20 Simulation of Deep Brain Stimulation

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20.1 Introduction

Parkinson’s disease (PD) is a significant health problem for the aging population of the U.S. Despite the success of levodopa-based treatment for PD, many patients develop disabling motor side effects over time. One alternative for these patients is deep brain stimulation (DBS), a therapy in which a neurostimulation system is implanted in the brain during stereotactic surgery. This treatment has been FDA approved for approximately ten years and its effectiveness in treating the motor symptoms of PD has been well established. However, DBS is not without its own side effects profile. In particular, clinicians have observed a high prevalence of neuropsychological effects. This problem is compounded in two ways: first, DBS is a complex procedure with many free parameters (voltage, frequency, pulse width and configuration of anodes and cathodes) and is heavily dependent on the intuitive skill of the clinician; second, no atlas exists for clinicians to share therapeutic or side effect outcomes for these patients. Hence, a significant problem for this patient population is the titration of stimulation parameters to provide symptomatic relief without neuropsychological effects. Because these effects may take days or weeks to present, the patient must keep returning to the clinic for reprogramming. Fortunately, researchers at the Medical College of Wisconsin (MCW) are uniquely positioned to address this problem. Specifically, the PI and co-investigators have developed:

1. A systematic procedure for pre- and post-operative evaluation of DBS patients.
2. A database of neuropsychological outcomes.
3. Computational methods that predict the effects of DBS on an individual patient basis.

In this project, we propose to integrate these methods into a knowledge base that is viewable as an interactive, 3D atlas (Specific Aim 1) and to use this framework to examine neuropsychological outcomes in DBS patients with PD (Specific Aim 2). The central hypothesis is that cognitive and psychological outcomes in these patients are correlated with stimulation-induced activation of specific brain regions. Therefore, one long-term objective is to better manage such outcomes by using the knowledge base created in this study to prescribe stimulation protocols that avoid activating these regions. Another potential result of this work is the ability to predict neuropsychological outcomes in DBS patients, which would help alleviate some of the long-term treatment costs this group experiences. Specifically, this work would enable better identification of surgical candidates who could benefit from DBS and more precise prescription of DBS therapy on an individual patient basis. This research has significant potential to improve mental health and quality of life for PD patients by reducing neuropsychological side effects. The proposed collaboration will translate ongoing clinical and bioengineering research by MCW faculty into health improvements for this patient population.

20.2 Background

Dr. Butson is currently an assistant professor in the Departments of Neurology & Neurosurgery at the Medical College of Wisconsin, as well as an Adjunct Professor in the Department of Biomedical Engineering at Marquette University. He holds a BS in Mechanical Engineering from the University of Maryland, an MS in Electrical Engineering from George Washington University, and a Ph.D. in Biomedical Engineering from the University
of Utah. He also completed a post-doctoral fellowship in the Department of Biomedical Engineering at the Cleveland Clinic. His areas of expertise are computational neuroscience, bioelectric field analysis, and neuro-modulation therapy. He has authored over 20 peer-reviewed publications, two book chapters, and five patent applications. He is a co-founder, shareholder, and consultant for Intelect Medical, a medical device company developing new neuromodulation therapies.

The proposed project draws on a body of work by Dr. Butson and other investigators, who use a combination of computational modeling and human experiments to gain insights that would be difficult using either method alone. This research relies heavily on a scientific computing platform to solve and visualize bioelectric field problems in the specific area of neurostimulation, and is integrated with clinical experiments in movement-disorder patients. The ultimate goal is to translate the results into better patient outcomes and new technologies.

20.3 Significance

To perform the proposed research we must solve two general computing problems. First is the ability to generate large, complex, multi-resolution finite element models. These models must meet the following requirements:

1. Node density must be higher in areas with electrical sources and sinks in order to provide sufficient accuracy in voltage predictions, but must be lower elsewhere to reduce overall model size.
2. The model must incorporate specific anatomical features such as the cerebral cortex and the stimulation electrodes.
3. The model must be solvable in a reasonable amount of time, on the order of minutes.
4. The scientific computing environment must allow us to dynamically interpolate biophysical properties, such as tissue conductivities on a per-element basis, into the model.

The second problem to solve is visualization of the model results. We anticipate that this study will generate a knowledge-base of clinical outcomes to be correlated with stimulation-induced activation of particular brain regions. This knowledge base will be expressed as an interactive, probabilistic atlas. The concept behind the atlas is that the user will choose one clinical outcome, which could be a therapeutic effect or side effect, and choose the effect magnitude they are interested in, such as a 50% improvement or worsening in that symptom. The atlas will then display the associated regions. In the past, we have used surfaces to display these regions in 3D. However, a more desirable method would be to display the atlas using volume rendering or other visualization techniques.

The PI does not have the time or expertise to develop a scientific computing platform to solve the problems described above. However, the clinical research that we are conducting requires such a platform. Hence, the PI relies on available software to analyze and visualize clinical results in an integrated computing environment. In particular, we will rely on this collaboration to solve the following technical challenges:

1. Generating and solving large scale finite element models to solve bioelectric field problems. Because of the time-dependence of the stimulation waveforms, these problems must be solved in time and space simultaneously.
2. Vector and tensor field visualization and analysis.
3. Visualization of probabilistic maps.

20.4 Preliminary results

The preliminary results, reported below, stem from our computer modeling and clinical expertise in DBS. These results provide the foundation for the development of new technology that may improve the clinical selection of DBS parameters to reduce or prevent neuropsychological side effects in PD patients. Through the support of an NIH F32, the PI developed the computational infrastructure necessary to quantify the volume of tissue activated (VTA, explained below) from DBS on a patient-specific basis. The co-investigators of this study are experts in the clinical evaluation of DBS patients. We believe that key insights will emerge from the combined investigation of theoretical model predictions of the VTA and the associated clinical outcomes.
**Differential effects of DBS:** The PI has developed a system to predict the effects of DBS on a patient-specific basis. This approach has been validated in two clinical studies and is now being used to prospectively evaluate DBS patients. An overview of the patient-specific modeling system is provided in Figure 20.1. Briefly, the modeling system consists of anatomical, electrical, and biophysical representations of stimulation. The anatomical model is based on a 3D atlas that is warped to the patient MRI using a non-linear warping algorithm. The electrical and biophysical models rely on finite element models (FEM) of the electric field generated by DBS and theoretical predictions of the neural response to extracellular stimulation. Pre-operative MRI and post-operative MRI/CT images are coregistered with a diffusion tensor MRI atlas brain. The purpose of the DTI data in the model is to define the 3D tissue anisotropy and inhomogeneity surrounding the DBS electrode. The VTA for any given electrode location in the brain and stimulation parameter setting is determined from the voltage solution of the FEM with a series of post-processing steps. The FEM solution provides a potential distribution $V_e$ in the tissue medium that is dependent on the electrode location in the brain, the electrode-tissue interface (electrode capacitance, electrode impedance), and the stimulation parameter settings (voltage, pulse width, frequency and configuration of anodes and cathodes). The neural response to extracellular stimulation is related to the second spatial derivative of the extracellular potential along a given neural process $\frac{\partial^2 V_e}{\partial x^2}$. We performed thousands of simulations of the response of multi-compartment cable models of myelinated axons to the applied electric field generated by DBS electrodes. These simulations were used to develop quantitative relationships that describe the threshold $\frac{\partial^2 V_e}{\partial x^2}$ for axonal activation as a function of distance from the electrode. In turn, we calculate $\frac{\partial^2 V_e}{\partial x^2}$ within the context of our patient-specific DBS FEM and, subsequently, define 3D surfaces that encompass the volume where $\frac{\partial^2 V_e}{\partial x^2}$ is suprathreshold for axonal activation for the given stimulation parameters. We have used this system on multiple patients to identify symptom-specific therapeutic targets. Specifically, our preliminary results show that bradykinesia and rigidity have overlapping but distinct target areas for stimulation (Figure 20.2; the details of this approach are provided in section 20.5 Methods). When this information is combined with interactive, 3D visualization methods, it can provide guidance to the clinician on how to choose stimulation parameters that optimally activate the target region with minimal spillover into other areas, which could cause undesirable side effects.

**Neuropsychological database:** In 2007, DBS providers at MCW acquired IRB approval for the development of a database that would capture demographic, neurologic, surgical, and neuropsychological variables for patients who have gone through DBS treatment. The database was designed as a multifaceted, multidisciplinary project that would address a range of clinical research questions. Specifically, the database was designed to allow research questions such as identifying variables or factors that predict positive versus negative outcome from DBS. The majority of the research was initially designed to compare pre- and post-surgical functioning from a physical, cognitive, and psychiatric perspective. In addition to neurologic and surgical variables, a number of neuropsychological variables and emotional variables are included in this database. The database currently contains outcomes for 50 patients; it is anticipated that 50-100 new patients will be added per year. The database is maintained by Dr. Julie Bobholz who is a neuropsychologist in the Department of Neurology at MCW and has been actively involved in the DBS program since its start in 2005.

In addition to cognitive testing, neuropsychological examination includes a detailed interview that captures variables related to medical, psychiatric, social, vocational, and academic history. The patients also complete self-report inventories of mood symptoms, quality of life, and personality/behavior symptoms. These variables are also included in the database and are available for research investigation. The entire database is maintained using SPSS software and is primarily coded using numeric variables.

Some results from this database have been published. One study examined post-operative cognitive outcomes in five elderly PD DBS patients. Example data for one patient from this study is shown in Figure 20.3. This study found that all patients declined on at least one measure and most decline was noted on tests other than verbal fluency (e.g. verbal memory, mental processing speed, problem solving). The decline observed on multiple tests other than verbal fluency may be evidence of possible under reporting of the extent of cognitive decline that is experienced by DBS patients. It is noteworthy that the oldest patient in the study did not experience the most severe cognitive decline compared with the others in the series. Based on this small sample, it appeared that age itself is not a significant predictor of cognitive decline and that the decline seen in these individuals may be related to other variables related to the progression of the disease or the prescription of DBS therapy.

Many high quality reviews of neuropsychological outcomes in DBS patients have been published over the last few years. While these reviews provide insight into the range of neuropsychological outcomes that might be observed across the entire patient population, they provide little insight into the outcomes that might be
Figure 20.1: Patient-specific DBS modeling system. A 3D brain atlas anatomical model is used to define the electrode location in the brain from the MRI. The anatomical model is coupled to an electrical model that captures the voltage controlled, asymmetrical biphasic stimulus waveforms generated by the implanted pulse generator. The DBS electrodes are surrounded by an anisotropic, inhomogeneous tissue medium. The tissue medium is accounted for with a 3D finite element model (FEM) that incorporates tissue conductivities derived from diffusion tensor imaging and a Fourier FEM solver that accounts for the capacitance of the electrode-tissue interface under voltage-controlled stimulation. The neural response to DBS is predicted by coupling the electric field data from the FEM to multi-compartment models of axons surrounding the electrode. The VTA is predicted by the relationships between the electric field and action potential generation in the axon models.
Figure 20.2: Stimulation targets for bradykinesia and rigidity. Target activation volumes for rigidity (top row), bradykinesia (middle row), and both superimposed (bottom row) are shown for 50% improvement and 75% improvement in normalized clinical score (left and right columns, respectively). These results show that patients with different symptoms may have overlapping but distinct stimulation targets for optimal therapeutic benefit. Color legend: thalamus yellow; subthalamic nucleus green; rigidity target blue; bradykinesia target pink.
expected for an individual patient.

DBS is a therapy in which a stimulation system is implanted in the brain during stereotactic surgery and subsequently programmed to provide symptomatic relief. This therapy has been FDA approved for several years for the treatment of movement disorders such as Parkinson's disease (PD), essential tremor, and dystonia and is now being explored for the treatment of other diseases such as depression, obsessive-compulsive disorder, and epilepsy. When prescribing this therapy, there are two major variables that must be decided on an individual patient basis: the electrode location and the stimulation protocol. The electrode lead location is planned by the neurosurgeon prior to surgery and, once decided, cannot be changed without explanting and re-implanting the electrode. The stimulation protocol, which consists of the voltage, pulse width, frequency, and configuration of anodes and cathodes, is prescribed several weeks post-surgery after any edema and swelling have had a chance to subside.

The effectiveness of DBS for the motor symptoms of movement disorders has well established, particularly with respect to tremor, bradykinesia, rigidity, and gait disturbances. However, as this therapy evolves and is prescribed for a growing number of patients, we have observed a high prevalence rate of undesirable motor, cognitive, and psychological side effects. The motor side effects are easier to address because changes in the stimulation protocol usually manifest themselves in seconds to minutes with respect to motor symptoms; therefore, the patient and neurologist can soon determine an improvement or worsening. Unfortunately, neuropsychological effects often take much longer to present and require repeated return visits to the clinic in an attempt to resolve them.

The discovery that high frequency DBS generates clinical benefits analogous to those achieved by surgical lesioning has transformed the use of functional neurosurgery for the treatment of movement disorders. In first world countries, thalamic DBS for intractable tremor has replaced ablative lesions of the thalamus and DBS of the subthalamic nucleus (STN) or GPi has replaced pallidotomy in the treatment of the cardinal motor features of PD (tremor, rigidity, bradykinesia). In addition, GPi DBS has emerged as an effective therapy for dystonia and the utility of DBS is being examined for the treatment of epilepsy, obsessive-compulsive disorder, Tourette's syndrome, and major depression.

The clinical successes of DBS have been tempered by limited knowledge of the effects of DBS on the nervous system. However, converging theoretical and experimental results suggest that the therapeutic mechanisms of DBS may rely on activating axons surrounding the electrode, resulting in an override of pathological neural activity patterns. These stimulation effects are subsequently transmitted throughout the basal ganglia and thalamocortical networks, modulating neural activity throughout the brain.

The focus of this study is on translating recent clinical and research methods into improved treatment for PD, a chronic progressive degenerative illness that gradually results in loss of independent function. There are 1.5 million PD patients in the United States, including 1% of Americans >50 years of age.
therapies exist for patients in early stages of the disease; however, as the disease progresses, activities of daily living are increasingly affected as motor functions become compromised. Advanced PD patients are typically not well controlled by pharmacological management alone and are increasingly turning to DBS to improve their quality of life.\textsuperscript{846}

**Neuropsychological outcomes in DBS patients:** As noted above, DBS has been shown to be effective in managing motor symptoms of movement disorders such as those seen in PD; however, there is a risk for undesirable cognitive and psychiatric side effects. Thus, the study of neuropsychological outcomes in DBS patients remains an important subject. Outcome studies examining cognitive symptoms after DBS report conflicting data. While some studies demonstrate little cognitive morbidity in patients well selected for DBS, others note decline in functions of word fluency, learning / memory of both visual and verbal information, processing speed, and complex problem solving skills (see review\textsuperscript{847}). It is important to note that these findings are somewhat varied. Furthermore, there are reports of individuals who suffer significant cognitive decline after DBS and the factors that predict who is at risk for significant cognitive decline are not well understood.

In recently published meta-analysis studies,\textsuperscript{847, 848} researchers concluded that there is a lack of quality studies that assess the cognitive and behavioral implications of undergoing DBS. They noted that there are even fewer studies that examine subtle, specific variables such as aging, white matter disease, electrode placement, and stimulation levels on a patient’s cognitive and behavioral functioning. Of the studies that have examine these issues, results have been conflicting and designs have included methodological limitations. At the present time, there is insufficient understanding of neuropsychological outcome in DBS. Without this knowledge, our ability to prevent poor outcome is limited. Since there are a growing number of patients receiving DBS treatment for movement disorders, this research is even more critical for minimizing poor cognitive and emotional outcome. This has become a significant health issue.

**DBS parameter selection:** The clinical outcomes of DBS are a testament to the efficacy of the current technology and clinical stimulation parameter selection strategies. DBS for movement disorders commonly provides more than 50\% improvement in clinical ratings of motor symptoms in appropriately selected patients.\textsuperscript{849} However, programming DBS devices for maximal clinical benefit can be a difficult and time consuming process, typically requiring a highly trained and experienced individual to achieve acceptable results. A recent study by Hunka et al.\textsuperscript{850} found that the total time spent programming the stimulator and assessing DBS patients ranged from 18-36 hours per patient. In addition, the work of Moro et al.\textsuperscript{851} stresses the importance of the involvement of a movement disorder specialist in adjusting the stimulation parameter settings. One current limitation in DBS programming is that these procedures are typically done with no visual reference of the electrode location in the anatomy or current spread as it depends on the stimulation parameters. While guidelines exist on stimulation parameter settings that are typically effective,\textsuperscript{852–855} it is infeasible to clinically evaluate each of the thousands of stimulation parameter combinations that are possible. As a result, the therapeutic benefit achieved with DBS is strongly dependent on the intuitive skill and experience of the clinician performing the programming. In addition, application of DBS technology to disorders such as epilepsy, dystonia, depression, and obsessive-compulsive disorder are especially problematic because the beneficial effects of stimulation can take from weeks to months to manifest. Further, it remains unclear what stimulation paradigms are optimal for these different disorders. Therefore, synergistic combination of clinical experience and scientific characterization of the effects of DBS on the nervous system should enable more efficacious application of DBS technology to patients.

The fundamental purpose of DBS is to modulate neural activity with applied electric fields, but most clinicians implementing DBS technology do not have a quantitative understanding of the effects of manipulating the various stimulation parameters on the neural response to the stimulation. Recently a number of studies have documented the electric field generated by DBS electrodes.\textsuperscript{516, 529, 817, 821, 840, 856–862} However, the computational power and computer science skills necessary to effectively implement such models are not available to most clinicians. Therefore, the fundamental goal of this project is to integrate tools to analyze DBS, clinically evaluate the efficacy of those tools, and subsequently provide those tools to DBS clinicians. We have created a novel computational framework that integrates magnetic resonance imaging data, finite element electric field models, and predictions on the volume of axonal activation generated by DBS on a patient-specific basis.\textsuperscript{840, 863} Our vision is a software package that generates an atlas of areas showing correlations between stimulation-induced activation and neuropsychological outcomes relative to the surrounding anatomical structures. The studies outlined in this proposal represent the necessary steps toward that vision.

**Multi-disciplinary approach to addressing the effects of DBS:** This study will synergistically integrate neurostimulation modeling and clinical analysis to address questions on the factors linked with neuropsychological
side effects of DBS. We will bridge the tools of medical imaging and computer science to develop patient-specific models of DBS that will define the volume of tissue activated (VTA) as a function of the stimulation parameters. Our models will enable analysis of the complex interaction between the electric field generated by the stimulation and the neural response to the stimulation. We will characterize the effects of DBS within the confines of the model, and couple our theoretical predictions to clinical measurements from the patients. We will use established clinical rating scales to establish relationships between the VTA and clinical outcomes. We believe our results will enhance our understanding of the therapeutic mechanisms of DBS by providing correlations between the anatomical and electrical effects of the stimulation.

20.5 Methods

The fundamental goal of this project is to characterize neuropsychological outcomes in PD patients who are receiving STN DBS. In order to create the greatest potential benefit with the simplest study design, we propose to use information gathered under existing standard of care for patient evaluation. Specifically, we propose to use pre- and post-operative imaging along with pre- and post-operative neuropsychological evaluation results. The imaging will be used to construct the patient-specific models. The DBS stimulation settings at the time of the post-operative neuropsychological evaluation will be used to generate model-predicted VTAs. These will be analyzed for correlations with neuropsychological outcomes that are captured in the existing database. The novel component of this work is the integration of state-of-the-art clinical and research methods to improve the health of PD patients by characterizing neuropsychological outcomes. Institutional Review Board (IRB) approval will be obtained before collecting or analyzing patient data.

Standard of care for DBS patients: Currently, patients undergo a standard pre-operative evaluation including an MRI of the brain, a standardized videotaping protocol performed by the treating neurologist with an evaluation using a standard core assessment program for intracerebral transplantations (CAPIT) protocol, and a neuropsychological evaluation. CAPIT consists of the Unified Parkinson’s Disease Rating Scale (UPDRS), in both the off-medication and on-medication conditions with videotaping in a standard fashion, the modified Hoehn and Yahr scale, the Scwab and England Activities of Daily Living Scale, and also includes time tasks of hand tapping, the Step/second test (which involves the patient walking 15 feet, turning around and returning to the starting point), dyskinesia rating scale, and the Parkinson’s Disease Questionnaire (PDQ39).

During the post-operative evaluation, programming of the DBS will start when the micro-lesioning effect subsides. Micro-lesioning is thought to result from the mechanical insertion of DBS electrodes into the brain, which can temporarily alleviate symptoms such as tremor. Hence, initial programming takes place two to four weeks after the insertion of electrodes. During the initial programming session, all four contacts on each electrode will be interrogated to determine the threshold for effectiveness and side effects and the type(s) of side effects will be documented. Impedance for each contact will also be checked to detect malfunctioning of the system. Contacts of stimulation will be chosen based on the effectiveness on symptomatic control and side effect profile. Monopolar stimulation will be first attempted. Initial voltage will be set to 3.0V (or the highest tolerated) with the goal of reaching 3.6-4.0V. An initial setting of pulse width 60 microseconds and frequency of 130Hz will be set. Further changes will be attempted should clinical effect not be satisfactory or if side effects from stimulation occur. Optimization of programming usually takes one to three months after the initial programming session. Patients will not be allowed to change the stimulation parameters. Charge densities above 30 microcoulombs/cm²/phase will not be used in order to prevent tissue damage.

Neuropsychological evaluation: The neuropsychology database contains outcomes coded for each test and for each patient. Patients are evaluated pre-operatively in the on-medication condition and post-operatively in the on-medication, on-stimulation condition. Changes in cognition soon after surgery (first 2-3 months) are often attributable to recovery from surgery, changes in medications, or titration of stimulation parameters. Therefore, post-operative neuropsychological evaluation is typically conducted after 6-12 months, which is considered sufficient time for medications and therapeutic stimulation parameters to stabilize, noting that most patients experience a decrease in medication dosage with DBS.

The first step in the correlation analysis is to identify differences in neuropsychological outcomes between the pre- and post-surgical conditions. Each difference is calculated, allowing us to determine both the presence and size of an effect. The following neuropsychological measures are administered: Mattis Dementia Rating Scale, Wechsler Abbreviated Scale of Intelligence, Wisconsin Card Sorting Test, Symbol Digit Modalities Test (oral), Controlled Oral Word Association (CFL), Boston Naming Test, Animal Fluency, WRAT-3 Reading, Judgment of Line Orientation, Rey Auditory Verbal Learning Test, WMS-III (Logical Memory, Faces, Digit Span, LNS).
These tests are designed to measure a range of cognitive functions including intellectual capacity, complex problem solving skills, processing speed, verbal fluency, word finding, spatial skills, and learning / memory. These cognitive variables were chosen in part based on previous cognitive research in DBS to identify those with dementia or those with mild cognitive impairments. Once the differences in outcome scores are measured, they will be standardized to a common scale (-1 to +1, negative values indicate worsening of symptoms) and a threshold value will be chosen for changes in outcome; only those changes that meet the threshold criteria will be included in the subsequent analysis. In prior studies, we have used a threshold value of 25% for motor symptoms of PD, but the exact value for the threshold will not be known until we more closely examine the patient data.

**Generation of clinical activation atlas:** The PI has recently developed methods to predict VTAs as a function of electrode location and stimulation parameters on an individual patient basis as described in the Preliminary Studies section (see Figure 20.1). We will use a similar approach to predict each patient's therapeutic VTA at the time of their post-operative evaluation. In order to compare results in a cohort of patients, we will coregister each patient with an existing atlas brain. An overview of this process is provided in Figure 20.4. First, the pre- and post-operative MRIs of each patient will be coregistered. The pre-operative MRI will be warped to a 3D anatomical brain atlas to identify the location of specific nuclei, such as the subthalamic nucleus and thalamus. This is performed using a non-linear vector warping algorithm implemented in software from Surgical Navigation Technologies (SNT) (Medtronic Inc., Boulder, CO). Second, the post-operative MRI is used to perform detailed localization of the electrode and four contacts. This is accomplished by isosurfacing the halo around the electrode shaft. At successively lower values, the isosurface converges onto the four electrode contacts. With these two steps completed, we know the position of the electrode relative to the patient's anatomical nuclei. Third, an algorithm is used to specify the weighted electrode contact locations relative to 1000 points on each surrounding anatomical nuclei. This process is then performed in reverse in the DTI atlas brain in order to localize the electrode by finding the position with the minimum mean squared error between the electrode contact locations and the equivalent points on the atlas nuclei. This process is repeated for each patient, and provides the position of each patient's stimulating electrode represented in the DTI atlas brain. Next, the electric field is solved using the therapeutic stimulation settings at the time of the post-operative neuropsychological evaluation and the subsequent VTAs are generated. This process, as explained so far, is for patients with unilateral stimulation; for patients with bilateral stimulation the VTAs from each hemisphere of the brain will be superimposed and treated as one VTA. All modeling analysis is performed using BioPSE and Matlab (Mathworks, Inc., Natick, MA).

All VTAs will be collected in the DTI atlas brain in order to compile the results across all patients. These VTAs are superimposed in order to create a region of interest (ROI) that encompasses all of them. This is typically a box, about 2 cm per side with 0.5 mm x 0.5 mm x 0.5 mm voxel dimensions, containing on the order of 100,000 voxels. For each individual VTA, voxels in the ROI that are within the VTA are assigned the value 1, all other voxels equal 0. At this point it is useful to think of the ROI as a column where each row represents one voxel. Hence, each column contains a set of 1s and 0s corresponding to whether that voxel is activated. For an individual neuropsychological outcome, this column is multiplied by the clinical outcome score. This process is repeated for each VTA and all of the columns are concatenated into table. Next, this process is repeated for each outcome measure and the sum of these tables constitutes our knowledge base of neuropsychological outcomes. This data is then analyzed by measuring basic quantities such as the average clinical score across each row, resulting in a column of values that are transferred back to the DTI atlas brain by mapping them directly onto the ROI. Since the clinical scores are standardized on a scale from -1 to +1, the average value for each row can be viewed as a percent improvement or worsening across the cohort of patients. Additional measures may also be applied such as maximum, minimum, and standard deviation.

The resulting knowledge base will be visualized in the 3D DTI atlas brain using BioPSE to show each activation volume relative to the surrounding anatomical nuclei. This will provide the clinician with a 3-dimensional, interactive viewer for examination of the results, which will entail the following steps:

1. Select one or more neuropsychological outcomes. This is done in the software by selecting the appropriate outcome table from which surfaces will be rendered. From a practical standpoint, this step maps the average activation values for all patients from the table onto the ROI. Each outcome will be assigned a unique color in the viewer for discrimination purposes.

2. Select an effect size. The effect size will be normalized on a scale of 1, where negative values indicate worsening and positive values indicate improvement. The volume is determined by creating an isosurface of the outcome data based on the desired effect size within the ROI.
3. Update the viewer and examine inter-relationships between volumes and anatomical structures.

Hence, the expected outcomes of this study will be twofold:

1. A knowledge base of correlations between stimulation-induced activation of particular brain regions and neuropsychological outcomes. The knowledge base will have a level of granularity that will permit its use to explore the presence and size of effects.

2. An activation atlas that expresses the knowledge base in an interactive, 3D viewer. The activation atlas produced by this study will be a research tool. If this tool is useful to the clinical community, then the PI has an established track record in migrating such results to a lightweight, Windows-based software client, and we will consider this option at the end of the study. However, migration of software is beyond the scope of this grant.

20.6 Impact of the center resources and technology on the project

The role of integration in this project is twofold. First, we will collaboratively solve large-scale bioelectric field problems on a patient-specific basis. Second, once the knowledge base has been constructed, we will seek assistance in how to visualize the results. One of the unique aspects of this DBP is the integration of researchers across a wide spectrum of expertise, from computer science to biomedical engineering to neuropsychology.

Neurostimulation is a complex therapy with many free parameters. In particular, the “prescription” for neurostimulation consists of the electrode location and the stimulation parameters. Many of the studies that have been completed to date report population averages of outcomes for stimulated versus non-stimulated patients, and this is useful data for understanding the range of possible outcomes that might be expected. However, this type of data does not provide insight on the specific outcomes that we might expect from an individual patient. The significance of this project is that it provides the capability to correlate clinical outcomes with model-predicted activation of particular brain regions and in this sense can be viewed as a functional imaging method where, rather than examining activation maps from BOLD response, we are examining stimulation-induced volumes of activation. The tools to perform this type of computational analysis and visualization have not existed until recently.

We anticipate that we will identify specific and general problems that could be solved jointly in the course of this collaboration. The PI currently has specific capabilities that need to be addressed as enumerated earlier. We also have many open-ended problems for future development. One example is the design of a simplified interface to our computational platform such that clinicians can enter data into the knowledge base as patients go through the clinic, which would drastically reduce the time required to analyze the results. We anticipate that this would facilitate the translation of results back to the clinic and could provide a new platform for evidence-based medicine.

We envision two types of papers coming from this collaboration. The first is clinical outcomes relative to this patient population and these will likely be submitted to clinical neurology journals. The second is analysis methods that are developed to solve these types of clinical problems. Such papers include in-depth analysis of the behavior of neurostimulation systems, which would likely be submitted to neural engineering journals. This could also include scientific computing papers on the platform used to perform the computations, as well as integrate and visualize the associated clinical data.

This collaboration will link biomedical engineers and clinicians from MCW with computer scientists from the CIBC to solve existing problems

20.7 Milestones and timeline

This collaboration will provide an opportunity for physicians and scientists at MCW to improve the health of patients by increasing our understanding of treatment side effects and developing new methods to treat DBS patients and prevent adverse neuropsychological outcomes. Hence, this would provide research support with a high likelihood of providing medical advances for the treatment of Parkinson's disease. It will leverage the expertise and assets at MCW and the SCI Institute to promote discoveries that translate into improvements in health and quality of life for movement disorders patients. We anticipate three phases to this project: patient selection and screening; assembling the computational pipeline; and patient outcome analysis and reporting.
Figure 20.4: Analysis Methods. Top row) A patient-specific model is created for each subject. Anatomical surfaces are identified from a pre-operative MRI; electrode location is determined from a post-operative MRI. The pre- and post-operative image volumes are co-registered to identify electrode locations relative to local nuclei (shown: thalamus in yellow; STN in green). Middle row) An atlas model is used to predict neural activation from the stimulation protocol. The atlas model consists of: the DTI-based conductivity tensors with color indicating fractional anisotropy (two leftmost images); electrode location co-registered from each patient specific model (center image); voltage distribution from the stimulation protocol (fourth image from left); model-predicted VTA (rightmost image). Bottom row) Each voxel in the VTA is assigned a clinical score for a neuropsychological outcome; hypothetical outcome scores are shown.
Institutional Review Board Approval

Patient Selection
- Chart review to identify patients for inclusion
- Prospective enrollment of new patients

Computational Pipeline
- Analysis pipeline customized to MCW clinic
- Database specification & construction
- Atlas visualization

Patient Analysis
- Generation of model-predicted activation volumes
- Comparison of pre- and post-operative neuropsychological outcomes
- AFNI-based statistical analysis
- Compile and document results

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<td><strong>Event</strong></td>
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<td>1 Pre-operative evaluation</td>
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</table>

Figure 20.5: Research Time Line.

Each of these phases is summarized in the research timeline shown in Figure 20.5. Also included is a timeline of the events for each individual patient. Note that institutional review board (IRB) approval has been received for the proposed analysis.