

Control of Neural Activity in Parkinson's Patients Using Deep Brain Stimulation

3-4 million people in the US have Parkinson's disease (PD), a chronic progressive neurological disorder that results in motor symptoms such as resting tremor, bradykinesia (slowness of movement), and rigidity. No treatment is available to stop the progression of the disease, however, a new and highly promising treatment for PD 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. The neurostimulator injects current back into the brain region to regulate the pathological neural activity (Figure 1). At major centers the surgery has become routine, accurate, minimally invasive and is reversible. Most importantly, patients claim that they get their lives back as most or all of their motor symptoms disappear and they can reduce their medications which have serious side effects.

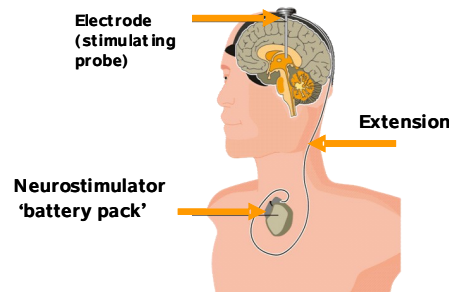


Figure 1: Schematic of DBS System

Although DBS is virtually a breakthrough for PD, it takes several weeks to months to calibrate the device post surgery. For patients this not only means many hospital visits, but 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, calibration is time consuming because the process is trial-and-error. During a visit, the neurologist asks the patient (post surgery) 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)

I have been **awarded \$500K by the Burrough's Wellcome Fund** for my current research efforts to 1. decrease 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 stimulation signals to be used by the DBS device. Despite the fact that DBS is simply a control signal applied to a neural system to achieve desirable motor behavior from a patient, no one has approached the problem from a control systems engineering perspective before.

CALIBRATION TODAY

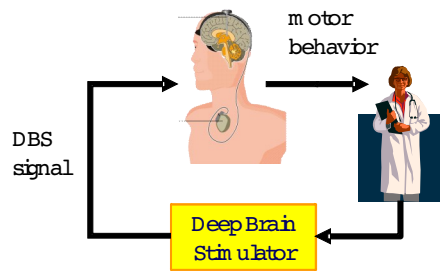


Figure 2a: Calibration Today

CALIBRATION VIA FEEDBACK CONTROL

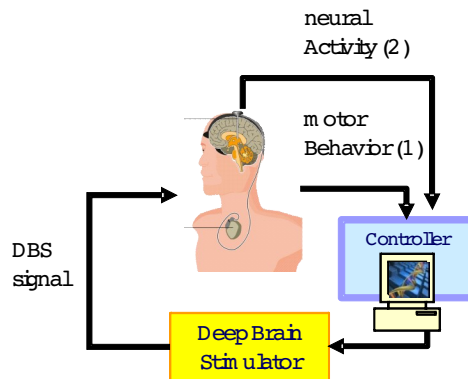


Figure 2b: Automated Calibration

1. Cutting Calibration Time: Quantifying 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 (eg. movement velocity, tremor frequency, reaction times) that will then be used to design a feedback controller to automatically select a set of stimulation parameters to achieve a given motor performance objective (Figure 2b). Quantifying such behavioral variables will enable more accurate and faster prediction of how different stimulation signals impact motor function, enabling calibration to be done more systematically, effectively and rapidly.

2. Developing New Stimulation Strategies: Measuring Neural Activity for Feedback Control: Currently, once the patient appears to respond optimally to DBS, he/she continues the final stimulation regime (typically a high frequency 100 Hz pulse wave) for years without much intervention from the neurologist. I will test the feasibility of changing the existing DBS system to not only allow a more broad class of stimulation signals to excite the brain area, but to also dynamically change the signal to maintain motor performance in the patient whose pathological state is evolving. This will be done by measuring neural spiking activity directly. The idea is to design a stimulation strategy (control input) to make the pathological activity look more “normal”, 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 (Figure 2b).

To build such a controller, one requires models that relate external stimuli to neural activity for both healthy and diseased subjects. Such models must be constructed from rare neurophysiological data entailing neural recordings from the same brain region of both healthy subjects and PD patients executing the same behavioral task. My collaborators at Massachusetts General Hospital have recently collected such data on healthy primates and PD patients executing a directed-hand movement task while single unit recordings were taken from the subthalamic nucleus of the basal ganglia (the most common target area for DBS). Using this data, I have employed advanced signal processing and estimation techniques to representing healthy and pathological neural activity as a function of movement direction and spiking history (intrinsic dynamics of neuron). These models not only fit the data well, but they uncovered prevalent abnormalities, i.e., pathological neural signatures, in PD activity not seen in healthy activity (using normal primates as surrogates to normal humans). In particular, 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. We have submitted these results for publication in the Journal of Neuroscience.