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Computational modeling of deep brain stimulation

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DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) is a powerful clinical technology, positively impacting the lives of tens of thousands of patients worldwide. DBS has Food and Drug Administration approval for the treatment of Parkinson's disease (PD) (Obeso et al., 2001), essential tremor (Benabid et al., 1996), dystonia (Vidailhet et al., 2005), and obsessive-compulsive disorder (Greenberg et al., 2010). In addition, numerous clinical trials are currently under way or recently completed to evaluate its efficacy for other disorders, most notably epilepsy (Fisher et al., 2010) and treatment-refractory depression (Lozano et al., 2008; Malone et al., 2009). As such, the DBS medical device market has experienced steady growth over the past decade, and Medtronic recently announced that the 100 000th patient having DBS was implanted in the summer of 2012. However, for all of the clinical successes of DBS, numerous questions remain regarding its therapeutic mechanisms and effects on the nervous system (McIntyre and Hahn, 2010).

The clinical outcomes achieved with DBS are a testament to the efficacy of the current device technology, surgical implantation techniques, and clinical programming strategies. For example, DBS for movement disorders can provide greater than 50% improvement in clinical ratings of motor symptoms in appropriately selected patients (Walter and Vitek, 2004). However, DBS typically requires highly trained and experienced clinical oversight to achieve maximal therapeutic benefit in each patient (Moro et al., 2006). In turn, an important and necessary step forward for wider scale use of this medical technology is the development of assistive technologies that optimize the clinical implementation of DBS.

Optimization of DBS technology, from both an engineering and a clinical perspective, will require improved scientific understanding of the effects and therapeutic mechanisms of electrical stimulation of the brain. The fundamental purpose of DBS is to modulate pathological neural activity with applied electric fields. However, the clinical staff who typically implement DBS technology do not necessarily have a quantitative understanding of the neural response to adjustment of the various stimulation parameters. Fortunately, guidelines do exist for general stimulation parameter settings that are typically effective

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Conflict of interest statement

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(Volkman et al., 2006), although it is not feasible to evaluate clinically each of the thousands of individual stimulation parameter combinations that may be useful for a given patient. As a result, the therapeutic benefit currently achievable with DBS is strongly dependent on the surgical placement accuracy of the DBS electrode and the intuitive skill of the clinician performing the stimulation parameter selection.

Computational modeling is playing an important role in exciting new developments to improve both electrode placement and stimulation parameter selection in patients undergoing DBS. Stereotactic neurosurgical navigation has a long history of relying on computational models to help identify target coordinates in the brain for electrode placement based on the patient's medical imaging and intraoperative neurophysiological data (e.g., Finnis et al., 2003). More recently, software technologies have also been designed to assist clinicians in identifying therapeutic stimulation parameter settings customized to each patient (Frankemolle et al., 2010).

Movement disorder symptoms such as tremor respond quickly to the onset of stimulation, providing the clinician with feedback on the effectiveness of a given setting. However, application of DBS technology to disorders such as epilepsy, dystonia, depression, and obsessive-compulsive disorder are more problematic because the beneficial effects of stimulation can take days to weeks to manifest. This makes stimulation parameter selection during a short clinical visit difficult, and this problem is compounded by the somewhat limited scientific guidelines on optimal stimulation paradigms for these different disorders. Therefore, synergistic combination of clinical experience and scientific knowledge is needed to enable more efficacious application of DBS technology to patients.

PATIENT-SPECIFIC MODELS

Computational modeling of DBS has established itself as a useful tool for investigating both theoretical mechanisms and techniques to optimize the clinical application of the technology. Much of this field has focused on the creation and use of patient-specific DBS models, as well as the corresponding electric field generated by the human DBS electrode (cylindrical electrode contact, 1.5 mm in height and 1.27 mm in diameter). The last decade has seen these models evolve from point source electrodes in an infinite homogeneous medium (Grill and McIntyre, 2001), to clinical electrodes in a human brain (McIntyre et al., 2004), to detailed representations of the electrode-tissue interface (Chaturvedi et al., 2010). The electric field predictions from modern DBS models have been validated against experimental measurements in the brains of nonhuman primates (Miocinovic et al., 2009) and electrophysiological measurements in human patients (Chaturvedi et al., 2010). The general field of DBS electrode modeling has expanded to include investigators from around the world addressing the biophysics of stimulation (e.g., Elwassif et al., 2006; Sotiropoulos and Steinmetz, 2007; Yousif et al., 2008; Walckiers et al., 2010), as well as clinical investigations of stimulus spread (e.g., Hemm et al., 2005; Vasques et al., 2009; Aström et al., 2010).

Patient-specific DBS models have had their greatest impact in analysis of the anatomical and electrical target of the stimulation. DBS surgical targeting traditionally focused on electrode

placement within the confines of subcortical gray matter nuclei, following the assumption that stimulation of the cell bodies of the neurons in the given nucleus was responsible for therapeutic benefit. However, numerous theoretical and experimental studies have shown recently that the primary effect of DBS is to stimulate axons that surround the electrode (e.g., Hashimoto et al., 2003; McIntyre et al., 2004; Miocinovic et al., 2006; Gradinaru et al., 2009). These axons may be associated with the implanted nucleus (i.e., axonal projections originating from the nucleus) or any other axon projecting to or passing by the nucleus. In the case of subthalamic DBS for Parkinson's disease, patient-specific models have demonstrated that activation of the white matter dorsal to the subthalamic nucleus (STN) is most associated with therapeutic benefit (Maks et al., 2009; Butson et al., 2011). Further, when this region is explicitly via surgical electrode placement (Plaha et al., 2006), or stimulation parameter targeted selection (Frankemolle et al., 2010), outcomes improve relative to stimulation concentrated on the STN itself (Maks et al., 2009; Butson et al., 2011). These results support the concept that detailed computational models can provide clinically relevant input on surgical targeting and stimulation parameter selection.

MODELING NEUROSTIMULATION

The electric field generated by an implanted electrode is a three-dimensionally complex phenomenon that is distributed throughout the brain (McIntyre et al., 2004; Butson et al., 2007). This field is applied to the complex three-dimensional geometry of the surrounding neural processes (i.e., axons and dendrites). The response of an individual neuron to the applied field is related to the second derivative of the extracellular potential distribution along each neural process (McNeal, 1976; Rattay, 1986). In turn, each neuron (or neural process) surrounding the electrode will be subject to both depolarizing and hyperpolarizing effects from the stimulation (McIntyre and Grill, 1999). A neuron can be either activated or suppressed in response to extracellular stimulation in different ways and in different neural processes depending on its positioning with respect to the electrode and the stimulation parameters.

In general, three classes of neural element can be affected by the stimulation: local cells, afferent inputs, and fibers of passage. Local cells represent neurons that have their cell body in close proximity to the electrode and an axon that may project locally and/or to a different brain region. Afferent inputs represent neurons that project to the region near the electrode and whose axon terminals make synaptic connections with local cells. Fibers of passage represent neurons where both the cell body and axon terminals are far from the electrode, but the axonal process of the neuron traces a path that is in close proximity to the electrode. Experimental measurements indicate that local cells, afferent inputs, and fibers of passage have similar thresholds for activation (Ranck, 1975). In addition, local cells can be excited directly by the stimulus and/or have their excitability altered indirectly via activation of afferent inputs that make synaptic connections on their dendritic arbor (Gustafsson and Jankowska, 1976).

Neural modeling allows for simultaneous study of the effects of stimulation on all the different types of neuron around the electrode. In addition, models provide a highly controlled environment to study the effects of stimulation on neural activity, something that

is difficult to achieve experimentally. However, the strengths of modeling are tempered by the necessary simplifications made in any reasonable model. In turn, modeling should be coupled as closely as possible to experimental work, allowing for a synergistic analysis of results.

The modeling techniques presently used to predict the neural response to extracellular stimulation date back to McNeal (1976), who was the first to integrate an electric field model and multicompartment cable model to predict action potential generation from electrical stimulation (Fig. 5.1). In general, modeling extracellular stimulation of neurons in the brain relies on two fundamental components: (1) a model of the voltage distribution generated by the stimulating electrode(s), and (2) a model of the neuron(s) being stimulated. Voltage distribution models range from simple (theoretical point source electrode in an infinite homogeneous isotropic medium) to complex (finite element volume conductor with explicit representation of electrode geometry, time dependence, and tissue inhomogeneity/anisotropy). Irrespective of the voltage distribution model selected, the simulated extracellular potentials ($V_e(n)$) at the location of individual compartments of neurons in the surrounding tissue medium can be predicted. The neural response to the stimulation can then be simulated with electrical circuits of conductances ($G_m(n)$) and capacitors ($C_m(n)$) in parallel (Hodgkin and Huxley, 1952). The individual compartments of a single neuron are then connected in series by resistors representing the intracellular resistance ($G_i(n)$) (Rall et al., 1992). Neuron models of this type are commonly referred to as multicompartment cable models. When extracellular stimulation is applied to the neuron model, the membrane current at compartment n is equal to the sum of the incoming axial currents and the sum of the capacitive and ionic currents through the membrane:

$$\begin{aligned} C_m(n) (dV_m(n) / dt) \\ + I_i(n) = G_i(n-1) (V_i(n-1) - V_i(n) + V_e(n-1) - V_e(n)) \\ + G_i(n) (V_i(n+1) - V_i(n) + V_e(n+1) - V_e(n)) \end{aligned}$$

where the transmembrane voltage at each compartment ($V_m(n)$) is defined by difference between the intracellular ($V_i(n)$) and extracellular ($V_e(n)$) potentials (McNeal, 1976) (see Fig. 5.1).

DEEP BRAIN STIMULATION MODELS

Miocinovic et al. (2006) used these general modeling techniques to investigate neural activation during therapeutic DBS of the subthalamic region in parkinsonian nonhuman primates (Fig. 5.2). The general model system integrated three fundamental components: an anatomical model, an electric field model, and a neural activation model. The anatomical model was a histological reconstruction of the monkey DBS electrode implanted in the subthalamic region. The electric field model was a finite element model of the monkey DBS electrode. The neural activation model coupled populations of multicompartment cable neuron models to the electric field model to predict action potential generation.

The model system predicted that when stimulating STN projection neurons with DBS, action potential initiation always took place in the myelinated axon (see Fig. 5.2). This

resulted in an interesting phenomenon where the soma and axon of the same neuron could exhibit dramatically different firing patterns. During stimulation, somatic firing was suppressed while the axon fired in a nearly one-to-one ratio with the stimulation frequency (Miocinovic et al., 2006) (see Fig. 5.2). This basic model prediction has been used to reconcile seemingly contradictory experimental results on DBS. For example, numerous experimental studies have shown inhibition of somatic firing in the stimulated nucleus (e.g., Meissner et al., 2005), but when recordings are made in efferent nuclei the neural activity changes have been consistent with activation of the stimulated nucleus (e.g., Hashimoto et al., 2003).

Model systems have also been developed to analyze DBS in human patients. Moks and colleagues (2009) created 10 patient-specific models of STN DBS, each using a series of five steps: (1) definition of the neurosurgical stereotactic coordinate system within the context of preoperative imaging data; (2) entry of intraoperative microelectrode recording locations from neurophysiologically defined thalamic, subthalamic, and substantia nigra neurons into the context of the imaging data; (3) fitting a three-dimensional brain atlas to the neuroanatomy and neurophysiology of the patient; (4) positioning the DBS electrode in the documented stereotactic location, verified by postoperative imaging data; and (5) calculation of the volume of tissue activated (VTA) by therapeutic stimulation parameters using a diffusion tensor-based finite element neurostimulation model (Butson et al., 2007). These patient-specific models showed that therapeutic benefit was achieved with direct stimulation of a wide range of anatomical structures in the subthalamic region.

Butson and coworkers continued to explore this concept with prospective testing of a wide range of different stimulation settings in a patient population of STN DBS with the goal of creating a probabilistic stimulation atlas (PSA) (Butson et al., 2011). They tested 163 different stimulation conditions in patients, while patient-specific DBS models were used to calculate the VTA for each experiment (Fig. 5.3B,C). Clinical scores for bradykinesia and rigidity were assigned to each VTA and then compiled into an atlas brain to identify activation targets that maximized therapeutic response with minimal side-effects (Fig. 5.3D). The resulting subthalamic PSA for Parkinson's disease suggested that bradykinesia and rigidity have similar target stimulation locations with some degree of overlap depending on the level of therapeutic benefit. However, when considering only regions associated with more than 75% improvement in the given symptom, the two stimulation targets were distinct from each other, with rigidity slightly more anterior than bradykinesia (Fig. 5.3D). In either case, the best therapeutic outcomes were associated with activation of the white matter dorsal to the STN. These results suggest that selection of both electrode placement and clinical stimulation parameter settings could be tailored to the patient's primary symptoms using patient-specific DBS models and PSAs.

CLINICAL APPLICATION OF DEEP BRAIN STIMULATION MODELS

A clinical limitation associated with bilateral subthalamic DBS has been declines in cognitive function (Hershey et al., 2004; Alberts et al., 2008), and it is hypothesized that this side-effect results from spread of current to nonmotor regions of the STN. Frankemolle et al. (2010) assessed prospectively 10 patients with Parkinson's disease, implanted with

subthalamic DBS systems, during either clinically determined stimulation settings or settings derived from their patient-specific DBS model (Fig. 5.4). The clinical settings for each patient were defined via standard clinical practice (which did not include the use of DBS visualization software) and were stable for at least 6 months prior to study participation. Blinded to the clinical settings, patient-specific DBS models were used to define settings that minimized current spread to nonmotor areas of the STN. This process relied on a target stimulation volume (Fig. 5.4A) derived from the results of Butson et al. (2011) (Fig. 5.3D). Randomized and blinded clinical comparisons with quantitative outcome measures showed that the model-defined (Fig. 5.4B) or clinically defined (Fig. 5.4C) parameter settings were equally effective in improving motor scores on the traditional clinical rating scale (Unified Parkinson's Disease Rating Scale III), both achieving an average OFF MEDS, ON DBS improvement of 46%. However, the model settings provided a 67% average reduction in power consumption because of the more focused stimulation delivery. When patients were tested simultaneously with the combination of a working memory (n-back) and motor (force-tracking) task (i.e., dual-task), cognitive-motor performance was significantly better with the model settings than the clinical settings (Fig. 5.4D). These results suggest that the cognitive-motor declines associated with bilateral stimulation can be mitigated by minimizing current spread into the nonmotor regions of STN. Further, overall improvement in motor function does not have to be compromised to limit cognitive-motor declines as long as stimulation is focused on the appropriate target volume (Frankemolle et al., 2010).

CONCLUSION

DBS is a powerful clinical technology that allows for customization of the therapy to individual patient needs over time via alteration of the stimulation parameters. Furthermore, DBS does not destroy tissue, allowing patients potentially to benefit from emerging restorative therapies. However, defining the optimal surgical placement for the DBS electrode and programming DBS devices for maximal clinical benefit can be a difficult and time-consuming process. In addition, current DBS electrode designs and stimulation pulsing paradigms were derived empirically and are probably not optimal. Computational modeling represents a useful technique to analyze current DBS practice, and to enable the creation of virtual testing grounds for the evaluation of future innovations. For example, new DBS technical developments in current-controlled stimulation (Lempka et al., 2010), current steering between electrodes (Butson and McIntyre, 2008), stimulus waveform shape (Foutz and McIntyre, 2010), temporal patterning of stimuli (Birdno et al., 2012), and electrode contact design (Martens et al., 2011) have been vetted in computational models and are beginning to enter clinical testing. In turn, advances in scientific knowledge and technology are laying the groundwork for the re-engineering of DBS technology better to serve clinicians and patients.

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Fig. 5.1.

Multicompartment cable model of extracellular stimulation. Electrical network representation of a neural process consists of conductances representing the transmembrane ion channels ($G_m(n)$), the membrane capacitance ($C_m(n)$), and the intracellular conductances connecting different compartments together ($G_i(n)$). The extracellular potential ($V_e(n)$) generated in the tissue medium by an electrode can be applied to the cable to predict the neural response to the stimulus. (Adapted from McNeal, 1976.)

Fig. 5.2.

Modeling deep brain stimulation (DBS) in the parkinsonian monkey. **(A)** Three-dimensional (3D) reconstruction of the DBS electrode location in the neuroanatomy (subthalamic nucleus (STN), light gray volume; internal globus pallidus, dark gray volume) and the DBS polarization of a 3D STN neuron model. **(B)** Lowercase letters indicate location in the STN neuron where the transmembrane voltage was recorded: a, soma; b, first node of Ranvier; c, 30th node of Ranvier; d, 50th node of Ranvier. The action potential initiated in the axon and propagated toward the cell body and axonal terminals in the globus pallidus. The traces in the top row represent the stimulus voltage waveform applied to the neuron. **(C)** Trains of DBS suppressed somatic firing, but enhanced axonal output. (Adapted from Miocinovic et al., 2006.)

Fig. 5.3.

Target stimulation volume for Parkinson's disease. (A) Patient-specific model (yellow volume, thalamus; green volume, subthalamic nucleus). (B) Seven different cases of deep brain stimulation (DBS) (28 electrode contact locations all displayed within a common atlas space). (C) Overlap of volumes of tissue activated (VTAs) from 163 different stimulation parameter settings. The combined red volume depicts the total anatomical region mapped by the DBS experiments. All VTAs were overlaid on a 0.5-mm voxelized matrix that encompassed the subthalamic nucleus region. (D) Each VTA had a quantitative clinical outcome score for rigidity and bradykinesia. When a VTA overlapped with a given voxel, its scores were included in the voxelwise statistical analysis. The blue and pink volumes represent voxels that when stimulated generated more than 75% improvement in rigidity or bradykinesia, respectively. (Adapted from Butson et al., 2011.)

Fig. 5.4.

Clinical testing of patient-specific deep brain stimulation (DBS) models. **(A)** Example patient model. The target stimulation volume is shown in gray. The dots represent the stereotactic location of intraoperative microelectrode recordings (yellow dots, thalamic neurons; green dots, subthalamic nucleus neurons). **(B)** Model-defined stimulation parameter settings and volume of tissue activated (VTA) (red volume) defined to match the target volume. **(C)** Settings defined by traditional clinical practice and the resulting VTA. **(D)** Experimental comparison of force-tracking and force-tracking with the n-back working memory task under the different DBS conditions. Model-defined DBS settings generated significantly better results than clinically defined DBS settings during the dual-task experiments. (Adapted from Frankemolle et al., 2010.)