

Improved Therapies for Parkinson's Disease Using Advanced Engineering Methods

Overview

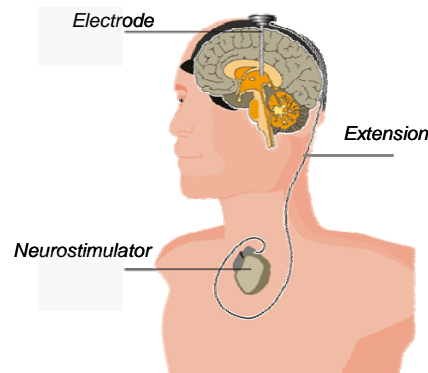
Parkinson's disease is a prevalent neurological disorder that results from the breakdown of feedback control systems in the brain which govern movement. While there has been some success with medications, a new and highly promising therapy is the use of deep brain stimulation (DBS) through electrodes implanted in target areas. When appropriately stimulated, patients often regain normal movement behaviors and can even reduce their medications for several years. However, one of the surprising drawbacks of this sophisticated treatment is that post surgery calibration of the device is done by trial-and-error with the patient and neurologist working together for several weeks before achieving an optimal stimulation regime. My first objective is to apply basic control principles to develop an automatic feedback calibration system for Parkinson's patients already implanted which will efficiently tune their DBS systems to control their movements. In this study, I will gain a deep understanding of movement behaviors as a function of stimuli. My second objective is to characterize and contrast neural activity dynamics in target brain areas as a function of external stimuli and intrinsic factors in both diseased and healthy brains using extremely unique data recently collected in Parkinson's patients and healthy macaque monkeys. This study will enable me to directly connect the neurophysiology behind Parkinson's disease to motor behavior. My third objective is to combine information gleaned from my first two aims to design optimal control strategies through the dynamic selection of external stimuli to alter neural activity and thus behavior in Parkinson's patients to mimic that of healthy humans. This design problem is challenging and requires advanced control theory that is not taught in the classroom nor is readily available in literature. Such theory is the focus of my PhD thesis. In the long term, I will collaborate with doctors and engineers to translate these control strategies into new stimulation paradigms to better treat Parkinson's disease.

Introduction

An estimated 3 to 4 million people in the United States have Parkinson's Disease (PD), a chronic progressive neural disease that occurs when specific neurons in the basal ganglia (BG) degenerate, causing movement disorders such as tremor, rigidity, and bradykinesia. Currently, there is no cure to stop disease progression. However, surgery and medications are available to relieve some of the symptoms in the short term. Such treatments for PD have been developed based on significant understanding of the BG anatomy and physiology.

It has been long appreciated that PD is caused when dopaminergic neurons degenerate in the substantia nigra pars compacta (SNc) of the BG. This triggers a cascade of functional changes in the BG which leads to hyperactivity of the BG output nuclei. Therefore current treatments try to reduce the hyperactivity by creating lesions in target areas, enhancing concentrations of dopamine in the SNc (via levodopa), or by deep brain stimulation (DBS). DBS is a surgical procedure in which an electrode is inserted through a small opening in the skull and implanted in a targeted area in the BG (typically the thalamus, subthalamic nucleus, or the globus pallidus). The electrode is connected to another insulated wire (called the 'extension') that is passed under the skin of the head, neck and shoulder and terminated at the neurostimulator ('battery pack'). The neurostimulator, similar to a heart pacemaker, is as large as a silver dollar and typically sits under the collar bone. It delivers electrical stimulation to the tip of the electrode via the extension

and blocks abnormal neural signals that cause tremor and other PD symptoms. The neurostimulator must be replaced via minor surgery every 3-5 years. See schematic in Figure below.



While DBS is not a cure, it is the most effective treatment for improving quality of life for PD patients. It significantly reduces their medications leading to improvement in side effects such as dyskinesias (involuntary movements caused by long-term use of levodopa), and is completely reversible as it does not damage healthy brain tissue. Therefore, a DBS patient may benefit from improved treatments in the future. Preliminary long-term studies in Europe even show that patients who receive DBS earlier have slower disease progression than those who are only on medications. [Eskandar et al., 2006, Interviews with Eskandar Fellows].

Despite the enormous benefits of DBS, the treatment comes with challenges. First, the procedure is a surgery where risk increases with patient age. Second, DBS has only been applied in the US in the last decade and therefore is only installed in patients whose symptoms cannot be adequately controlled with medications (the later stages of the disease). Third, if the electrode is off target by as little as 2 mm, the patient can experience emotional changes such as depression or anxiety. This occurs because the limbic area of the STN (which is related to emotional behaviors) is only a few mm anterior to the motor area of the STN. However, target detection is improving dramatically with imaging techniques. Finally, much is still unknown about how DBS works. Post surgery, the device must be calibrated (via trial and error) to maximize effectiveness and this can take up to several weeks and cannot easily be re-calibrated if the patient's condition changes.

I propose to seize a unique opportunity to revolutionize DBS in both the short and long term. In the short term I will improve calibration of the DBS device. In the long term I will build an intelligent DBS system in which the device itself will record measurements of target neural activity, use this data to calibrate the patient's pathological state, and adjust its stimulation strategy to the electrode in real-time.

My Opportunity

Access to Parkinson's Patients Post DBS Surgery

Today, after a patient gets a DBS system installed, he or she must sit with a Neurologist for several sessions to get the device calibrated so that the patient receives optimal stimulation parameters. I have teamed up with Dr. Emad Eskandar, a prestigious neurosurgeon and

neurophysiologist at Massachusetts General Hospital who treats up to 30 patients a year with DBS, to build an automatic feedback calibration system based on basic feedback control principles. Working with Dr. Eskandar will enable me to observe DBS installations in the operating room, work directly with patients after surgery, and develop a prototype of a technology that will allow efficient tuning of the DBS.

Access to Parkinson's Neurophysiological Data

The first step in building an intelligent DBS system is to have data that enables us to understand how neurons in humans encode information about the outside world and how this processing changes when the brain is diseased. Until recently, neural activity has only been recorded in animals. Measuring neural activity in humans is highly invasive and includes risk of permanent damage. The only situation where human data may be collected is when a patient with a neurological disorder is already undergoing neurosurgery. Dr. Eskandar recently received permission to use depth electrodes to record neural activity from the sub-thalamic nucleus (STN) of the BG while measuring kinematic variables, i.e. arm position, velocity, and acceleration, in PD patients executing a directed hand movement task. In this way, one can relate the impaired kinematics of the PD movements to the altered dynamics of the STN neurons. Even more rare, Dr. Eskandar has also conducted parallel experiments in healthy macaque monkeys. Therefore, for the first time in history, we have data from both diseased humans and healthy monkeys (which can be surrogates to healthy humans) of neural activity recorded from the *same* brain region while each subject performed the *same* task. I will use these data sets to not only understand the differences in neural encoding between PD and healthy brains, but also to aid in designing new technologies that can 'control' diseased neural activity to generate healthy behaviors.

Training with Leading Expert in Neuroscience Data Analysis

The second step in building an intelligent DBS system is to model both diseased and healthy neural dynamics from data. Sophisticated signal processing and modeling techniques are required to successfully characterize the dynamics of neural activity, which is stochastic, noisy, and a complex function of extrinsic and intrinsic factors. To master this challenging modeling problem, I joined Prof. Emery Brown's laboratory as a postdoctoral fellow. Prof. Brown is a statistician, medical doctor and leading expert in signal processing methods for neuroscience data analysis.

Training in Advanced Control Theory

The third step in building an intelligent DBS system is to use neural models to design stimulation strategies that will produce healthy behaviors from diseased brains. The solution to this design problem cannot be found in literature nor is taught in the classroom. It requires advanced control theory, which is the focus of my graduate research. My PhD thesis was supervised by Prof. Munther Dahleh, a world-recognized expert in modern control. In my thesis, I analyzed engineering systems in which certain signals carried only a few bits of information (as opposed to an infinite number of bits). My objective was to design optimal control strategies for such systems to generate acceptable levels performance (eg. tracking commands, rejecting noise) despite the defects in the system [Sarma et al., 2007a; Sarma et al. 2007b]. Altering the dynamics of neural activity in Parkinson's patients to mimic that of normals can be viewed in a similar

fashion. We want to design a control input to the Parkinson's system to "track" normal neural activity despite the fact that certain neurons are degenerating and transmitting defective signals.

My Plan

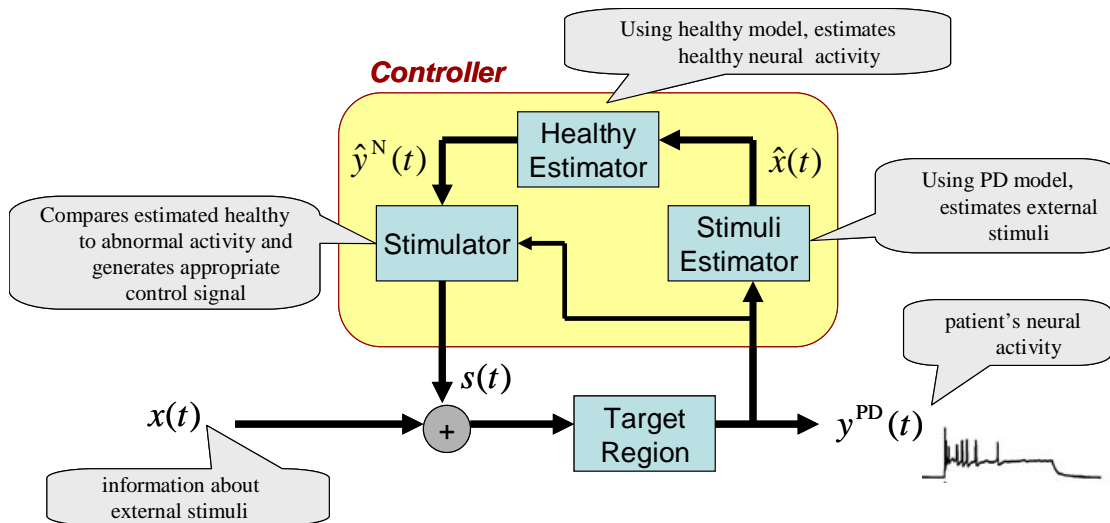
My specific aims are to work with Dr. Eskandar and Dr. Brown to 1. apply basic feedback control principles to better calibrate stimulation signals in newly installed DBS systems, 2. develop rigorous characterizations of STN neural dynamics in PD patients and surrogate normals, and 3. design optimal control strategies to alter the STN neural dynamics in a PD patient to mimic that of a surrogate. In the long term, I plan to test my control strategies in the operating room, and ultimately build new devices to better treat Parkinson's Disease.

Specific Aim 1: Apply basic feedback control principles to better calibrate stimulation signals in DBS systems. Before tackling challenging modeling and control problems, I will gain hands-on experience with Parkinson's patients. I will start by observing Dr. Eskandar perform pallidotomies and install DBS systems in the operating room. I will then work with Dr. Eskandar's patients to set up an improved method to calibrate the DBS system post surgery. Currently, a neurologist sets the stimulus at a constant frequency, and then waits for up to 30 minutes to observe corresponding motor behavior such as rigidity, bradykinesia and tremor. Based on observable changes, the neurologist adjusts the stimulation to generate improved behavior. This trial-and-error process is manual and time consuming. To minimize calibration time and to ultimately remove the neurologist from the loop, I will first use videography, infrared laser and other sensors to measure a patient's hand tremor, reaction time and movement velocity as a function of administered stimuli while the patient executes a directed hand movement task. Based on this data, I will then build a mathematical model that relates stimuli to tremor behavior, reaction times and movement velocities. Finally, I will use the model to design a feedback controller that automatically adjusts the stimulation signal in real-time to block movement disorders. In this aim I will gain a quantitative and deeper understanding of how stimulation modulates movement.

Specific Aim 2. Develop rigorous characterizations of STN neural dynamics in PD patients and surrogate normals. Using a small subset of the PD human data, a preliminary analysis characterized movement planning and execution, directional selectivity, and refractoriness, bursting and oscillatory dynamics of STN neurons, [Eden et al. 2006]. I will complete the development of the STN model using the entire human PD data set. Moreover, I will use the primate data, collected under identical conditions, to develop equivalent models for surrogate normal BG dynamics. In both cases, I will exploit the point process paradigm to characterize neural spiking activity. Prof. Brown's research has shown that point process models capture the stochastic nature of sequences of action potentials of neurons as a function of both extrinsic and intrinsic factors [Barbieri et al 2001; Brown et al. 2002 Brown et al. 2005; Truccolo et al. 2005]. A point process model is characterized entirely by the conditional intensity function, which represents the probability over time that a neuron will fire given both extrinsic (stimuli) and intrinsic conditions (neuron's own spiking activity and neighboring neurons' activity). I will apply maximum likelihood estimation procedures to generate generalized linear model estimates of conditional intensity functions, and I will use the time-rescaling theorem to measure goodness-of-fit of these models [Brown et al. 2002]. Finally, I will bootstrap, using new techniques for general point process models, to characterize uncertainty in the estimates [Sarma et al. 2007]. Such uncertainties must be quantified to ensure that control strategies remain robust

despite modeling errors. This aim will enable me to directly connect the neurophysiology behind Parkinson's disease to motor behavior.

Specific Aim 3. Design optimal control strategies to alter STN neural dynamics in PD patients to mimic that of surrogates. Next, I will develop a feedback controller to alter the STN dynamics of a PD patient to mimic that of a healthy human (surrogate normal). The controller will be made of three components as shown in Figure below. The stimuli estimator observes the neural activity of the patient, $y^{PD}(t)$, and then estimates external stimuli, $x(t)$. The second estimator uses the healthy model and the estimate of the external stimuli to produce an estimate of healthy neural activity, $y^N(t)$. Finally, estimated healthy neural activity is compared to the patient's activity to produce a control signal, $s(t)$, that minimizes the error between the two.



This control problem is challenging for several reasons. First, it is not known a priori to what extent one can alter the neural dynamics in a PD patient to mimic a normal state, i.e., we do not know how small the error between $y^{PD}(t)$ and $y^N(t)$ can be made. The error depends on how much the disease has progressed and the allowable class of controllers. Secondly, the controller is limited in that its estimate of $x(t)$, which represents information about the outside world, and its estimate of normal activity, $y^N(t)$, must be done with minimal delays otherwise stability and performance of the closed-loop system will be questioned. Third, it is not clear how to choose practical estimators and stimulator that perform optimally. Finally, all control strategies must remain robust despite model uncertainties.

Long-Term Goals

Test control strategies in the operating room. Initial tests of my control strategies may be performed by Dr. Eskandar on patients in the operating room itself. From such tests, I can assess whether my algorithms can detect the pathological state correctly, and furthermore stimulate neurons in the target area with signals that generate desirable responses to structured tasks. Such tests are as safe as those used to collect the initial data set from these patients.

Build new hardware and software devices, and/or medicines to better treat Parkinson's Disease. Once my control algorithms are successful in the operating room, I will collaborate with

the appropriate team of mechanical and electrical engineers, and material and computer scientists to build an intelligent DBS system. I am fortunate enough to be in an environment where the worlds' best engineers and scientists are within a mile radius from my lab. Furthermore, I will continue to work with Dr. Eskandar and his medical team to assess whether the information gleaned from my work will aid in development of new drugs to better treat PD.

Career Objectives

My ultimate career goal is to develop and lead a new interdisciplinary field that crosses control theory with neuroscience.

I will first establish myself as a new leader by completing the ambitious project proposed here and becoming an expert on the analysis of human physiological data and the mechanisms of deep brain stimulation. It is worth mentioning that deep brain stimulation is being increasingly used to treat a broad range of disorders including dystonia, Tourette syndrome, obsessive-compulsive disorder and major depression. Therefore, I see my work having a much broader impact in neuroscience.

I will then build a laboratory at a top notch institute that supports sharing of resources and personnel across engineering and neuroscience departments. I intend to have students and postdocs engaged in both pure control theory and control applications in neuroscience. Having learned advanced control theory from one of the best in the world, I fully intend to continue developing cutting-edge theory so that I remain a respected member of the small controls community and so that I am up to speed on the state-of-the-art in modern control. Furthermore, I intend to uncover, pursue and expose to the controls community important applications in neuroscience. I recently created an Invited session at this year's IEEE International Conference on Decision and Control titled "Modeling, Estimation and Control: Applications in Neuroscience." This invited session is the first of its kind and consists of talks given by the top researchers in computational neuroscience with many different backgrounds and I am confident it will be received very well.

I will develop a graduate-level course that focuses on control problems in neuroscience. Much of my post-graduate work will be integrated into the course along with other relevant research. The intention of such a course is to inspire graduate control engineers and scientists to pursue cross-disciplinary fields by exposing them to extremely exciting and high-impact problems in the medical sciences.

My career goals are perfectly aligned with the mission of the Burroughs Wellcome Fund Careers at the Scientific Interface award, which is to help cross-trained scientists early in their careers to develop as independent investigators and to advance fields in the basic biomedical sciences. This award will launch a splendid career by financially supporting my salary, equipment expenses, travel needs, setting up my own laboratory in academia, and development of my courses.