

## RESEARCH STATEMENT

### Overall Goals

Over the next 5 to 7 years, my research focus will be on controlling neural activity in patients with Parkinson's disease using deep brain stimulation. This work is divided into two ambitious projects which entail 1. collecting neurophysiological and behavioral data from primate and human subjects, 2. applying advanced estimation techniques to construct mathematical models that relate extrinsic (eg. environment) and intrinsic (eg. dynamics of neuron and neural network) factors to observed neuronal activity and to construct models that relate stimulation signals to motor behavior, 3. developing new theory to design dynamic controllers to achieve desirable neural activity and motor behavior from patients, and 4. inventing new deep brain stimulation hardware to develop and test on primates and Parkinson's patients in clinical trials. These projects will be the first of several continuing efforts to develop new methodologies in estimation and control to address both theoretical and implementation challenges that arise when modeling and altering the behavior of pathological neural systems. Overall, I aim to create and exploit advanced engineering tools to improve treatments for neurological diseases.

### Deep Brain Stimulation for Parkinson's Disease

3-4 million people in the US have Parkinson's disease (PD), a chronic progressive neurological disorder that results in motor symptoms such as tremor, bradykinesia (slowness of movement), and rigidity. Currently, there is no treatment to stop progression of the disease, however, a highly promising therapy for PD symptoms is deep brain stimulation (DBS), which entails implanting an electrode in a target brain region that is connected to a neurostimulator (sits under the skin and inferior to the collar bone) via a wire extension (Figure 1). The neurostimulator injects current back into the brain region to regulate the pathological neural activity. At major centers the surgery has become routine, and most importantly patients regain quality of life as most of their motor symptoms disappear and they can reduce their medications which have serious side effects.

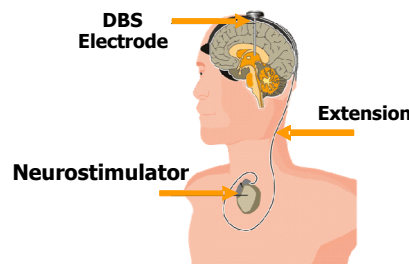


Figure 1: Schematic of DBS System

Although DBS is virtually a breakthrough for PD, it is necessary to search for the optimal stimulation signal post-operatively. This calibration often takes several weeks or months. For patients this means many hospital visits and their expectations of experiencing miracles immediately are not met, which often leads to depression and the need for further medication use. For neurologists, lengthy calibration is costly in terms of medical resources and they cannot treat many patients simultaneously. Today, DBS calibration is time consuming because the process is trial-and-error. During a post-operative visit, the neurologist asks the patient to perform various motor tasks and makes subjective observations. Based on these, he/she tweaks the stimulation parameters and asks the patient to return in hours, days or even weeks. The difficulty is that there are millions of stimulation parameters to choose from (eg. pulse width, pulse frequency, pulse amplitude, electrode contact), though experience has reduced this to roughly 1000 options (Figure 2a). My current parallel research efforts are to 1. reduce calibration time down to days by developing a systematic testing paradigm using feedback control principles, and to 2. develop a new stimulation paradigm that allows for broader classes of DBS signals to be administered. Despite the fact that DBS is simply a control signal applied to a neural system to achieve desirable motor behavior from a patient, investigators are only beginning to approach these problems from a control systems engineering perspective.

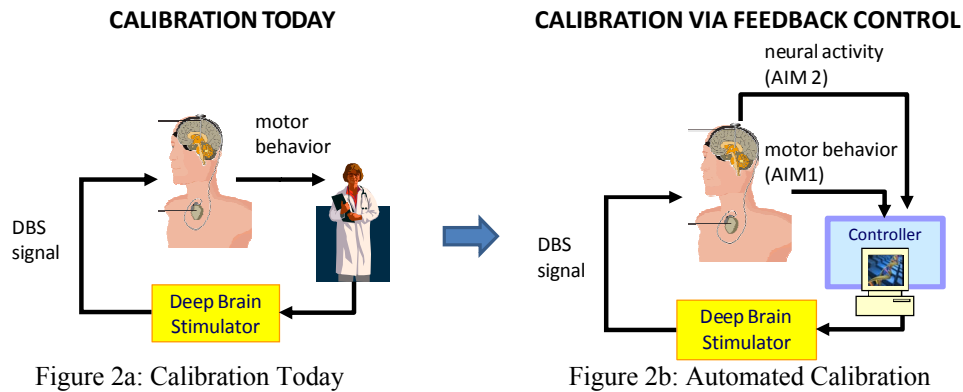


Figure 2a: Calibration Today

Figure 2b: Automated Calibration

## 1. Cutting DBS Calibration Time using Motor Behavior for Feedback Control

Using the existing DBS system, I will design an organized set of motor tasks to capture the intuition of the neurologist with precise measurements of motor behavior that will then be used to design a feedback controller to automatically select a set of stimulation parameters to achieve a given performance objective (Figure 2b). Performance will be measured in terms of an error between motor behavior of the PD patient and a healthy human. Quantifying such behavioral variables will enable more accurate and faster prediction of how different stimulation signals impact motor function, enabling calibration to be done systematically, effectively and rapidly.

### Phase 1: Collecting Behavioral Data from Human Subjects

To build the feedback controller, one requires an appropriate data-driven model that relates DBS signals to motor behavior for each patient. The data collection process is time-consuming because for each patient and DBS signal, defined by electrode polarity, amplitude, pulse width and frequency, one must record the corresponding motor behavioral response (e.g. average movement velocity, average tremor frequency and reaction time). It is also necessary to vary the DBS signal as much as possible to observe statistically significant trends in the data. Testing various scenarios on a patient must be done carefully as the patient may not respond immediately to new parameter settings (requiring multiple sessions) and the patient may feel discomfort if the settings are changed too rapidly. Furthermore, I must understand which behavioral signals are most sensitive to DBS parameters before quantifying behavior. I am currently collaborating with neurosurgeons and neurologists at Massachusetts General Hospital (MGH) and Boston University Medical Center to design structured tasks to capture appropriate behavioral signals. Once the tasks are developed, I will collect data on PD patients over several months.

### Phase 2: Applying Advanced Estimation Techniques to Construct Mathematical Models

Although rough relationships between DBS parameters and a patient's motor symptoms are known [1,2], it is necessary to construct mathematical models that establish how specific motor behavior varies with each DBS parameter. In addition, the models must capture variations between patients with different pathological states, and delayed responses to new DBS inputs (both beneficial and adverse side effects). Such models are typically nonlinear and time-varying and will require advanced estimation and optimization techniques to construct from data.

### Phase 3: Developing New Theory to Design Feedback Controller

In addition to the models of patients being complex, the DBS control input is highly constrained. Firstly, the current DBS hardware generates signals defined by a fixed number of parameters, each of which can take on a finite set of values. Secondly, the DBS signal settings cannot change too rapidly because the patient may feel a lot of discomfort. For example, the voltage amplitude must be changed in increments of 0.1 Volts. Finally, the DBS stimulator should consume minimal power so that battery life lasts longer resulting in fewer replacement surgeries. Therefore, new theory which leads to computable algorithms to design controllers for complex systems to achieve real-time performance with constrained control must be developed.

## **2. Developing New Stimulation Strategies by Measuring Neural Activity for Feedback Control**

Currently, once the patient appears to respond optimally to DBS, he/she continues the final stimulation regime for years without much intervention from the neurologist. I will test the feasibility of changing the existing DBS system to allow a broader class of signals to excite the target brain area, and to dynamically change the signal to maintain motor performance in the patient whose pathological state is evolving. This will be done by measuring neuronal spiking activity directly (Figure 2b). The idea is to design a stimulation strategy to make the pathological activity look more “healthy”, i.e., the feedback controller will measure neural spike trains of a PD patient and generate a DBS signal output that minimizes a given error between the patient’s spike train and a predicted spike train of a healthy subject.

### **Phase 1: Collecting Neurophysiological Data from Primate and Human Subjects**

To build the above controller, one requires models that relate extrinsic factors (environment and behavioral stimuli) and intrinsic dynamics (history of neural activity and local neural network activity) to neural spike trains for both healthy and diseased subjects. Such models must be constructed from rare neurophysiological data entailing neuronal recordings from the same brain region of both healthy subjects and PD patients executing the same behavioral task. My collaborators at MGH have recently conducted parallel experiments on healthy primates and PD patients (undergoing DBS surgery) executing a directed-hand movement task while single neural unit recordings were taken from the sub-thalamic nucleus of the basal ganglia (most common target for DBS in PD).

### **Phase 2: Applying Advanced Estimation Techniques to Construct Mathematical Models**

In general, it is difficult to characterize the dynamics of neuronal activity, because it is stochastic, noisy, and a complex function of extrinsic and intrinsic factors. Using the above data, I exploited the point process paradigm to model healthy and pathological neuronal activity as a function of movement direction and spiking history. A point process model is characterized entirely by the conditional intensity function, which represents the probability over time that a neuron will fire given extrinsic and intrinsic conditions. The models I developed quantified for the first time prevalent abnormalities in PD activity not seen in healthy activity (using healthy primates as surrogates to healthy humans). In particular, neural activity of PD patients exhibited 10-30 Hz oscillations, bursting, and reduced directional plurality, all of which may directly relate to the well known PD motor symptoms of resting tremor, bradykinesia, and rigidity. I have submitted these results for publication in [3].

### **Phase 3: Inventing New DBS hardware**

To implement the feedback controller, the DBS electrode must be capable of both stimulating and measuring single-unit neuronal activity of the patient. Currently, DBS electrodes only stimulate and thus I must work with Medtronic (current supplier of DBS hardware) and/or an appropriate group of engineers to build a prototype of such hardware. In addition, the new DBS system should allow for a broader class of signals to be administered for improved performance.

### **Phase 4: Developing New Theory to Design Feedback Controller**

Once such a dual-mode DBS electrode is implanted, the controller must first predict neural activity of a healthy subject from real-time measurements of PD neural activity, which requires estimating the environment and behavioral stimuli from the measurements using the healthy and diseased models described above. Then, the controller must optimize in real-time the DBS signal that minimizes a given error between the patient’s spike train and a predicted spike train of a healthy subject. Finally, the controller must translate this information into a continuous voltage signal that will elicit the appropriate neural activity from the PD subject.

## **My Past and Future**

The above research requires extensive experience in constructing simplified models for complex systems and designing real-time controllers to achieve performance from the systems. In my PhD thesis, I studied complex systems whose components are connected via communication channels which can be noisy, induce delays, and

have finite-rate constraints. In such systems, there is a fundamental tradeoff between allowing enough time for reconstruction of signals over the noisy channels and achieving performance in finite-time. I analyzed finite-horizon performance when exogenous commands are applied to such systems and synthesized controllers and coding schemes to meet performance objectives. My approach entailed constructing novel simplified models of such systems and deriving computable methods to quantify tradeoffs between reconstruction time of signals and performance in finite-time. This work resulted in the following reports [4,5,6].

During my graduate studies, I also minored in Neuroscience and studied the biological motor control system. Here, the motor cortex generates commands which get processed by the basal ganglia and cerebellum, and ultimately travel through the spinal cord to innervate appropriate parts of the musculoskeletal system, which in turn sends back sensory feedback signals (Figure 3). Steve Massaquoi developed a detailed model of the primate single-joint arm-control system that is supported by physiological evidence in terms of neural recordings in the primate cerebellum and accounts for several features of voluntary arm movement control and movement disorders following damage to the cerebellum [7]. I constructed a reduced-order representation of Massaquoi's model that is analytically much simpler, and that retains a very large portion of stability and performance characteristics over a wide range of parameter values. This work received the best-session paper award [8].

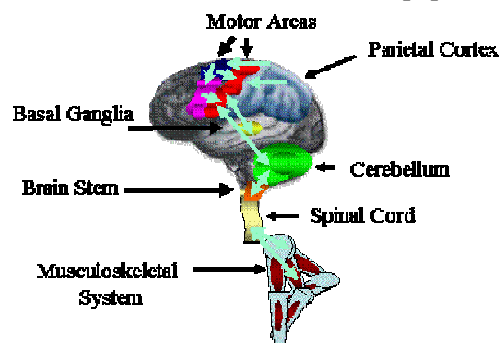


Figure 3: Biological Motor Control System

My graduate training along with my close collaborations with MGH, have fully prepared me to successfully tackle DBS control of neural activity in PD patients. I plan to lead a research group that will focus on theoretical and implementation issues that arise in each phase of each project. Therefore, I envision my students to comprise neurophysiologists, neuroscientists, control theorists, and circuit designers. The impact of successful completion of my projects is quick and maximal relief to more PD patients, and may also lead to new projects that aim to improve treatments for patients who suffer from other neurological disorders treated with DBS (eg. pain, dystonia, epilepsy, Tourette syndrome).

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