Current steering to control the volume of tissue activated during deep brain stimulation

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Background
Over the last two decades, deep brain stimulation (DBS) has become a recognized and effective clinical therapy for numerous neurologic conditions. Since its inception, clinical DBS technology has progressed at a relatively slow rate; however, numerous advances in neural engineering research have the potential to improve DBS systems. One such advance is the concept of current steering, or the use of multiple stimulation sources to direct current flow through targeted regions of brain tissue. The goals of this study were to develop a theoretical understanding of the effects of current steering in the context of DBS, and use that information to evaluate the potential use of current steering during stimulation of the subthalamic nucleus.

Methods
We used finite element electric field models, coupled to multicompartment cable axon models, to predict the volume of tissue activated (VTA) by DBS as a function of the stimulation parameter settings.

Results
Balancing current flow through adjacent cathodes can increase the VTA magnitude, relative to monopolar stimulation, and current steering can be an effective technique to sculpt the shape of the VTA to fit a given anatomic target.

Conclusions
These results provide motivation for the integration of current steering technology into clinical DBS systems, thereby expanding opportunities to customize DBS to individual patients, and potentially enhancing therapeutic efficacy.

Keywords electrode; model; electric field; neuromodulation; neurostimulation; subthalamic nucleus
The clinical efficacy of deep brain stimulation (DBS) has been clearly demonstrated for movement disorders,\textsuperscript{1-3} and DBS also shows promise in the treatment of other neurologic conditions.\textsuperscript{4,5} Clinical studies have established that the therapeutic outcomes of DBS are strongly dependent on three factors: (1) careful selection of appropriate patients for DBS;\textsuperscript{6} (2) accurate surgical placement of the electrode in the target brain region for the given disorder;\textsuperscript{7} and (3) attentive patient-specific titration of the stimulation parameter settings.\textsuperscript{8} Electrode placement and stimulation parameter settings synergistically interact to define the therapeutic window for stimulation, or parameter space where stimulation provides therapeutic benefit without stimulation induced side effects. However, once the electrode is implanted, revision surgeries are uncommon, and clinical outcomes are strongly dependent on the ability of the clinician to work within the stimulation capabilities of the implanted pulse generator (IPG).

The majority of DBS patients are presently implanted with IPGs that use single-source, voltage-controlled stimulation. Typically, a single electrode contact is stimulated as a cathode with the IPG case as an anodic return (i.e. monopolar stimulation). If adequate therapeutic effects cannot be achieved with monopolar stimulation, multi-contact stimulation strategies are often attempted. However, because the IPGs rely on a voltage-controlled source, the impedance of the electrode-tissue interface at each active contact will dictate current flow in the tissue. In turn, while these devices allow for simultaneous activation of multiple contacts at a single voltage level, the clinician cannot directly control current flow across the contacts.

An alternative direction for future DBS IPGs is the use of current-controlled stimulation with multiple independent current sources. These features open up opportunities to direct stimulation through multiple electrode contacts with known current delivery to the tissue. This concept, known as current steering, has been used in peripheral nerve cuff electrodes\textsuperscript{9} and spinal cord stimulation\textsuperscript{10} to enable targeted stimulation of specific fiber populations. In turn, it is possible that current steering could find similar use in the context of DBS.

Previously we developed a detailed methodology to predict the volume of tissue activated (VTA) during DBS as a function of electrode design and stimulation parameter settings.\textsuperscript{11,12} This study expands our analysis to consider current steering between two adjacent cathodes on a DBS lead. To provide an example of how current steering could theoretically be used, we considered stimulation of the subthalamic nucleus (STN). STN DBS for the treatment of Parkinson’s disease is the most common application of DBS technology, and numerous studies have identified anatomically distinct territories within the subthalamic region that are associated with stimulation efficacy.\textsuperscript{13,14} However, these therapeutic areas are flanked by the internal capsule, a major fiber pathway that when stimulated causes unwanted side effects. In turn, the clinical goal of STN DBS is to maximize stimulation coverage of the therapeutic target area without spreading into side effect areas. The precise anatomical target volume of tissue that should be stimulated by STN DBS to maximize therapeutic outcome is an area of ongoing research, and outside of the scope of this study. However, to demonstrate the general concept of current steering, we used a 3D model of the STN as a representative stimulation target. Our theoretical results show that current steering can expand opportunities to control the shape of the VTA, and current steering could find clinical use in the sculpting of the VTA to best fit the anatomy of the therapeutic target.

**Methods and materials**

This study addresses current steering technology in the context of DBS by predicting the activation of axons surrounding the DBS electrode. The underlying therapeutic mechanisms of DBS remain controversial, one leading hypothesis is that high-frequency stimulation overrides the underlying pathologic neural activity patterns.\textsuperscript{15-17} Therefore, the approach taken in this study was to address the volume of axonal tissue directly activated by clinically relevant stimulation parameter settings.

The general methodology of this study followed and extended our previous publications.\textsuperscript{18-21} Neural stimulation was estimated with an integrated system that combined finite element model (FEM) electric field solutions with compartment cable models of myelinated axons. The electric field generated by the DBS electrode was calculated from the Poisson equation with a Fourier FEM solver to determine the time- and space-dependent voltage distribution within the tissue medium.\textsuperscript{22} The voltage waveforms were subsequently interpolated onto model axons distributed around the electrode, and threshold values of the stimulation amplitude necessary for action potential generation were calculated. The second spatial difference of the extracellular potential distribution ($\Delta^2V_e/\Delta x^2$) at the site of action potential initiation in each axon ($\Delta x =$ intermodal spacing of 0.5 mm) was calculated at the stimulus threshold for action potential generation. The $\Delta^2V_e/\Delta x^2$ solutions were then used to create a VTA prediction scheme as a function of stimulation parameters. The VTA prediction scheme was then used in a detailed model of human DBS\textsuperscript{18} to explore how current steering could be used to control the VTA in a clinically relevant context.

**Finite element model**

An axisymmetric FEM with 17,561 nodes was constructed in COMSOL v3.2 (Comsol Inc, Burlington, Massachusetts) (Figure 1).\textsuperscript{12} Electrode dimensions were based on the
Medtronic 3389 quadripolar DBS electrode (contact size = 1.5 mm height, 1.27 mm diameter; contact spacing = 0.5 mm) (Medtronic Inc., Minneapolis, Minnesota). The bulk tissue conductivity was set to 0.2 S/m to mimic neural tissue, and a 0.5 mm thick encapsulation layer with 0.1 S/m conductivity surrounded the electrode. The model exhibited an electrode impedance of approximately 1 kΩ, consistent with clinical impedance measurements. In turn, a simple conversion of 1 mA to 1 V can be used to approximate the relative voltage-controlled stimulus magnitudes for the current-controlled stimulation reported in this study. Current was simultaneously injected through two adjacent contacts with specified percentages (0/100, 10/90, 20/80, 30/70, 40/60, 50/50) of the total current diverted to each contact.

The Precision IPG (Advanced Bionics Corp., Valencia, California) represents a commercially available IPG capable of current steering because of its multiple independent current sources. Therefore, we used stimulus waveforms derived from the Precision IPG in our simulations (Figure 1). The waveforms consisted of an initial cathodic phase with a duration specified by the pulse width, a 0.1-msec interpulse delay, and a charge-balancing anodic phase of passive recharge over a 6-msec time window. The current levels specified in the results were equal to the amplitude of the cathodic phase of the waveform. All simulations presented in the results used a 0.1-msec cathodic pulse width and 130 Hz stimulation frequency, consistent with typical clinical DBS parameter settings.

Neural stimulation prediction

Axonal activation was predicted by coupling the DBS FEM to 5.7 μm diameter myelinated axon models. A collection of 147 model axons were distributed in a 7 × 21 matrix-oriented perpendicular to the electrode shaft (Figure 2). This orientation of axons was used to identify the spatial extent of activation in the vertical and horizontal directions relative to the electrode shaft. Each model axon included 21 nodes of Ranvier with 0.5 mm internodal spacing. The time-dependent potential distribution generated in the tissue medium from the DBS FEM solution was interpolated onto the length of each cable model, and the time-dependent transmembrane potentials induced in the axon were calculated in NEURON v5.7. Threshold stimulus amplitudes were defined for each axon model such that action potentials were generated in a 1:1 ratio with a stimulus frequency of 130 Hz.

The second difference of the extracellular potential distribution along a neural process ($\Delta^2 V_e/\Delta x^2$) provides an estimate of the polarization of the neuron in response to an applied electric field and can be used to predict action potential initiation. However, $\Delta^2 V_e/\Delta x^2$ has limitations as a direct predictor of action potential threshold, and when multiple current sources are active simultaneously, simple relationships between $\Delta^2 V_e/\Delta x^2$ and axonal threshold breakdown. Therefore, we constructed a prediction scheme for axonal activation based on an extended version of the current injected through each active contact divided by the distance from each active contact to each axon. The $\Delta^2 V_e/\Delta x^2$ threshold predictor function was determined by plotting the $\Delta^2 V_e/\Delta x^2$ thresholds versus the normalized electrode-to-axon distance, where normalized distance (D) was defined as:

$$1/D = \{[(contact 1 normalized amplitude)/(axon to contact 1 distance)] + [(contact 2 normalized amplitude)/(axon to contact 2 distance)]\}.$$  

The resulting data were fit to a curve (Figure 2B), and an analytical predictor was then used to determine $\Delta^2 V_e/\Delta x^2$ thresholds for the given stimulation pulse width (0.1 msec), and frequency (130 Hz):

$$\Delta^2 V_e/\Delta x^2 \text{ threshold} = 12.3 * D^{-0.43}$$
The Butson et al.\textsuperscript{13} human DBS model was designed to provide anatomically and electrically accurate predictions of the VTA as a function of the stimulation parameter settings. The model included the capacitance of the electrode-tissue interface and electrode encapsulation described above, as well as explicit representation of the 3-dimensional (3D) anisotropic and inhomogeneous tissue electrical properties that surround STN DBS electrodes. We converted the Wakana et al.\textsuperscript{31} diffusion tensor MRI atlas brain into a set of conductivity tensors as described by Tuch et al.\textsuperscript{32} These conductivity tensors were then mapped into a 3D finite element mesh, allowing for solution of the time- and space-dependent potential distribution generated by a DBS electrode implanted in the STN.\textsuperscript{13} The model system also included 3D anatomic volumes of individual brain nuclei warped to the MRI, thereby allowing estimates of the anatomic borders of the STN.

The human DBS model simulations were performed on an 8 processor SGI Prism (Silicon Graphics Inc, Mountain View, California) with 36 GB of shared memory using SCIRun/BioPSE (Scientific Computing & Imaging Institute, University of Utah, Salt Lake City, Utah). The FEM solution created a potential distribution ($V_e$) in the tissue medium that was dependent on the electrode location in the brain and the stimulation parameter settings. In turn, we calculated the $\Delta^2 V_e/\Delta x^2$, and used the current steering $\Delta^2 V_e/\Delta x^2$ threshold predictor function (Figure 2) to define 3D surfaces that encompassed the volume of tissue suprathreshold for axonal activation for the given stimulation parameter settings (Figures 4 and 5).

**Human DBS model**

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**Results**

Monopolar DBS with either current-controlled stimulation (Precision IPG—as performed in this study) or
The results show that balancing current delivery across two contacts increases the size of the VTA, compared with monopolar stimulation. Further, current steering can be used to sculpt the VTA to achieve the desired overlap with target tissue structures. This additional functionality may expand opportunities to achieve therapeutically optimal stimulation in a given patient. The important engineering designation that enables “steering” is the concept of independent sources (voltage or current). It would also be possible to manipulate the shape of the VTA with voltage steering, given that independent voltage sources were available on the IPG. However, current-controlled stimulation provides assurance that the current delivered to the tissue is consistent and unaffected by changes in the impedance of the electrode-tissue interface.

Clinical DBS parameter selection is an art that balances stimulation induced therapeutic benefit while trying to avoid any stimulation induced side effects. This process can be difficult and time consuming, and the outcomes are strongly dependent on the experience of the programming clinician. The results of this study show that it is theoretically possible to sculpt the VTA with current steering to maximize stimulation coverage of a given anatomic target (ie, the STN). However, clinical identification of the theoretically optimal stimulation parameter setting may not be intuitively obvious without computational assistance. And, many of the symptoms of neurologic disorders treated with DBS do not provide instantaneous clinical feedback on their control (or lack thereof) as stimulation parameter settings are changed. To address these issues, multiple groups have been working to develop 3D visualization systems that use engineering optimization to predict theoretically optimal electrode placements and stimulation parameter settings. However, the prospect of using patient-specific computer models to augment clinical DBS practices requires two important pieces of information: (1) precise knowledge of the DBS electrode location in the anatomy, and (2) clear definition of the therapeutic target volume of tissue that should be stimulated. Unfortunately, given existing imaging techniques and scientific understanding, substantial limitations surround both of these prerequisites.

Identifying the location of DBS electrodes in postoperative MRIs is complicated by the metallic artifact generated by the contacts, and although postoperative computed tomograms (CTs) can provide a more accurate estimate of the 3D electrode location relative to the skull, the image must be coregistered with an MRI to provide neuroanatomic detail. Because of artifact and/or registration errors, current imaging technology can only provide an estimate to within approximately 1 mm of the true location of the electrode in the brain anatomy. Uncertainties of this magnitude have not substantially impacted clinical care in the past because postoperative imaging data are not extensively used to guide the stimulation parameter selection process under existing practices. However, as DBS electrodes

Discussion

The goals of this study were as follows: (1) to develop quantitative techniques for predicting the DBS VTA when balancing specific amounts of current through adjacent electrode contacts, and (2) to theoretically evaluate the clinical utility of using current steering to control the VTA.
and IPGs become more advanced, detailed knowledge of the lead location in the anatomy will be especially important in defining the electrode contacts and stimulation paradigms that maximize device use in specific patients.

To provide a clinically relevant example of how current steering might be used in DBS, we examined stimulation of the STN. Extensive effort has been dedicated to identifying the anatomic location of therapeutic electrode contacts in the STN region. The results of these studies suggest that stimulation of the STN per se may not be the only anatomic structure in the region responsible for therapeutic benefit. However, aside from detailed modeling studies of 2 patients, estimates of the electrical spread of stimulation, and its overlap with various anatomic entities in the STN region, have not been correlated with therapeutic outcomes. In turn, scientific definition of the target volume of tissue that should be stimulated for maximal therapeutic benefit remains an issue of debate.

For simplicity we used the atlas-defined anatomic borders of the STN to represent our target volume of stimulation, and we placed the DBS electrode in the center of the STN. However, the numerous anatomic studies of DBS electrode implant locations have shown substantial variability across patients. This variability in electrode placement can be attributed to multiple factors (stereotactic frame accuracy, surgical philosophy on target coordinates, and/or use of microelectrode recordings), but the end result is that not every electrode will be perfectly placed in the intended target region. In turn, techniques like current steering, that expand the stimulation coverage and/or flexibility of any given implanted electrode, could be an important asset in a clinical setting. However, when defining therapeutic stimulation parameter settings in a patient, it is unrealistic to clinically evaluate each of the thousands of different stimulation parameter settings available for a given electrode and IPG model. Therefore, new clinical stimulation parameter selection techniques will be necessary to maximize the use of advanced DBS systems.

Assuming that the above-mentioned limitations in imaging and stimulation target definition can be resolved, coupling current steering DBS technology with computer-assisted patient-specific stimulation parameter selection may be an attractive option for the future.

Predicting the spread of stimulation during DBS requires the definition of a neural response outcome measure. The VTA predictions used in this study represent simplified estimates of the response of myelinated axons to DBS. We originally developed the general threshold prediction scheme used in this study to address monopolar current of 2 mA. VTAs are shown as a function of different current mixtures from 100%/0% (monopolar on contact 2) to 50%/50% (through contacts 1 and 2) to 0%/100% (monopolar on contact 1). STN, Subthalamic nucleus; 3D, 3 dimensional; FEM, finite element model; DBS, deep brain stimulation; VTA, volume of tissue activated.

Figure 4  Current steering in the STN. A diffusion-tensor-based 3D FEM of DBS was used to predict the VTA (red volume) from various percentage mixtures of current delivery through 2 DBS contacts in the STN. The stimulation parameters were held constant with 0.1 msec pulses delivered at 130 Hz and at a total...
We have attempted to validate this technique by comparing our model predictions of axonal activation to clinical measurements of internal capsule activation (ie, DBS induced EMG thresholds from corticospinal tract activation). When adapting this methodology to study current steering it became readily apparent that both active electrode contacts needed to be considered in the prediction scheme. Several formulas were evaluated, and the solution presented in the Methods provided the best overall fit to our data. However, alternative techniques may provide more accurate solutions in the future.

Our previous theoretical and experimental analysis suggests that interesting correlations can be defined between axonal activation and therapeutic DBS. However, several important underlying assumptions in our study should be noted. First, the tissue medium was undifferentiated with regard to the distribution of myelinated axons. Second, activation of more tissue was considered better than less. Third, there was no relative benefit to stimulation of different sub-regions of tissue in the target volume. In addition, it is distinctly possible that the underlying therapeutic effects of DBS are actually related to neural responses unconnected to axonal activation. Nonetheless, the basic mechanisms of DBS are related to modulating neural activity with electric fields, and current steering represents an additional tool to enhance control of the applied electric field.

Three general design techniques exist to control the electric field generated by DBS: (1) construction of the stimulus waveform/train, (2) shape of the electrode contact, and (3) configuration of active electrode contacts.
contacts.21,56 This study focused on one aspect of the configuration of active electrode contacts (ie, current steering between adjacent cathodes). However, numerous questions remain to be addressed on all of the above mentioned DBS design techniques. For example, in relation to current steering a logical next step is evaluation of the spacing between contacts. Figure 6 shows the voltage distribution generated by simultaneous activation of two DBS contacts with various spacing. These different voltage distributions will result in different VTA shapes and thereby provide additional opportunities to customize the shape of the VTA.

In summary, the results of this study show that current steering can expand opportunities to sculpt DBS to fit the anatomic target of the stimulation. However, numerous technical hurdles remain before the full spectrum of DBS technology can be optimally used in clinical settings. In turn, future improvements in DBS systems will rely on parallel development of engineering hardware (for example, advanced stereotactic targeting, IPG technology), computer software (namely, 3D visualization, optimization algorithms), imaging technology (for example, advanced imaging sequences, intraoperative imaging), and clinical training on maximizing the use of these new technologies.

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References


