0.287
QP	15×10^{-4}	0.04	1.362	-1.172
LP	22×10^{-4}	0.091	3.573	-2.953
Efferent VPLc				
	Mean (V/mm ²)	Std (V/mm ²)	Max (V/mm ²)	Min (V/mm ²)
MD	-9.31×10^{-4}	0.002	0.009	-0.046
QP	-8.867×10^{-4}	0.007	0.049	-0.186
LP	-8.605×10^{-4}	0.012	0.119	-0.381
Afferent VPLo				
	Mean (V/mm ²)	Std (V/mm ²)	Max (V/mm ²)	Min (V/mm ²)
MD	-15×10^{-4}	0.027	0.576	-0.342
QP	14×10^{-4}	0.045	1.599	-0.809
LP	39×10^{-4}	0.069	3.912	-0.785
Afferent VPLc				
	Mean (V/mm ²)	Std (V/mm ²)	Max (V/mm ²)	Min (V/mm ²)
MD	-8.835×10^{-4}	0.003	0.043	-0.022
QP	2.174×10^{-4}	0.001	0.012	-0.004
LP	4.975×10^{-4}	0.001	0.009	-0.003

Table III

P-values

Efferent Data			
	Max Deviation	Sum of Square of Differences	Sum of Differences
MD	< 0.001	< 0.001	0.001
QP	0.8348	< 0.001	< 0.001
LP	0.8593	0.0037	< 0.001
Afferent Data			
	Max Deviation	Sum of Square of Differences	Sum of Differences
MD	< 0.001	<0.001	0.0583
QP	0.2758	< 0.001	< 0.001
LP	0.2758	< 0.001	< 0.001