Behavioral Closed-Loop Deep Brain Stimulation for Parkinson's Disease

By

Daniel Esteban Amaya

B.S., Brown University, 2017

Thesis

Submitted in partial fulfillment of the requirements for the Degree of Master of Science in the Department of Molecular Pharmacology, Physiology and Biotechnology at Brown University

PROVIDENCE, RHODE ISLAND

MAY 2019

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Date: _____ Signature: _____

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Date: _____ Signature: _____

Dr. Michael Frank, Reader

Date: _____ Signature: _____

Dr. David Borton, Reader

Approved by the Graduate Council

Date: _____ Signature: _____

Dr. Andrew Campbell,
Dean of the Graduate School

Vita

Daniel Amaya was born on December 12th, 1994 to Maria and Oscar Amaya in Los Angeles, CA. He attended Brown University for his undergraduate studies with his awarded Gates Millennium Scholarship. Upon completion of his studies he graduated with a Bachelor of Science in Neuroscience. He then entered the Master's Program at Brown University in biotechnology. While at Brown he researched closed-loop deep brain stimulation for Parkinson's disease in Dr. Wael Asaad's research lab.

Acknowledgements

I begin by acknowledging my parents and family whose constant love and support were always a much-needed push in completing what I set out to do. A special thanks to my mother for always making sure that I was taking care of myself, and to my brother and sisters for always lending me an ear to talk to. I am also grateful for all the support received from my friends and colleagues.

Lastly I would like to acknowledge all the people at Brown who made this thesis possible. Starting with Dr. Wael Asaad, for his mentorship and for his creating of a comfortable working environment to work in. Dr. Shane Lee for his consistent patience and aid in guiding my project to its current state. Peter Lauro for always lending his expertise and lending a hand whenever asked. Finally all other members of the Asaad Lab for teaching me the skills necessary to start my project and showing me the ropes when I first started out.

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Abstract

Objective: Deep brain stimulation (DBS) has become a widely adopted treatment for the advanced progression of Parkinson's disease (PD) and is thought to modulate the balance of activity between the direct and indirect pathways of the basal ganglia. However, the current implementation of DBS is "Open-Loop" meaning stimulation is always being delivered, irrespective of the patient's condition and/or state of symptoms. To counter this, we delivered stimulation by closing the loop between the patient's DBS system and their current behavioral state. By delivering "Closed-Loop" stimulation, we can potentially show which set of parameters can push or pull a patient's behavioral state from being more or less symptomatic through the modulation of the direct and indirect pathway of the basal ganglia.

Methods: We tested "Closed-Loop" stimulation of the subthalamic nucleus (STN) and substantia nigra pars reticulata (SNr) in 6 PD patients as they engaged in our task, with 6 controls recruited as comparison. Our platform consisted of an external assessment of patient behavior where performance was then translated into stimulation control decisions that allowed for rapid modification of individual stimulation parameters such as voltage, frequency and contact location. Results compared behavioral performance at both the clinically therapeutic contact and the deepest implanted contact closest to the SNr.

Results: We found significant difference in patient performance using the deepest implanted contact. Specifically high and low frequency stimulation at the deepest contact decreased motor performance in comparison to the same stimulation at the therapeutic contact ($p<0.01$). Lastly low frequency stimulation at the deepest contact, in comparison

to high frequency, improved motor performance among patients showing nearly significant difference between the two parameters ($p=0.066$).

Conclusions: These results suggest that stimulation of the deepest contact at lower frequencies may in fact be more beneficial than high frequency at that location. Additionally, low frequency activation of both the SNr and STN in the direct and indirect pathways may work synergistically to improve patient behavior.

Introduction

Nearly 1 in eight Americans over the age of 65 is diagnosed with a neurodegenerative disease [5]. These diseases, such as Parkinson's disease (PD), have a dramatic effect on the quality of life of patients. Pharmacological treatment can be effective for treating these diseases but only for limited time until the effects wear off. As a newer option, deep brain stimulation has become one of the concrete treatments for those with ineffective medication treatment. Deep brain stimulation (DBS) is a clinical treatment technique first presented in 1980 for the surgical treatment of movement disorders, especially alleviating the symptoms of PD and Essential Tremor [1]. When a patient's medication is no longer sufficient in controlling their symptoms, DBS is used as a last resort option to alleviate their symptoms, as this method of treatment requires an invasive surgical procedure. Depending on the disease, the depth and location of the DBS electrode will vary and treat different neurological symptoms. The symptoms treated can vary from rest tremor seen in PD to psychological disorders such as obsessive-compulsive disorder [2]. In general, DBS treats symptoms that are typically associated with aberrant activity of "control centers" within the brain. The direct mechanism by which DBS modulates these "control centers" is still unknown.

Even though DBS has been shown to be effective in treating patients with neurological disorders, it does not always lead to the perfect outcome. In some cases DBS leads to unintended side effects, such as speech difficulty or tingling sensations in limb extremities [3]. Moreover the battery that supplies power to the DBS system is not an indefinite fixture, as it requires replacement approximately every 3–5 years. Additionally the tuning of stimulation parameters on a patient-by-patient basis has proven to be very

difficult over time as they are never static, and their effects at times fade as well [3]. After the initial programming session, DBS is not always guaranteed to be a significant change in the patient's condition. Furthermore, many of these movement disorders are not static and can change intermittently on a moment-to-moment basis, raising the question of whether or not stimulation needs to be constantly delivered.

In most DBS systems, voltage is constantly being delivered as therapy despite the patient's behavioral/psychological condition [4]. This open-loop paradigm of stimulation may prove effective as an initial treatment but conflicts with the closed circuit of sensory feedback signals that is naturally present within the human nervous system. Given that at any time point a patient can go from being non-symptomatic to symptomatic brings to light an urgent matter within the DBS system, which is the need for the therapy to respond to these changes in symptomatic state. In order for the system to reliably do so, a biomarker must be identified and used as a feedback signal to trigger stimulation changes.

Closed-loop DBS is a solution to the current limitations of open-loop DBS. Closed-loop DBS (CLDBS) creates a feedback loop where stimulation is adjusted according to the patient's condition or symptom severity. In the case of PD it could be interpreted as the presence/absence of rest tremor or fluidity in movement. This requires the development and investigation of both a feedback signal and control algorithm that can measure, detect and modulate the fluid states of movement symptomology. In the development of closed-loop methods for PD we researched three fundamental questions: how do we engineer a feedback signal capable of measuring the patient's symptomatic state, how can we communicate that signal to the patient's implanted DBS system, and

how effective can different paradigms of stimulation be in controlling the patient's symptomatic state?

The most important component of a closed-loop system is the availability of a real-time feedback signal. This signal must be representative of the patient's symptomatic state on a time scale at least equal to that over which their symptoms can change. While tremor may be the most obvious symptom visible in PD it is by far not the only measure available. A true feedback signal should encompass multiple facets of PD symptomology and concatenate that information into a single metric. Additionally the system should be able to change rapidly from the detection symptoms. The system must also be capable of updating its parameters within the same time-window. This requires the processing of the feedback signal in real-time within the time course of symptomatic changes.

The closed-loop system we created for the sole purpose of real-time feedback processing and stimulation changing enables the user to perform such a paradigm. Our system utilizes the Nexus–D stimulatory device, an investigational device capable of real-time communication of stimulation changes on one of their most commonly implanted neurostimulation devices, the Medtronic Activa PC. The Nexus-D is capable delivering rapid changes to stimulation as well as serve as the communication link between our system and the patient's battery [6]. The development of this system allowed us to test the capabilities of closed-loop stimulation in PD.

In order to investigate the efficacy of closed-loop we had to determine a legitimate source for a feedback signal. We first looked into a behavioral analysis of the patient's symptoms as it was the most correlated to the patient's state at any given time point. Kinematic behavioral analysis has been shown to be effective as a possible

feedback signal to measure the rapid changes in a patient's state [7,8]. Additionally some work has been done to show that beta-band activity can be used as a prediction of symptoms in PD [9]. For the purposes of this system, our trigger for stimulation was based on a multitude of behavioral kinematics that covered a range of possible symptoms. Future systems would encompass neural signals as well to predict any possible changes in symptomatic state.

With the wide range of possible stimulation patterns that we are capable of delivering with this system, here we will focus on two specific aims. The first is to investigate the ability to quantify and detect symptomatic states in PD using real-time, rapid symptom assessment. The second develop and test a closed loop stimulation using dynamic spatial and temporal modulation within PD. A further description of each aim is detailed below.

Aim 1: Investigate real-time motor assessment on short-timescales as a measurement of symptom severity.

PD subjects can exhibit varied motor symptoms such as increased (tremor) or decreased (bradykinesia) extremity kinematics. For this aim we will use our measurements of behavioral kinematics in a Cartesian space to quantify and justify their use as a potential feedback signal to run future CLDBS experiments. This will serve as the backbone of our online assessment of stimulation changes on subject motor performance.

Aim 2: Develop and test a closed loop system using dynamic temporal modulation driven by real-time rapid symptom assessment.

Here we will use real-time behavioral data to adjust the specific timing and manner of CLDBS within the substantia nigra (SN) and subthalamic nucleus (STN) and then compare its impact on task performance to open-loop DBS and no stimulation. Specifically, we will use different types of stimulation to not only "punish" symptoms but also "reward" improved task performance. If plasticity is indeed generated, we should observe persisted stimulation effects.

In summary, our goals are to design a CLDBS system that improves upon the therapeutic efficacy of traditional, open-loop DBS, by using the Nexus-D System. A successful outcome of this proposal will demonstrate that our CLDBS strategy produces more effective and more durable motor symptom control in PD patients.

Deep Brain Stimulation for Parkinson's Disease

Parkinson's disease is a neurodegenerative movement disorder that can debilitate the quality of life of those diagnosed. One of the most common therapies used to treat an advanced progression of this disease is deep brain stimulation. Below is a description in detail of the disease, the deep brain stimulation therapy, therapy drawbacks and closed-loop stimulation as a proposed improvement.

Parkinson's Disease

Parkinson's disease (PD) is the second most diagnosed neurodegenerative disease (after Alzheimer's) [10]. The prevalence of the disease averages to be 14 per 100,000 people in the total global population. This prevalence is age-related, with about 160 per 100,000 of the total global population over 65 years old being affected, with increasing prevalence among even higher ages [10]. Economic estimates predict that the total economic burden of PD in the United States is approximately 14.4 billion dollars, and that because of a rapidly growing and aging population, this value will nearly double by 2040 [12].

Clinical symptoms of PD comprise both motor and nonmotor symptoms. Classic symptoms of PD patients include slowness of initiation of voluntary movements (bradykinesia) with a progressive reduction in speech (aphasia), muscular rigidity, resting tremor, and postural instability [13]. Among all symptoms, resting tremor is typically the first reported by patients and easily the most noticeable, usually occurring at low frequencies from 2-7 Hz [14]. When either left alone or combined these symptoms can have a substantial effect on the quality of life of diagnosed individuals [15].

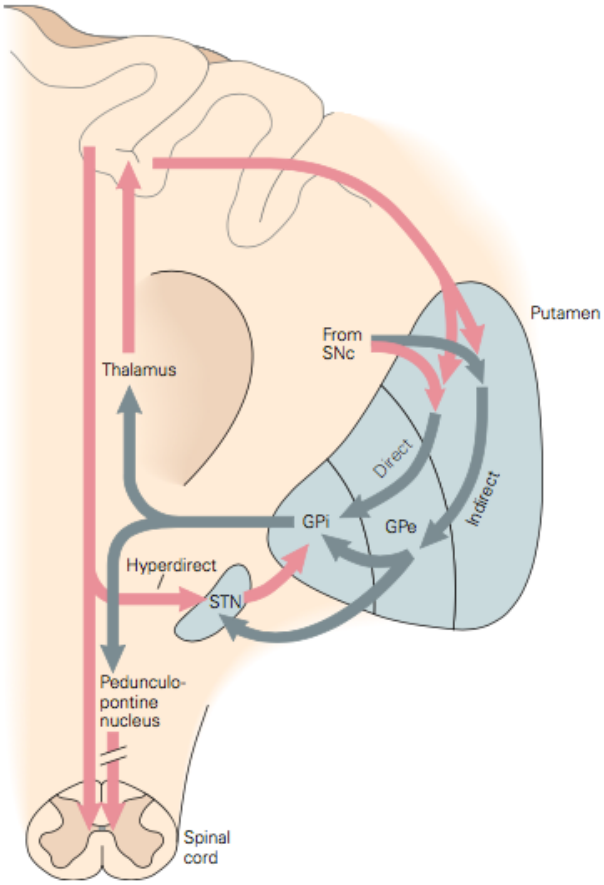


Figure 1: Above is a schematic of the direct and indirect pathways within the basal ganglia. Excitatory connections are shown in red and inhibitory connections are shown in green. Taken from *Principles of Neural Science* [26].

PD is generally characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta. These dopaminergic paths project to the striatum and regulate activity in two distinct paths: the direct and indirect pathway (see Figure 1). With normal activation of D1 receptors in the substantia nigra, projections to the striatum in the direct pathway lead to inhibition of the globus pallidus internus (GPi), disinhibiting the thalamus, thereby causing increased activity of motor cortex, whereas D2 receptor activation via the indirect pathway leads to activation of the globus pallidus pars externa (GPe) causing decreased thalamic activity and a decrease in motor cortex. Given their

normal push pull activity, the progressive loss of dopaminergic neurons associated with this circuit are thought to shift the balance of activity towards the indirect pathway [15]. Despite our general understanding of the pathophysiology of PD, the underlying cause of substantia nigral degeneration have yet to be discovered.

As of now, there is no known cure for PD, and most therapies available to patients only treat the symptoms of the disease without delaying its progression. Current therapies for PD involve the administration of the dopamine precursor known as L-3,4-dihydroxyphenylalanine (L-DOPA). While L-DOPA may initially combat the progression of PD, the accumulation of oxidized dopamine can eventually lead to unintended side effects [16]. When drug therapy is no longer effective in treating PD symptoms, many patients opt for a more advanced treatment. Deep brain stimulation is one advanced treatment where patients undergo the implantation of a deep brain stimulator (see section on Deep Brain Stimulation below).

History of Deep Brain Stimulation for Parkinson's Disease

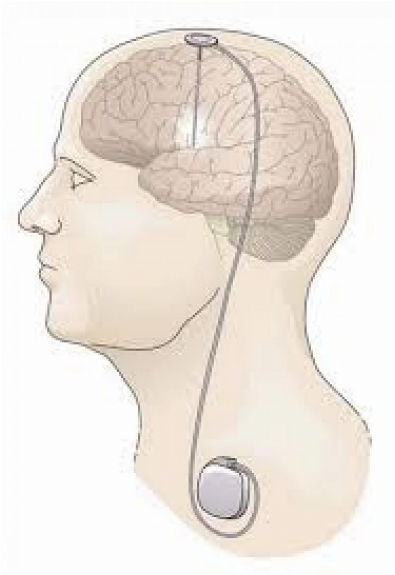


Figure 2: Depiction of deep brain stimulation system [25].

Giovanni Aldini initially utilized deep brain stimulation in the early nineteenth century as a method of invoking muscle activation on recently decapitated prisoners. From his experiments he concluded that evoked stimulation of the human cortex could be used with therapeutic benefit in treating neuropsychiatric disorders [8]. Aldini's hypotheses led to investigation into two fields of research that would later even further develop during the ninetieth and twentieth century: the first being the use of brain stimulation as a neurophysiologic investigation to understand the functioning of the brain, and the other as an alternative therapy for neurodegenerative disorders. By 2002, deep brain stimulation for PD eventually was granted approval by the United States Food and Drug Administration (FDA) and since then, DBS has been used to treat over 150,000 people with PD worldwide [17]. Since that time, deep brain stimulation has been to shown to be an effective and highly beneficial treatment for patients with PD.

Clinical Use

Despite the large gap in knowledge behind the mechanisms of DBS, the clinical use of the system is well established. The general layout of a DBS system consists of surgically implanted electrodes placed in specific and deep brain structures as well as an implanted pulse generator that provides power to the electrodes. The typical electrode archetype used in DBS consists of four electrical contacts that are evenly spaced apart, allowing for multi-region stimulation and fine-tuning of the patient's therapeutic system. For the Medtronic system, the commonly used lead models are the 3387 and the 3389. The 3387 model is a 40 cm long and 1.27 mm wide cylindrical wire with 4 cylindrical electrodes that are 1.5 mm in length, where each is placed 1.5 mm apart. The 3389 model carries the same specifications, except for an inter-electrode spacing of 0.5 mm. Stimulation parameters vary from patient to patient, but typically an electrode delivers "monopolar" or "bipolar" stimulation using a charged-balanced biphasic pulse with a pulse width of 60-90 μs. Monopolar stimulation consists of having one electrode contact acts as the anode whereas the surround medium (e.g. brain tissue) act as the cathode. For bipolar stimulation two electrode contacts are utilized as the anode and cathode [21]. The range in frequency and amplitude of these pulses vary from patient to patient but typically range from 130-180 Hz and 0-6 V [21]. The patient's clinician tunes these parameters over a period 9-12 weeks post operation.

For people with PD, the most common targets for DBS are the subthalamic nucleus (STN) and the globus pallidus internus (GPi). Due to the necessity of these brain regions in determining movement they have been implicated as viable sources of alleviation of PD symptoms. The choice between STN and GPi is more of a patient

specific approach. Both STN and GPi have been shown to be equally effective in reducing tremor symptoms but STN targeting reduces medication intake and has an overall better economic profile whereas GPi has been shown to allow for better dyskinesia suppression and ease of DBS programming [18]. Despite the extensive amount of research in DBS, the mechanism by which DBS treats PD in these areas is still not well understood. In general it is thought that Parkinson's disease causes irregular neuronal activity within these control centers of the brain; in response DBS disrupts this irregular activity by stimulating these control centers, improving communication between brain areas [19].

After implantation, all DBS patients eventually undergo a series of clinical visits with their clinician in order to fine-tune the stimulation parameters of DBS. Fine-tuning of a patient's DBS system begins approximately 2-4 weeks after the implantation of the electrode to allow for the effects of micro-lesions to fade away. Micro-lesion effects are believed to arise from the trauma of implanting a DBS electrode, perturbing the balance of movement related processes and in some cases returning them back to normal. Thus, for an accurate assessment of stimulation benefits, it is recommended that DBS programming begin only when the initial effects fade away [20]. Parameter programming can also be a difficult process, at times clinicians must reduce treatment efficacy in order to mitigate unintended side effects. Clinicians must keep in mind the average power usage while programming. The lifetime of patient's battery depends on the capacity of the battery as well as the adjusted stimulation parameters set by the clinician. This can lead to highly variable battery life when comparing across patients.

Despite the overall benefit in using DBS for PD there are still some side effects

that can diminish its therapeutic effect. These side effects are typically correlated to the region into which the DBS electrode is implanted [21] and may be caused by sub-optimal electrode placement [22]. These stimulation-related side effects include dyskinesias (aberrant, uncontrolled movements), postural instability, speech dysfunction, tonic muscle contractions, paresthesia (numbness/tingling), eyelid and eye disturbances, and cognitive problems [22].

Closed-Loop DBS Overview

In this section we discuss open-loop and closed loop systems in regards to neuromodulation. Descriptions and terms used in this section are collected from various components across both platforms. The purpose of this section is to define the scope and terminology used in the upcoming sections that discuss specific topics relating to closed-loop vs. open-loop DBS.

Open Loop versus Closed Loop

Previously we reviewed the current DBS systems that modulate the movement centers of the brain. Stimulation of these systems is currently a continuous system, meaning that after the initial programming session, the patient's battery is turned on and is intended to stay on indefinitely. This means that the parameters of DBS stimulation are left at some static setting and are rarely if ever changed despite any changes in the patient's physical/mental state. Thus despite its overall benefit, continuous stimulation may not be the paradigm in treating rapidly changing symptomatic states. Many of the current drawbacks of DBS result from this open-loop paradigm [4]. Open-loop stimulation can result in side effects as mentioned in previous sections, causing rapid battery power consumption and can lead to multiple programming sessions to find the best set of stimulation parameters. In general, open-loop DBS may be a suboptimal therapy.

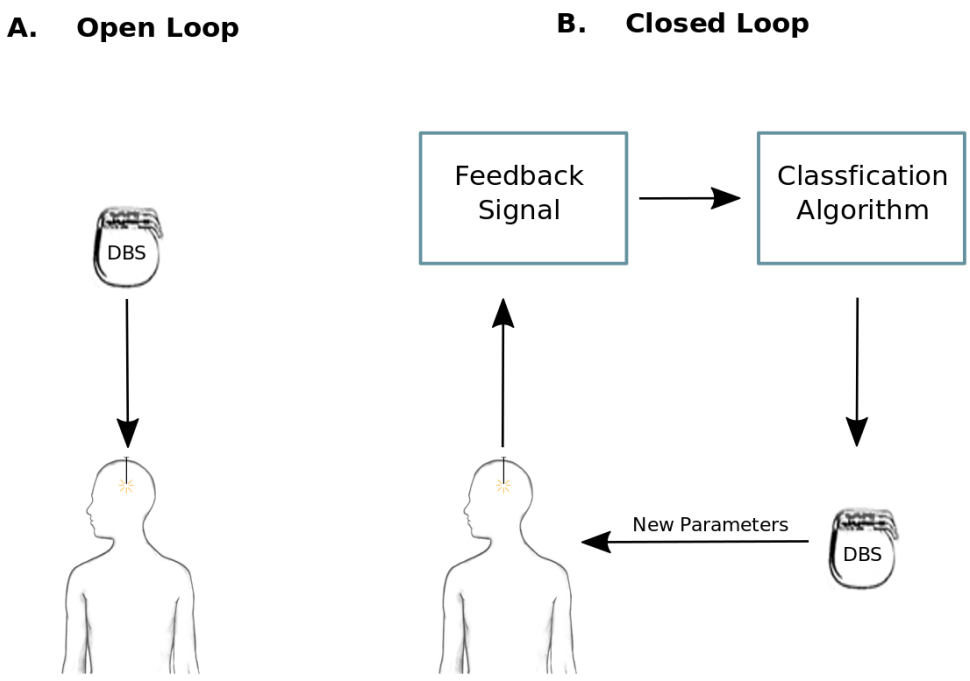


Figure 3: Diagram showing open-loop vs. closed-loop stimulation systems. Open loop systems constantly deliver stimulation whereas closed loop take into account some patient behavior

Closed-loop efforts to improve the stimulation paradigm have been made to handle the rapidly changing symptomology of PD. Such efforts utilize a feedback signal used to determine when a patient is being symptomatic and to what degree are they experiencing their symptoms (see Figure 3 B). For example, a symptom that could be treated with this system would be tremor. Utilizing a smart sensor such as an accelerometer could track when a patient's involuntary tremor begins. The accelerometer device could then communicate with the patient DBS system to modulate stimulation. Delivering stimulation in a closed-loop fashion would then change the normal stimulation pattern they always experience in response to real-time changes to the patient's condition. Theoretically delivering stimulation based on patient symptomology might reduce side effects created by open-loop, decrease the amount of time spent by the clinician to

optimize a patient's parameters, and even extend the amount of time between surgical battery replacements due to less power consumption. Therefore a closed loop system might be more effective and efficient than the current open-loop therapy.

Closed-Loop Overview

Closed-loop Feedback signals

In the scope of closed-loop research there have been several types of feedback signals that have been investigated as possible markers to trigger stimulation and even detect the presence of symptoms in humans. These feedback signals range in their complexity, from measuring the amplitude of limb movements, to neural recordings from structures within the basal ganglia [4][8].

There are specific strengths in using particular feedback signals in closed-loop DBS. Recording neural signals is highly sought after as a feedback signal as the patient does not require any external monitors and can potentially utilize the same hardware used in DBS. One downside however is that it most likely requires the implantation of more hardware and again really expresses the importance of precise placement of the DBS electrode. This new hardware would need to either classify the data online or will need to stream the data to some external processor. Additionally even if the system were to be placed onto existing hardware sensing, classifying, and the streaming of data all will require more resources from the implanted battery, potentially mitigating the potential power efficiency the closed-loop paradigm may provide. Non-invasive measures such as the measurement of limb movements are simple, safe, and are highly representative of the patient's current symptomatic state. Since behavior is the most accurate representation of

the patient's symptoms, a signal comprised of such measures would be ideal in triggering stimulation.

Prior Closed-Loop Work

In the field of DBS there is scarce research being done in humans utilizing a closed-loop paradigm. That being said there are rodent and non-human primate models of PD that have shown a proof-of-concept that closed-loop deep brain stimulation (CLDBS) is a more effective paradigm in treating chronic movement disorders [7-8]. Even so, the research of CLDBS has also begun to show its effectiveness in humans. From cortically sensed neural oscillations in PD patients, clinicians were able to turn on and off stimulation in a in a closed-loop fashion [9]. This work showed that CLDBS can significantly reduce the amount of stimulation is needed to treat tremor symptoms and in addition showed that even the motor performances of CLDBS individuals improved when compared to open-loop stimulation. Additionally a CLDBS system for essential tremor showed that muscle activity driven by movement of the affected limb was a useful feedback signal in triggering stimulation and successfully suppressed the patient's tremor [24]. Despite their differences both experiments showed a stimulatory pattern determined by a CLDBS algorithm was more effective than some static preset stimulation pattern usually determined by the patient's clinician. However despite advances, both studies emphasized the need for a better or more robust control signal to trigger stimulation changes in real time.

Symptom Severity Classification for PD

Introduction

In this section we discuss our attempt to investigate a method into classifying PD symptomology in a Cartesian plane. To develop a closed-loop system the presence of a feedback signal must be representative of a patient's symptomatic state at any given moment. Given that this signal must be variable in nature much like a patient's symptoms, there are two theoretical feedback signals that could work for our purposes, behavioral kinematic measurements such as muscle activity or neural activity. Neural activity would be the most practical of the two as it could take advantage of already implanted hardware in the near future, but as it stands now it has not been shown to fully predict the spectrum of symptoms a typical PD patient may experience. Behavioral kinematic data on the other hand is the gold standard by which all closed-loop can be assessed, as any changes to stimulation should directly correlate to changes in behavior. Additionally not all implanted DBS systems at the moment carry the ability to record data and stimulate simultaneously, making the transition to utilizing neural signals more difficult to assess.

Due to the accessible nature of kinematic data the ability to process and integrate these signals into a closed-loop system raises a significant issue. While the most noticeable symptom present in some advanced forms of PD is tremor, it is not the only symptom to characterize the disease. As mentioned previously, PD symptoms are not static and can vary from patient to patient. While one patient may experience significant tremor in their dominant hand, it is equally possible that another patient may only experience difficulty in initiating and/or continuing movement. Patients experiencing

bradykinesia/dyskinesia would present a different kinematic profile than compared to those presenting tremor. This discrepancy in symptoms emphasizes the significance of a feedback signal capable of capturing multiple facets of PD symptomology. To capture the multi-faceted nature of symptoms in PD we recorded kinematic data in a XY space to quantify multiple symptoms on a single scale.

Methods

Subject Recruitment

Experimentation was performed on site at Rhode Island Hospital in association with Brown University, and all subjects that participated gave informed consent, with the approval of the IRB. Data for this experiment were collected from several subjects who had been diagnosed with PD and had undergone implantation of a DBS system. All subjects recruited had implanted Activa PC DBS systems, with bilateral electrode implantation in the sub-thalamic nucleus (STN). Patients are typically programmed 1-month post-implantation to allow for ample time to heal and then subsequently every 2-3 months are scheduled a follow up visit to reprogram their stimulation. Subjects were recruited at least 6 months post-DBS implantation to allow for ample time of surgically related effects to dissipate as well as allow for optimal programming of their therapeutic system in order to better isolate the effects of DBS on their behavior.

During each experimental session data were recorded while the subject was sitting stationary in a closed-environment. For this portion of the experiment there is approximately in total 15 minutes of recorded data for each subject during each of their visits. Subjects consented in allowing for alterations to be made to their DBS

programming during the entirety of this experiment. To begin, subjects had their stimulation switched off before any measurements were made to assess their behavior. All subjects began in the stimulation off state allowing for consistency among subjects and allowing for a return of their symptoms after a 5-7 minute settling period. For this portion of the experiment all changes made to the subject's DBS system were done externally via the Medtronic Clinician Programmer model CT900 with Activa™ Application Application A610 and Communicator 8880T2. After allotting 5–10 minutes to settle post-stimulation changes, subjects began the experiment by engaging in a game-like behavioral task.

Behavioral Task

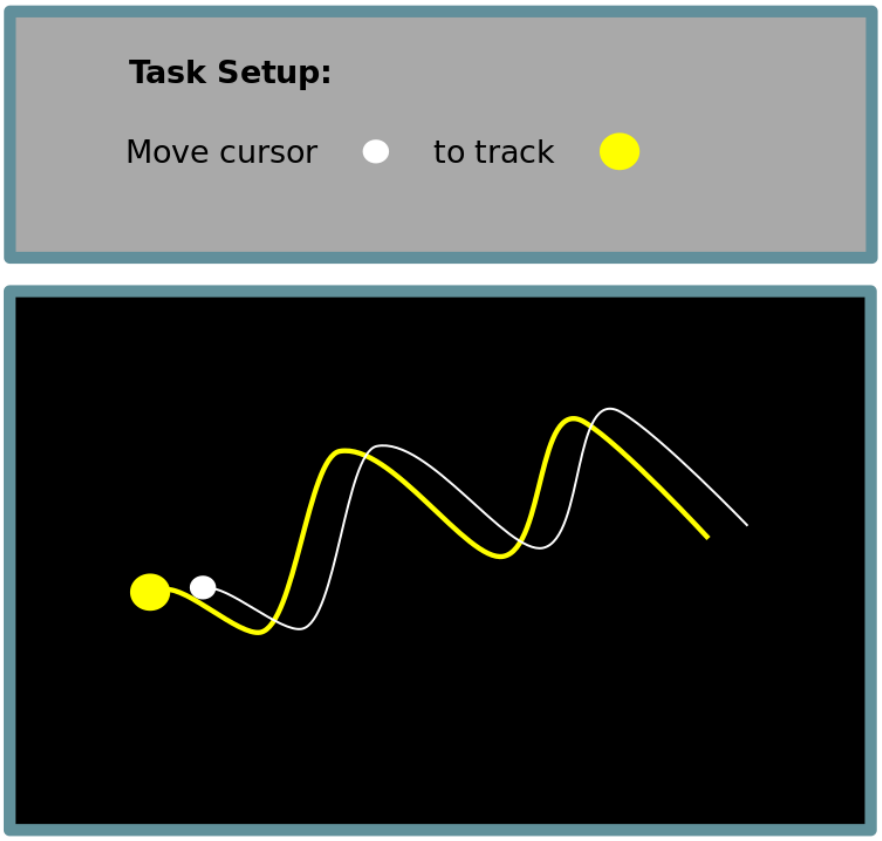


Figure 4: Behavioral Task. Subjects were directed to manipulate a pen-based tablet controlling a white cursor on screen to track a moving yellow target as close as possible. This task provided for a continuous measurement of motor performance during our experiments.

This experiment employed a target-tracking task to continuously measure the degree of patient symptoms as they were playing. Specifically, PD subjects sat straight up in front of a mounted swivel display positioned approximately 2 feet away. The behavioral task was implemented in NIMH MonkeyLogic [27-30] and utilized a graphics tablet that sampled spatial transformations at 200 Hz. For the task, a graphics tablet was positioned in front of them where subjects used their dominant hand to manipulate a pen-like stylus in order to track a target circle that moves smoothly across the screen with the

goal of maintaining their position in the center of the circle as it moves (Figure 4). The target circle followed a random path invisible to the subject, with each trial lasting approximately 20 seconds. Each session for this portion of the experiment consisted of 30 trials where subjects only needed to perform 1 of these sessions during their visit. Control subjects performed this task in a similar setting.

Motor Metrics

For this experiment we implemented several measures of motor performance on short timescales. These metrics were applied in small 1-second epoch windows with no overlap. Typical measures of PD such as tremor are represented in our library as the magnitude of a 3-10 Hz band-pass filtered x- and y- tablet traces whereas all other metrics were calculated after low-pass filtering of the same x- and y-tablet traces below 3 Hz. Our complete library of metrics includes correction angle (CA), absolute distance (AD), excursion distance (EDi), excursion difference (ED), excursion ratio (ER), slowness (SL), speed difference (SD), speed ratio (SR), tremor magnitude (TM), vector angle (VA), and vector error (VE). Due to the heterogeneous nature of PD motor performance, for each PD subject we sought to determine the combination of motor metrics that best represented their individual constellation of symptoms.

Support Vector Machine Training and Symptom Score Calculation

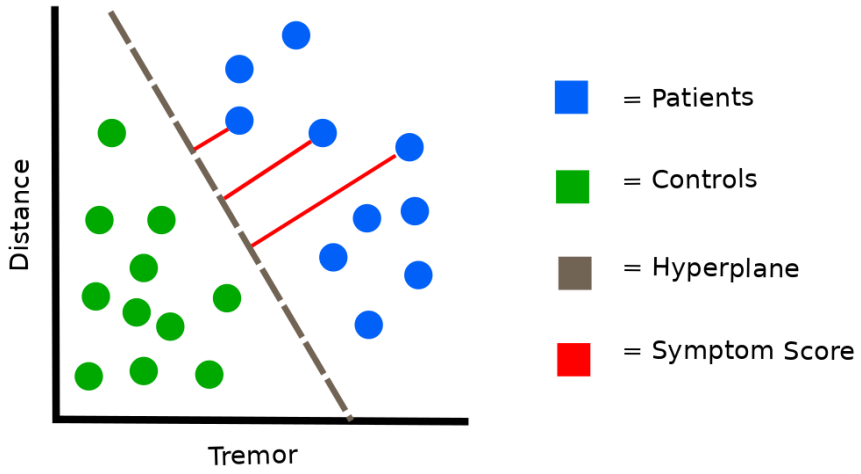


Figure 5: SVM Training and Symptom Score calculation. SVM training was performed on an aggregate distribution of subject (blue) metric points with a sub-sampled distribution of control points (green) to match in size. Symptom Scores (red) were calculated as the orthogonal distance of each point from the hyperplane (brown). For simplicity, the hyperplane derived above is based off two features Tremor and Distance.

Motor performance features for building our support vector machine (SVM) classifier were extracted from our metrics library by chunking each metric into 1-second windows with no overlap. Each of the chunks were then concatenated together across the entirety of the subject's session and used to train our classifier. Training our classifier was performed on a subject-by-subject basis, where our concatenated metric chunks were matched in size from a sub-sampled distribution of controls. Chunks were labeled based on which population they were sampled from, in order to use in our SVM algorithm. Distributions were then Z-normed and the optimal separation between the two

distributions (our hyperplane) was selected using a 10-fold cross validation. Each hyperplane would then be used to rank the effective weight of every individual metric fed into the algorithm and allowed for post-hoc calculation of the subject's symptoms. Based on the coefficients of the subject's hyperplane, symptom scores (SS) were calculated as the orthogonal distance of each data point from the SVM-generated plane (Figure 5), therefore allowing us to quantify the amplitude of symptom severity on a subject-by-subject basis.

Results

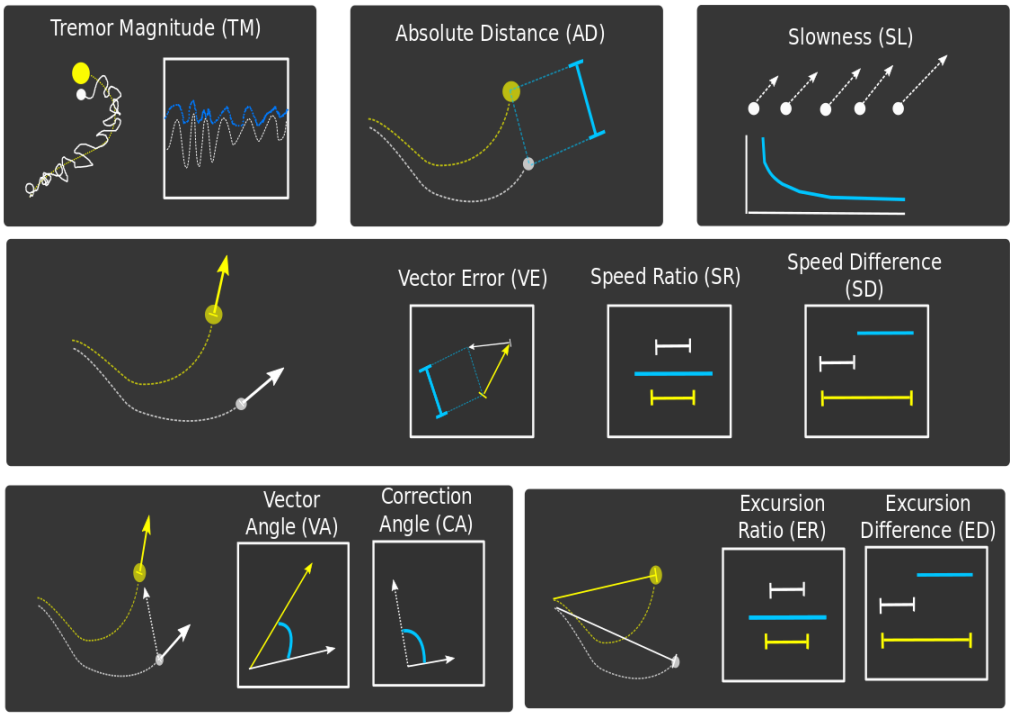


Figure 6: Metrics. Above is a visual representation of our metrics library, each of which constitutes a separate measure of PD symptoms represented in a Cartesian plane.

Quantification of Motor Performance on Short Timescales

Our continuous tracking task required subjects to track an on-screen target using a tablet-controlled cursor (see Figure 4). Our task was designed as a continuous assessment of movement on short timescales. Recruited PD subjects with bilateral electrode implantation in the STN (n=6) and control subjects in the clinic setting (n=6) performed this motor task. Due to the multi-faceted nature of PD symptoms we assumed it to be unlikely that any single metric would be appropriate as a continuous measure of the subjects performance, so we defined a library of metrics (Figure 6) that could capture a variety of motor deficits in a two dimensional space. In order to ensure that the deficits that we are capturing are not redundant we calculated correlations among our metrics (Figure 7) and found a large range of correlations among individual pairs of metrics (R^2 [0.01-0.97] in controls and R^2[0.01-0.98] in PD subjects). Showing that among all our metrics our features that were used to train our SVM classifier were mostly non-redundant and that they may be working synergistically.

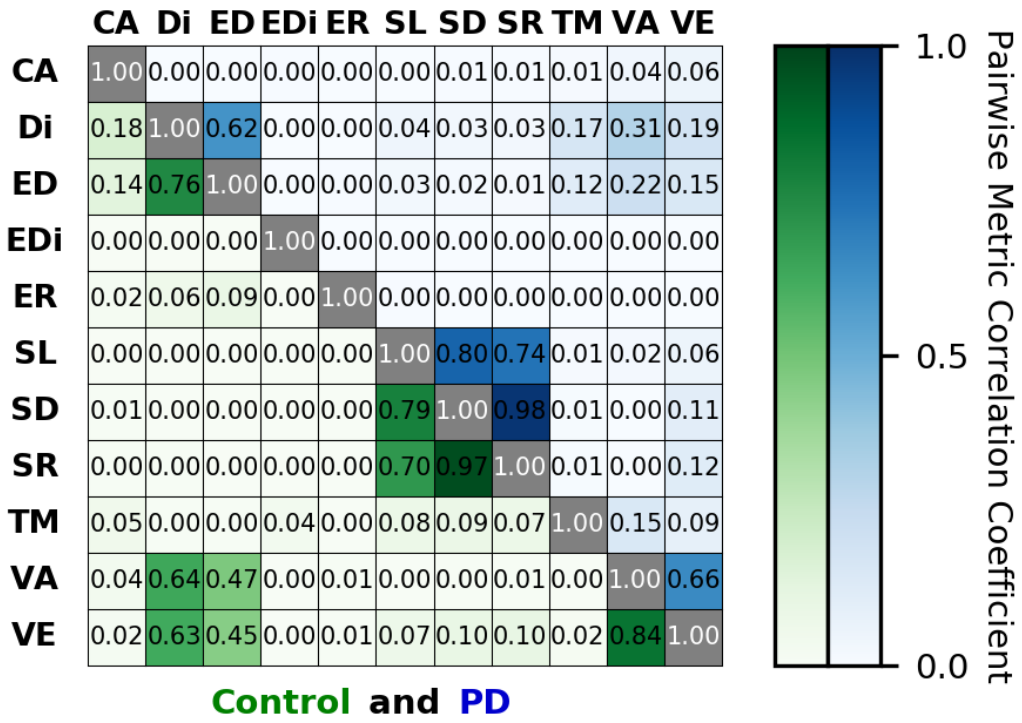


Figure 7: Metric correlations matrix displaying pair-wise correlations among our metrics library in both PD subjects (blue) and control subjects (green).

Next we combined all individual metrics into a single composite score reflecting the degree of motor deficit within a given time window. In order to create this composite score a support vector machine was applied to our library of metrics in order to determine the weight of each metric that allows for optimal separation of PD motor performance and control performance (see Figure 6 and Figure 8). Motor performance was assessed in 1-second epochs, and the orthogonal distance from the hyperplane was defined as our "Symptom Score" (SS). In other words, SS serves as a single composite measure of motor error that weighs any particular metric or combination of metrics that best separates their performance from that of control subjects. It is also heterogenic in nature, much like the disease, as the main feature weights calculated from the SVM hyperplane

showed large differences in weighted features for each subject. Our resulting distributions for PD subjects and controls were significantly distinguishable, the receiver operating characteristic (ROC) area-under-the-curves comparing each control to each PD patient ranged from 0.63 to 1.00 (mean ROC area ± standard deviation = 0.8661 ± 0.978 with all bootstrapped p-values < 0.001, Figure 9). Subsequently the average hyperplane from every subject's SVM training session was then used to calculate final symptom score values and hyperplane coefficients for future estimations.

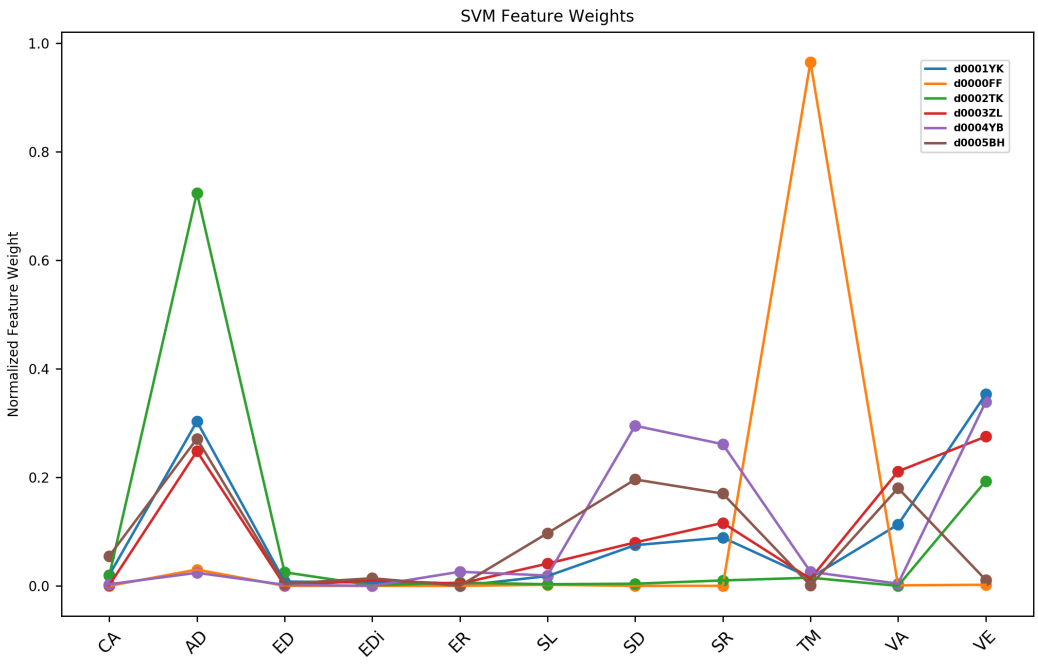


Figure 8: SVM Feature Weights. Above are patterns of metric weights generated by each subject specific SVM to show the heterogeneity of PD symptoms and the features emphasized by our training algorithm.

Figure 9: ROC AUC. Results of pair-wise ROC analysis of SS distributions comparing individual PD vs. control subjects, demonstrating accurate discrimination of performance across these populations.

Symptom Score distributions for both the PD and control subject populations were mostly skewed away from the hyperplane. The distribution of SS for the PD distribution showed a more positive skew than the controls, reflecting very symptomatic epochs during experimentation (Figure 10). ROC analysis also showed significant difference between the two distributions (AUC = 0.817).

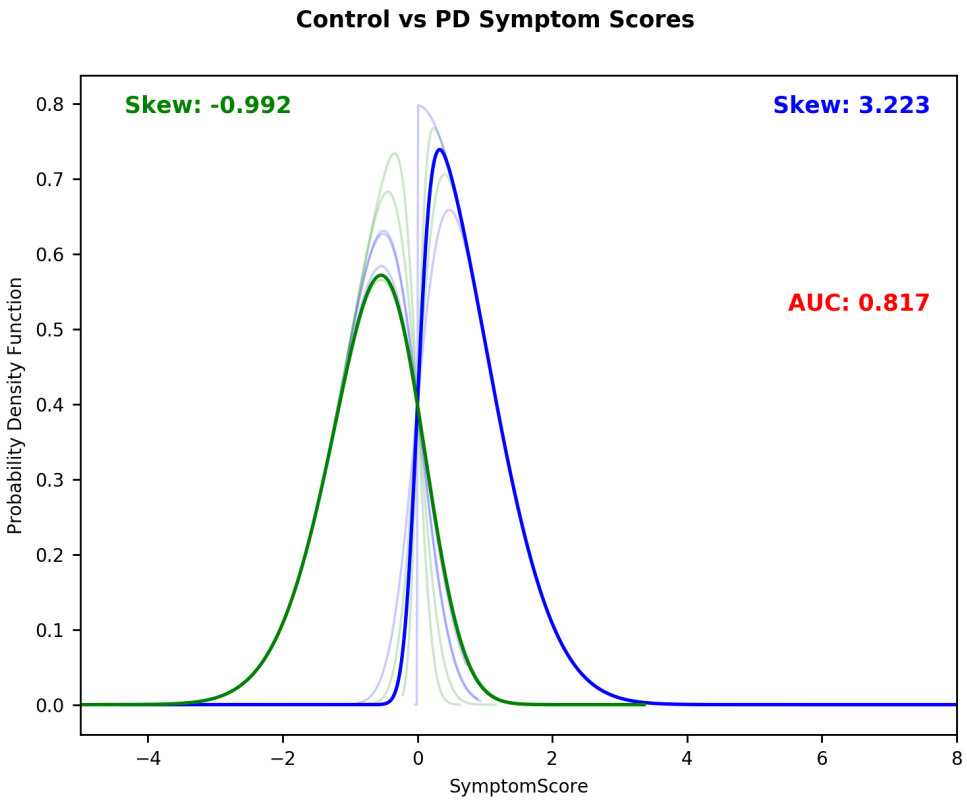


Figure 10: Probability Density Symptom Scores. Averaged distributions of symptom score for controls (green) and PD (blue) subjects, overlaid upon individual subject traces.

In order to determine the timescale of behavioral changes in each group, we investigated the temporal autocorrelation of symptom scores by recalculating or previous 1-second epochs into smaller 100 ms epochs with no overlap. For control subjects this showed a narrow correlation peak, suggesting that the symptom scores for controls were no more correlated in time than they are with noise. In contrast, PD subjects displayed a broader peak in correlation (Figure 11; full-width at half-max ± 0.176 seconds in controls and ± 0.314 seconds in PD subjects). The choice of a 1 second window for calculation of symptom scores was roughly consistent with the observed timescale of change in the performance of the subjects that participated in this task. These observations suggest the

task and metrics captured aspects of motor performance that were distinct between PD subjects and controls.

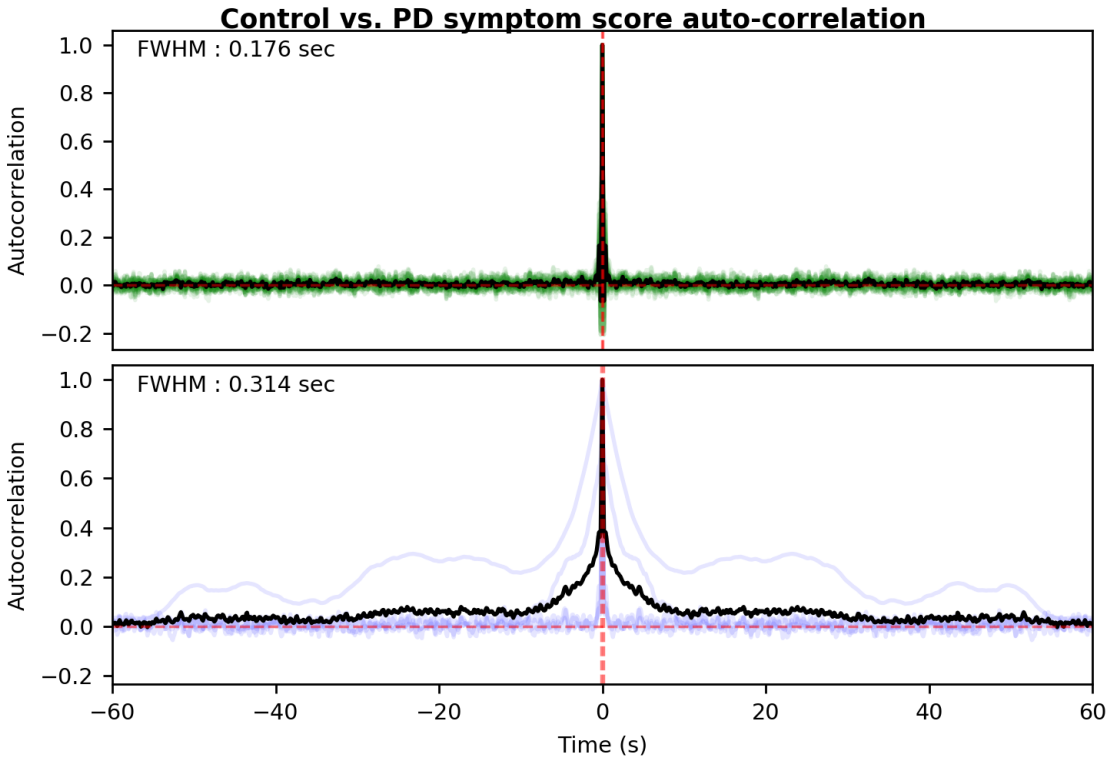


Figure 11: SS Autocorrelation. Temporal autocorrelation of symptom score distributions in controls (top/green) and PD (bottom/blue) populations, demonstrating broader peaks of correlation in PD.

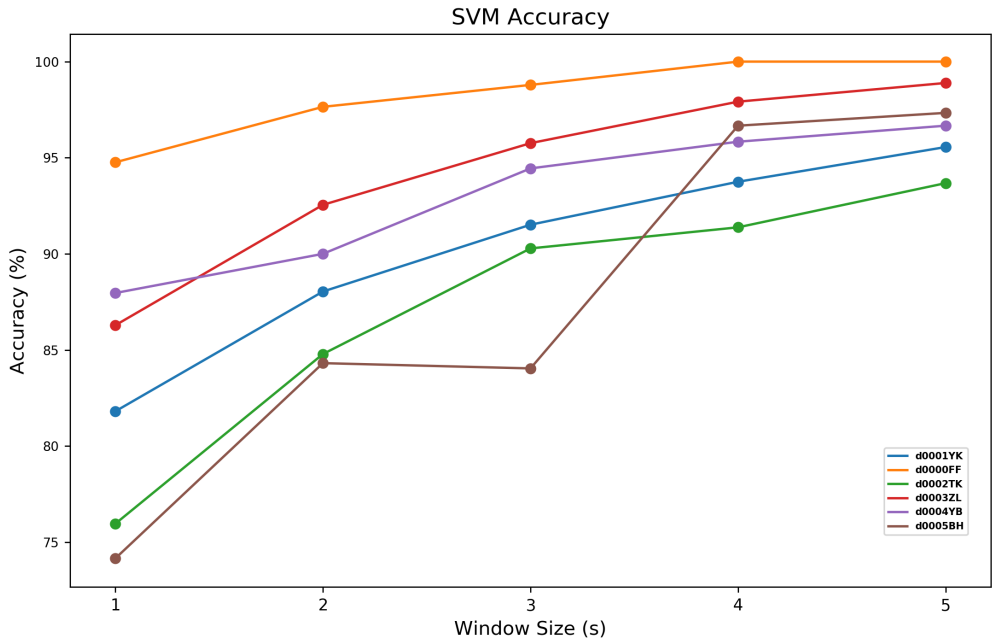


Figure 12: SVM accuracy based on increasing window sizes.

Discussion

The purpose of these analyses were to determine the extent to which PD symptomology recorded in a 2D space can be measured and quantified to detect the initiation and amplitude of symptoms in PD subjects. To examine this issue, symptom score distributions were calculated from subject specific SVM classifiers to in order to set an objective measure of symptoms while the patient was engaged in the behavioral task. This SVM classification was able to use simple 2D spatially derived metrics as viable features to quantify motor performance on short timescales (1-second epochs). While prior work has shown the viability of other simple tasks such as finger tapping or repetitive stepping as quantifiable measure of symptomatic changes of PD [31-32] they

lack the ability to perform multi-dimensional symptom assessment that is enabled by our machine learning feature extraction method.

We found that in order to capture the heterogeneous nature of PD symptoms we needed a metric that was heterogeneous itself. Given that our metrics library is mostly non-redundant our classifier is capable of extracting sensible features from simple 2D spatial transformations and then distinguishing them from non-symptomatic subjects. The overall accuracy of our classification method varies widely (see Figure 12), ranging from approximately 75-95% using 1 second epochs. By increasing epoch size we can achieve even greater accuracies, thus enabling better symptom state classification, but doing so would also result in less frequent behavioral epochs to analyze and would result in longer delays between classification and detection. Therefore we view utilizing 1-second epochs as a better performing classifier even if it is slightly less accurate.

After showing that our method of analyzing subject performance is accurate and flexible the limitations of this approach are also very apparent. Analysis of motor performance is not all encompassing and indicative of symptoms of PD. While motor deficits are definitely debilitating, there are other possible psychiatric consequences such as depression and sleep disorders are present [33-34]. The biggest limitation in this approach is again that it only analyzes movement of the subject's extremities, specifically only their dominant hand, possibly resulting in a slightly inaccurate profile of a subject's symptomatic state if their hand is not affected

Closed-Loop Stimulation for Parkinson's Disease

Introduction

The work presented in this section attempts to investigate aim 2 of this dissertation: develop and test a closed loop system using dynamic temporal modulation driven by real-time rapid symptom assessment. The previous section explored the quantification of symptom severity on a rapid timescale. Through the use of symptom scores (SS) the results of the previous section demonstrated that support vector machine derived SS had both the temporal and spatial resolution to capture the rapidly changing symptomatic states of any particular subject as well as reflect an accurate assessment of the subject's symptomatic state at any given time-point. This suggests that SS would be a viable option as a feedback signal to detect symptomatic changes and alter stimulation parameters in a closed-loop deep brain stimulation system.

There is not much prior work utilizing the closed-loop paradigm for deep brain stimulation in humans, one particular study that investigated the ability of neural signals to control stimulation showed particularly interesting results [9]. This study utilized low to high beta-band power (12-35 Hz) as a threshold trigger for stimulation changes in PD subjects. From their investigation they were able to show that responsive changes of stimulation based on changes in beta frequency led to a greater reduction of a subject's Parkinsonian related clinical state. Despite their results this implementation of closed-loop proved tasking as the investigators had to manually tune beta-band thresholds for each subject, and did not even include other frequencies that could also be potentially signifying of other PD-like symptoms, such as gamma oscillations (30-100 Hz) signifying PD hyperkinetic states [35-36]. Additionally, this study only performed the

closed-loop paradigm in a perioperative manner, possibly introducing noise into their system from surgically related effects of electrode implantation [37].

In contrast, a separate investigation made the tuning of symptomatic thresholds semi-automatic through the use of support vector machine learning [40]. Machine learning has been used to detect symptoms in both motor and neural signals within PD subjects with great success [38-39]. However these same studies did not use machine learning as a method of symptom classification for closed-loop stimulation, meaning they did not utilize their classifier to change stimulation parameters. Investigators at the University of Washington managed to present true closed-loop work by utilizing their SVM classification of neural beta-bands and accelerometer traces to detect the initiation of tremor. Based on their feedback signals they were able to extract frequency and motor features to use in a closed-loop setting for essential tremor patients [40], marking one of the few times CLDBS has shown to be feasible, at least in essential tremor patients. Despite their findings, essential tremor is relatively monotonic in its symptoms, as pure tremor classification is relatively simple to distinguish from controls, leaving Parkinson's disease a completely different paradigm to address.

One of the crucial next steps towards further developing a closed loop stimulation paradigm for Parkinson's Disease is again to capture and respond to the heterogeneous nature of the disease. This is done in order to quantify their clinical state at any given time-point. Therefore the goal of this section is to develop a closed-loop system that is novel in following two areas: 1) utilize a subject specific machine learning classifier relating 2D spatial transformations and PD symptoms and 2) use these 2D spatial transformations as a feedback signal to alter stimulation protocols. For the purposes of

this dissertation this closed-loop system was developed and tested on PD subjects and its performance was analyzed on its ability to detect symptomatic states, deliver pre-defined stimulatory patterns based on their state, and ability to "push" subject behavior in specific directions.

Methods

Subject Recruitment

The Rhode Island Hospital-Lifespan and Brown University IRB approved this experiment. For this portion of the experiment 6 subjects diagnosed with idiopathic Parkinson's Disease participated (see Table 1). Subjects had been implanted with Medtronic Activa PC (Medtronic; Minneapolis, Minnesota, USA) deep brain stimulation (DBS) system for treatment of their Parkinson's Disease (PD) diagnosis at least 6 months prior. Subjects had either Medtronic 3389 or 3387 electrodes bilaterally implanted into their subthalamic nuclei. For this experiment and all sub-investigations involved, electrode pair configurations were based on two separate criteria: the first being its therapeutic effect based on clinical notes from their most recent programming session with their clinician and the second being the deepest implanted electrode (see Table 1 for specific contact pairs used). Stimulation changes were delivered through the subthalamic nucleus (STN) electrode (see Table 1 for all combinations of stimulation changes). All stimulation changes were interfaced through the Medtronic Nexus-D device custom software for real-time communication between our host-computer and the subject's pulse generator (see Figure 13 for diagram).

Table 1: Subject Information

Subject	Sex	Age	Dominant Hand	Implant Side	Therapeutic Contact Pair (Left/Right)		DBS Settings (V, μs, Hz)	
d0000FF	M	65	R	Bilateral	C+, 1-	C+ 1-	3.2, 60, 130	2.5, 60, 130
d0001YK	M	62	R	Bilateral	C+, 2-	C+, 2-	2.0, 60, 130	2.5, 60, 130
d0002TK	M	65	R	Bilateral**	NA	C+, 1-	NA	2.5, 60, 130
d0003ZL	M	66	R	Bilateral	C+, 1-	C+, 1-	3.7, 60, 130	3.6, 60, 130
d0004YB	M	76	R	Bilateral	C+, 3-	C+, 1-	2.0, 90, 130	3.3, 90, 130
d0005BH	M	76	R	Bilateral	C+, 1-	C+, 1-	2.5, 90, 130	3.2, 90, 130

** Subject d0002TK had bilateral electrodes implanted, but at the time of experimentation, had only one side programmed.

During this study, motor performance was measured in a similar manner as described in Section 4. Subjects were prompted to engage in a behavioral task using a graphics tablet sampled at 200 Hz to record their 2D spatial transformations. This task was comprised of long, continuous, goal-oriented movements in which subjects tracked the motion of a smooth and randomly moving target on screen (see Figure 5). For the entirety of this experiment, subjects were asked to stay seated as they played the task but were allowed breaks if at any point felt significantly uncomfortable.

This section of the experiment, being the longest, was split into 4 separate sessions with an approximate 5-10 minute break in between sessions. Sessions typically increased in length and on average subjects took 3 hours to complete all four sessions. Each session shall refer to the separate stimulatory patterns being delivered but shall categorize periods of stimulation in a binary fashion as being DBS On or DBS Off. This shall signify periods where subjects received stimulation of any kind vs. no stimulation.

Session A- SVM Training

Session A is defined as our machine learning session and the only session where stimulation was never delivered. Subjects began this session in the DBS Off state and stayed in this state for the duration of this session. Subjects engaged with the behavioral task for a total of 15 minutes (or 30 trials) of movement traces being recorded. Each trial of this session lasted approximately 20 seconds each with 1-2 seconds in between each trial. Subjects were allowed 1-2 minute breaks after every 10 trials for two separate reasons: 1) to allot more time for subjects to settle into their DBS Off state and 2) to allot

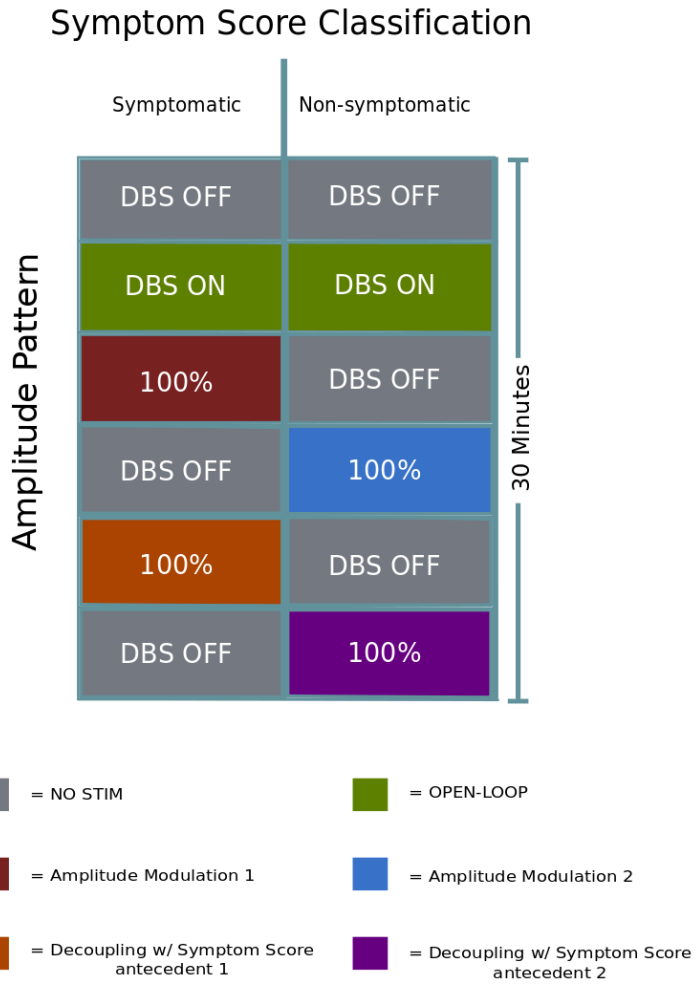
time for the researchers to correct any mistakes in instruction that the subject could not comprehend.

After this first 15-minute session, subject data was stored and analyzed to feed into our SVM algorithm. Features were extracted from the raw 2D spatial transformations in the DBS Off condition in the following way. The 2D spatial transformations were used to calculate all 11 metrics in our metrics library. These metrics were then averaged into 1-second epochs with no overlap. These 1-second epochs were then aggregated across the entire session to create a subject specific distribution of metrics. Window size was chosen to be 1-second as it was temporally closest to match raw motor behavior and increased sample size for training. We then subsampled from our control population of metrics in order to have both distributions match in size, to eliminate sample-size related bias in the construction of the SVM hyperplane. Labels for SVM training were marked based on which distribution each contributing epoch came from. Epochs from both distributions were then normalized and used as features to train our linear SVM algorithm.

After training on the first session's dataset, symptom score calculations were made to define the range of symptom severity captured in this session. Additionally the coefficients that constitute the shape of the hyperplane were saved and stored on the host-computer in order classify future epochs as being symptomatic or non-symptomatic. The threshold for being classified as symptomatic or non-symptomatic was defined as the median point of symptom scores based on the previously calculated distribution of scores in the DBS Off state.

Session B – Amplitude Manipulations

Table 2: Session B- Amplitude Symptom Score Classification



Session B is defined as our amplitude manipulation session and the first of the three sessions that investigate a simple pattern of stimulation. In this session, each trial played follows a semi-random picked stimulation pattern detailed in Table 2. In order to tease apart the effects of one stimulation pattern versus another, after every stimulatory trial the subject performed a non-stimulatory condition that we called the "Washout-

Period" in order to allow for the effects of the previous stimulatory pattern to wear off. Subjects continue the same behavioral task utilized as in Session A but now will have their 2D spatial transformations analyzed and classified in real-time. Like Session A, metrics are calculated based on the subjects behavioral performance, however in this session metrics are now calculated in real-time by averaging each metric trace into 1-second epochs with 50% overlap (1 second epochs with 0.5 second overlap). The reason we chose to utilize overlapping epochs in this session and all subsequent stimulation sessions is because we have already trained and tested our SVM classifier on non-overlapping epochs in order to avoid over-fitting our data sets and have defined what is symptomatic and what is not. Therefore by overlapping epochs we can increase the temporal resolution of our classifier and make classification more rapidly respond to changes in symptomatic state by potentially updating stimulation parameters every 0.5 seconds.

Session B stimulation patterns follow a simple binary trend. Based on symptom score classification as defined in Table 2, each symptomatic state shall either receive "100%" of "therapeutic contact stimulation" or not. In this context, "therapeutic contact stimulation" refers to the stimulation parameters set by the subject's clinical provider at the clinically determined optimal contact. Detailed stimulation parameters used for each subject that participated in this session are noted in Table 1 (see Table 1 "Therapeutic Contact Pair").

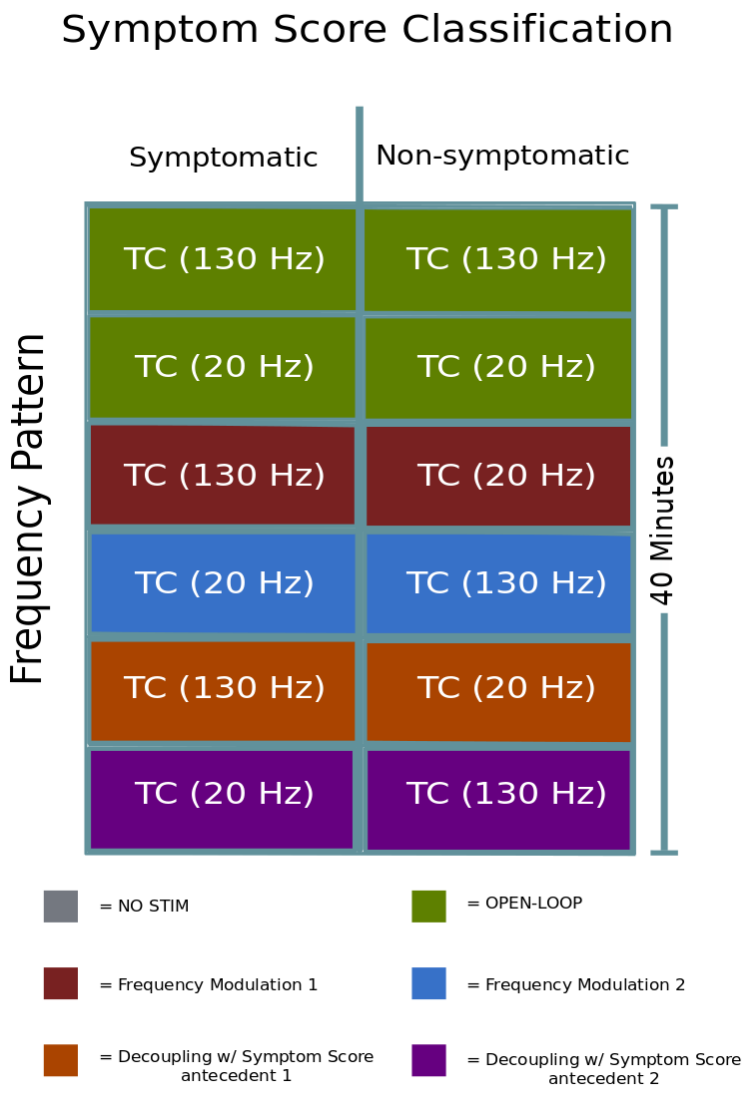
Table 3: Frequency and Location Stimulation Parameters

Subject	Therapeutic Contact Pair (Left/Right)		DBS Settings (V, μs, Hz)		Alternate Contact Pair (Left/Right)		DBS Settings (V, μs, Hz)	
d0000FF	C+, 1-	C+ 1-	2.5, 60, (130-20)	2.0, 60, (130-20)	C+, 0-	C+, 0-	2.5, 60, (130-20)	2.0, 60, (130-20)
d0001YK	C+, 2-	C+, 2-	2.0, 60, (130-20)	2.5, 60, (130-20)	C+, 0-	C+, 0-	2.0, 60, (130-20)	2.5, 60, (130-20)
d0002TK**	NA	C+, 1-	NA	2.5, 60, (130-20)	NA	C+, 0-	NA	2.5, 60, (130-20)
d0003ZL	C+, 1-	C+, 1-	3.4, 60, (130-20)	3.3, 60, (130-20)	C+, 0-	C+, 0-	3.4, 60, (130-20)	3.3, 60, (130-20)
d0004YB	C+, 3-	C+, 1-	1.5, 90, (130-20)	2.0, 90, (130-20)	C+, 0-	C+, 0-	1.5, 90, (130-20)	2.0, 90, (130-20)
d0005BH	C+, 1-	C+, 1-	2.5, 90 (130-20)	3.2, 90, (130-20)	C+, 0-	C+, 0-	1.5, 90, (130-20)	1.5, 90, (130-20)

** Subject d0002TK had bilateral electrodes implanted, but at the time of experimentation, had only one side programmed.

Session C – Frequency Manipulations

Table 4: Session C- Symptom Score Classification



Session C is defined as our frequency manipulation session and the second of the three sessions that investigate a simple pattern of stimulation. In this session each trial played follows a randomly picked stimulation pattern detailed in Table 4. Subjects continue the same behavioral task utilized as in Session B meaning metrics are calculated

based on the subjects behavioral performance in real-time and averaged into 1-second epochs with 50% overlap.

Session C stimulation patterns follow a simple binary trend. Based on symptom score classification as defined in Table 4, each symptomatic state shall either receive "therapeutic contact," shorthanded as (TC) in the table, stimulation at high frequency (130 Hz) or low frequency (20 Hz). In this context, "therapeutic contact" refers to the contact location set by the subject's clinical provider. The novelty of this session investigates the effects of binary changes to frequency stimulation. Detailed stimulation parameters used for each subject that participated in this session are noted in Table 3 (see Table 3 "Therapeutic Contact Pair").

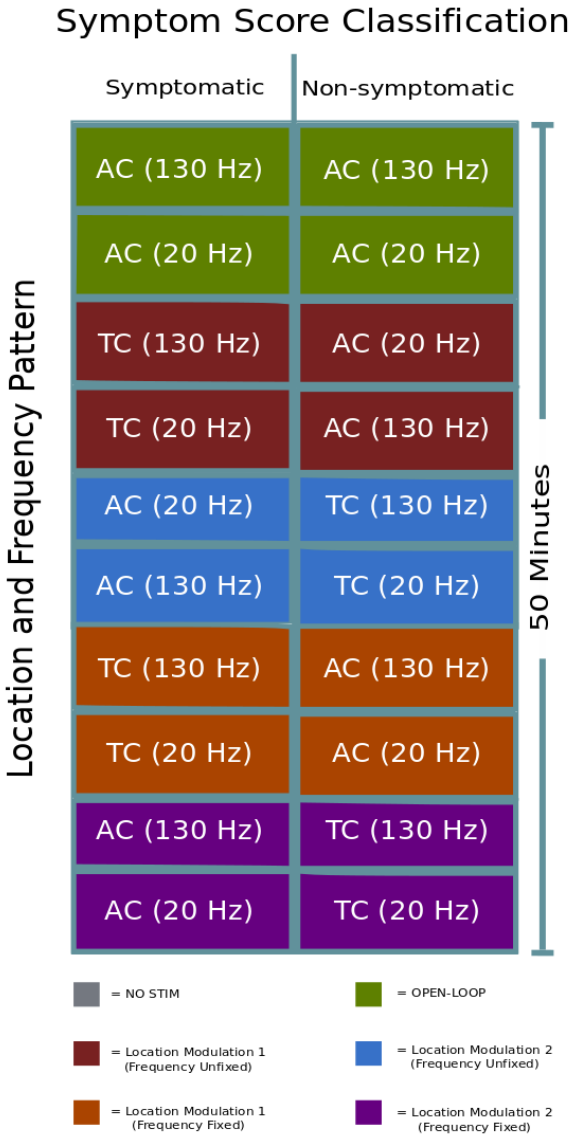
Session D – Frequency and Location Manipulations

Session D is defined as our frequency and location manipulation session. This is the third and last session during the subject's experimental visit that investigates a more complex pattern of stimulation. In this session each trial played follows a randomly picked stimulation pattern detailed in Table 5. Subjects continue the same behavioral task utilized as in Sessions A, B, and C.

Session D stimulation patterns follow a simple binary trend. Based on symptom score classification as defined in Table 5, each symptomatic state shall either receive "therapeutic contact" or "alternate contact" stimulation, shorthanded as (TC) and (AC) in the table. Additionally at each contact pair stimulation was delivered at high frequency (130 Hz) or low frequency (20 Hz). In this context, "therapeutic contact" refers to the contact location set by the subject's clinical provider and "alternate contact" was defined

as the deepest contact available as it is typically located at or near the substantia nigra pars reticulata (see Figure 13). The novelty of this session investigates the effects of binary changes to frequency and location stimulation. Detailed stimulation parameters used for each subject that participated in this session are noted in Table 3 (see Table 3 "Therapeutic Contact" and "Alternate Contact"). It should be noted that within this session, stimulatory voltage was altered to be the same within the therapeutic and alternate contact. This was meant to avoid any stimulation side effects induced by higher voltages at the alternate contact.

Table 5: Session D- Symptom Score classification



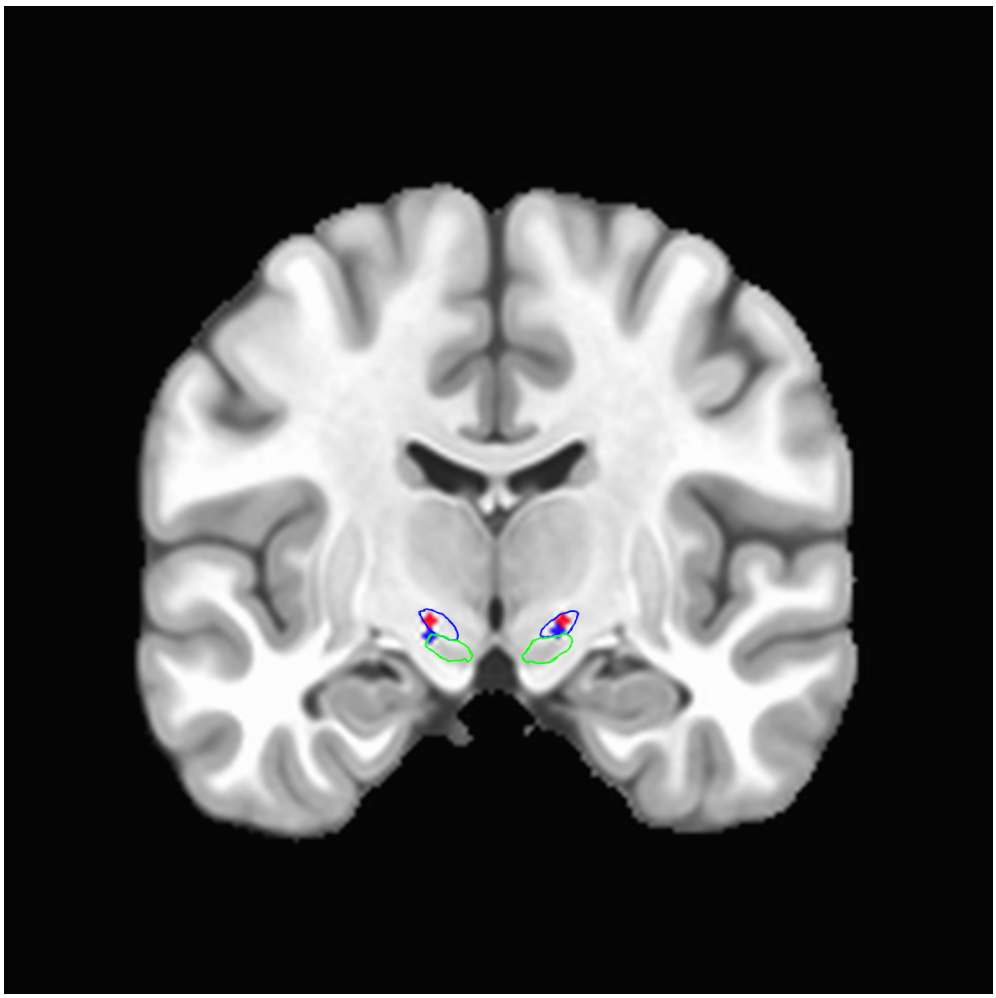


Figure 13: Co-registered aggregate CT scans for visualization of the therapeutic contact (red) and alternate contact (blue) warped to a coronal view of the MNI brain atlas. Subject specific contact locations were aggregated and averaged to represent both locations of stimulation used in our experiments. Outlines in blue and green represent the borders of the subthalamic nucleus and substantia nigra respectively. On average the alternate contact was closest to the substantia nigra whereas the therapeutic was within the subthalamic nucleus.

Closed Loop System Description

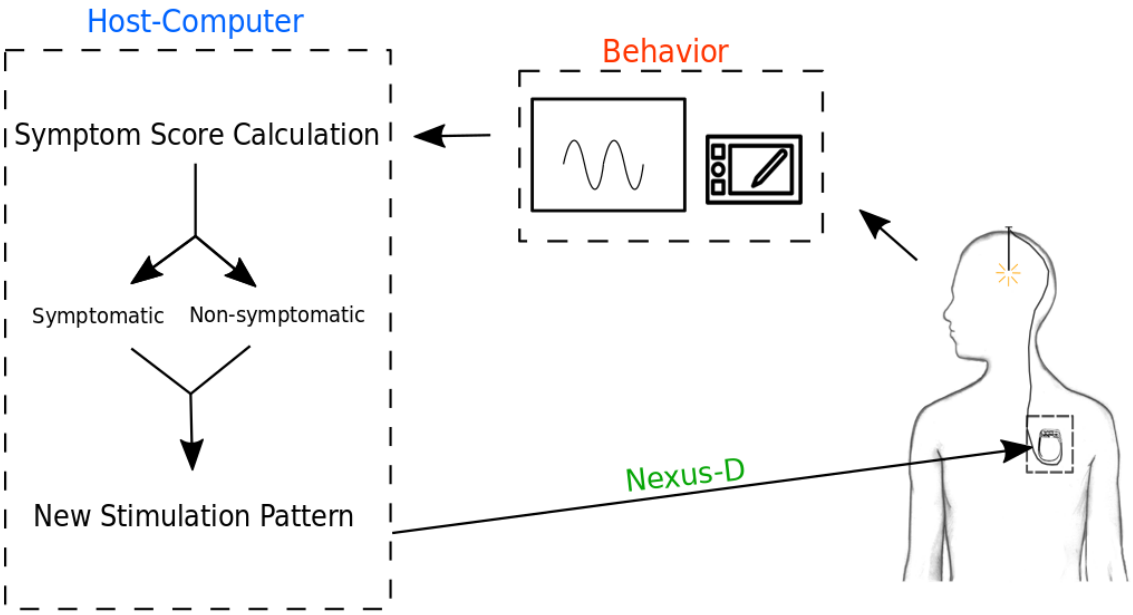


Figure 14: Closed loop system description. Behavioral performance is recorded and sampled at 200 Hz. Features are then extracted from the raw behavioral data and applied to previously trained classifiers to determine if the subject is in a symptomatic state or not. Stimulation is then changed based on the stimulation pattern being tested. Changes are updated via commands interfaced through the Nexus-D.

The trained classifier from Session A was utilized in the subsequent 3 stimulation sessions in order to detect the symptomatic state of a subject in a binary fashion. A description of the system can be seen in Figure 14. Briefly, behavioral data were sampled from a graphics tablet. This data was then analyzed and classified to update stimulation parameters. Changes were transmitted to a host-computer running custom software for interfacing with the Nexus-D. On the host-computer, epochs of behavioral data were used to estimate symptom severity in the same manner as the feature extraction phase of classifier training. These features were then normalized and then used by our linear

classifier to determine the symptomatic state of the subject. If the subject was classified as being symptomatic, a command is sent by the Nexus-D to change stimulation parameters based on the stimulation pattern being investigated. If they were not classified as symptomatic, a separate signal was sent. If the symptomatic state of a subject was the same as the previous epoch, no command signal to update stimulation was sent. Potentially stimulation updates can be sent every 500 ms during Sessions B, C, and D. Stimulation updates are reflected 1-epoch in time (~0.5 seconds) after a change in symptomatic state is detected. This is due to the inherent lag in the system caused by wireless interfacing of the Nexus D system. Stimulation updates occur roughly 200-300 ms after a change in symptomatic state is detected.

Results

Open-Loop Subject Performance

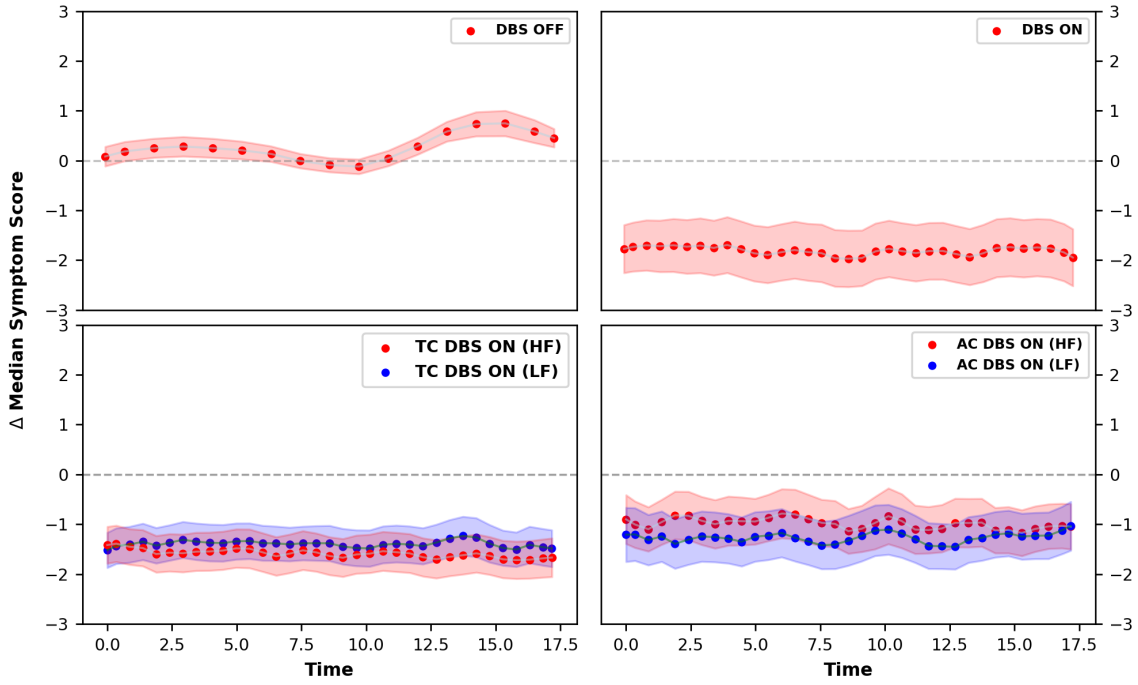


Figure 15: Average symptom score traces from subjects while receiving open-loop stimulation as they engaged in the behavioral task. Dashed lines represent the median threshold used to classify the subject's symptomatic state. A positive deflection reveals a symptomatic state whereas a negative deflection shows the opposite. Lightly shaded regions denote the mean squared error of each point.

Using data recorded from the behavioral task, symptom score traces were calculated using a sliding window of 1 second with 0.5 seconds overlap. These symptom score (SS) traces were then organized by which stimulatory pattern the subject was being tested on, as well as the experimentally paired washout trials. As shown in previous sections, symptom scores are an accurate measure of a subject's symptomatic state at any given time point. Given that symptom scores can vary from second to second, any manipulations to the stimulatory pattern of a particular subject's DBS system can

introduce some noise into the data. In order to compare the effect of any particular pattern of stimulation and the effect of changing stimulation we incorporated separate "Open-Loop" conditions for each pre-defined change in stimulation tested.

For this section of analysis we ask the question, what effect is visible by testing different Open-Loop stimulation parameters on subject behavior? In order to investigate this question SS traces were extracted from all subject's individual trials and time-synced, where correlating epochs in time were clustered together and averaged. From there overlapping epochs across all subjects were averaged and shown above (Figure 15). To describe, above is the averaged performance of a subject in each open-loop stimulatory condition. Dashed lines represent the median threshold used to classify subsequent SS epochs whereas the scale shows the distance from the median threshold for each averaged epoch. Shaded in areas are representative of the standard error of the mean in each epoch cluster that was averaged. Figure 15 above shows stimulatory conditions across the 4 separate stimulatory sessions: the top left referring to the performance during our SVM training session, the top right showing on average the performance while each subject received their therapeutically determined stimulation, the bottom left showing on average the performance of each subject while delivering different frequencies of stimulation, and the bottom right showing on average their performance while delivering stimulation at different locations and frequencies.

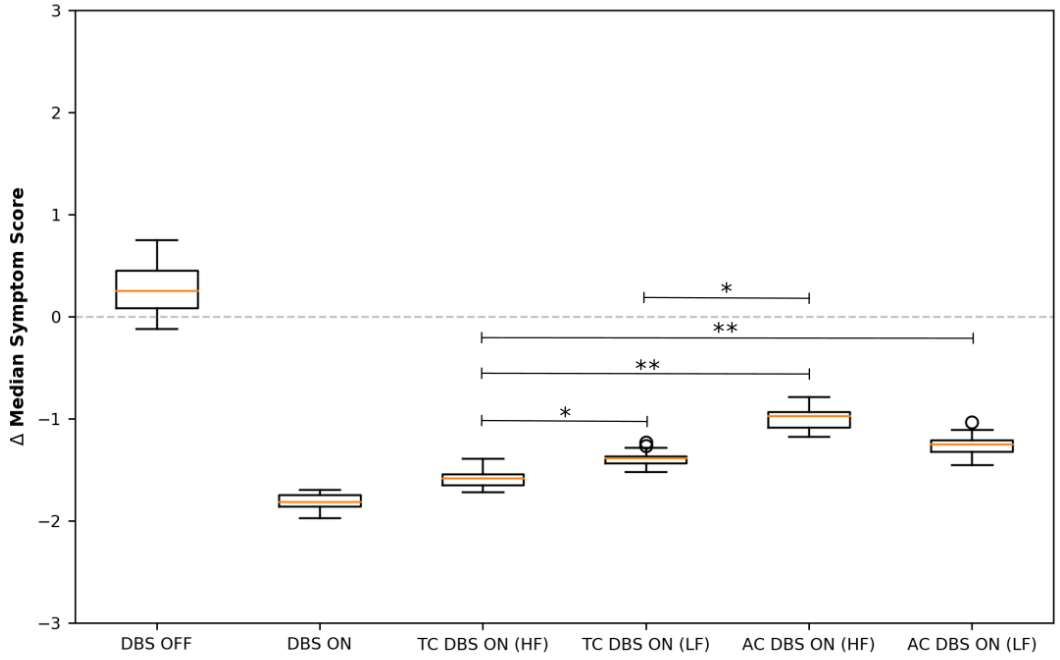


Figure 16: Average change from median symptom score, as defined by the SVM training session, for each open-loop condition. See text for description of each condition. ($p<0.05$; Mann-Whitney U test).

In order to further solidify the effect of each open-loop condition the distributions of change from the SS median are generated in Figure 16 as boxplots. On average each open-loop condition causes the subject to perform significantly better than their DBS Off state ($p < 0.05$). Therapeutic contact (TC) locations as well as alternate contact (AC) locations were able to display significant behavior under high frequency (HF) and low frequency (LF) conditions. Of note, stimulation at the alternate contact at low frequency consistently showed better performance than its high frequency counterpart.

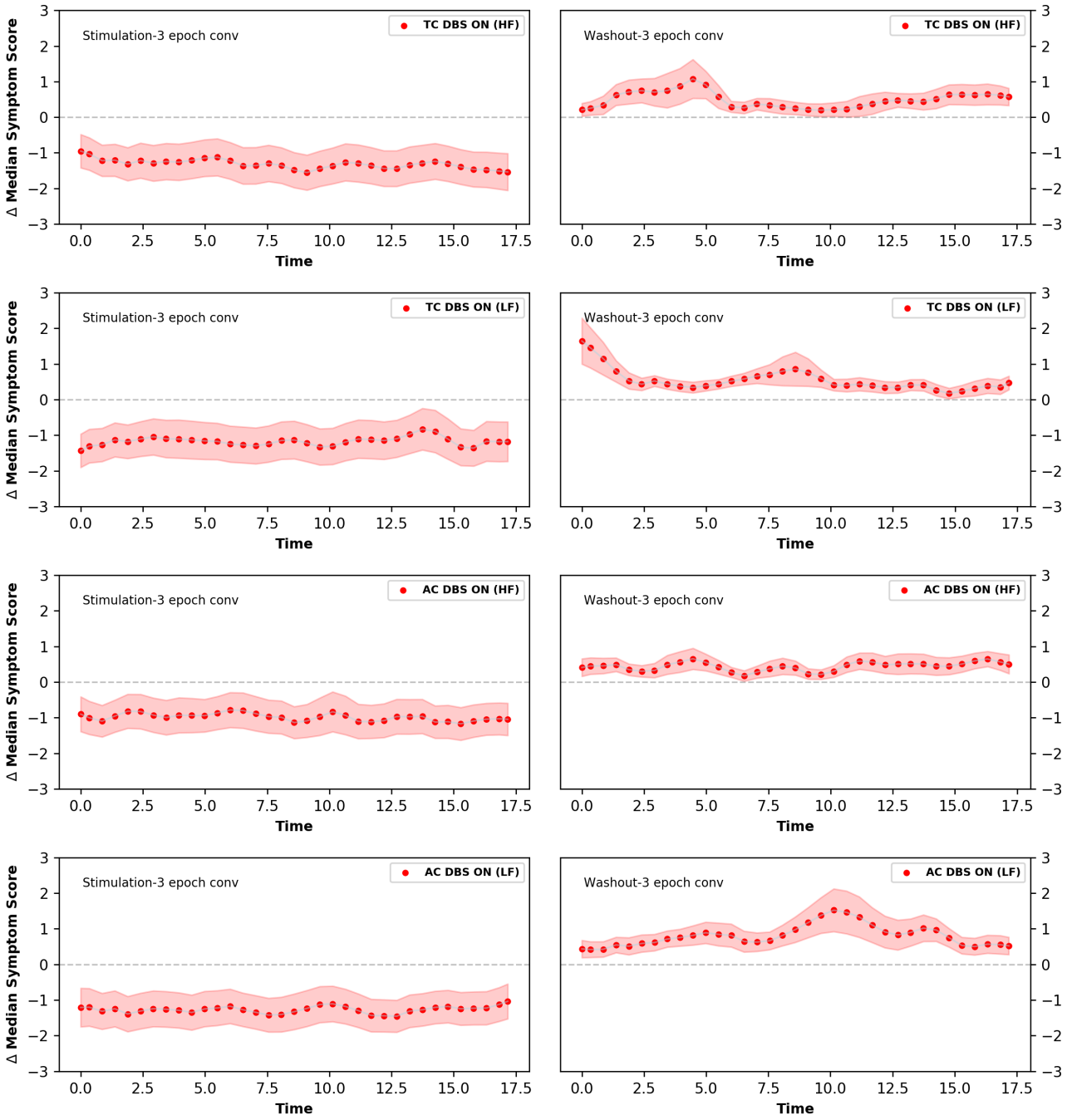


Figure 17: Average change from median SS traces with experimentally paired washout traces. The washout traces above show the stimulation effects of the preceding trial on average dissipate in the sequential DBS Off trial.

After completing each stimulatory condition, we ensured enough time was allotted to allow for the effects of the previous stimulatory pattern to diminish. In order to objectively state that the effects of a certain pattern of stimulation have completely

"washed out" we should see a return of symptoms over some period of time (Figure 17). The return of symptoms is synonymous as our definition of the symptomatic state used in our binary classifier. Behavioral epochs above the threshold of SS classification signify the return of Parkinsonian disturbances. Figure 17 demonstrates that on average stimulation effects were able to wear off within the timespan of a single trial.

Closed-Loop Behavioral Changes in Amplitude

Having trained and tested a separate classifier for each subject, closed-loop stimulation effects can vary widely among the same stimulatory patterns. The particular timing of a single pattern can change the overall effect of how we perturb the direct and indirect pathways of the basal ganglia. In order to properly assess the effect of the closed-loop condition on behavioral performance we investigated a 3 second window of behavior detailing the transition of one stimulatory state to another (Figure 18). Doing so requires a similar method of data processing as done in the previous section where for this analysis across all trials every time stimulation parameters were changed, a 3-second window was taken to analyze the direct effect of changing to that stimulatory pattern. Within every 3-second window, the average rate of change in symptom score was calculated. This created a distribution of slopes representing either a positive or negative deflection in which patient performance was being pulled towards.

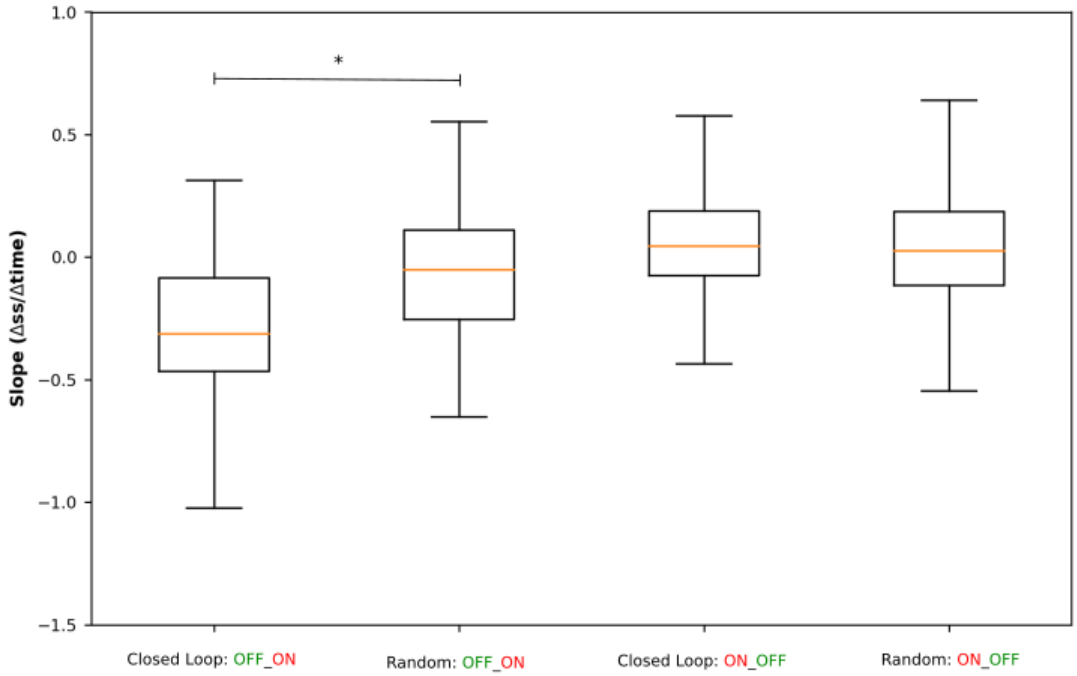


Figure 18: Rate of change in median symptom score during a behaviorally triggered changed in stimulation. Stimulation patterns are defined in the x-label of each boxplot, but follow the general trend of showing a transition between the DBS On state and the DBS Off state. Labels colored green signify an SVM classification of not being symptomatic whereas red represent the opposite. Plots represent conditions using a closed-loop pattern of stimulation versus a random pattern of the same condition. See text for further detail.

Figure 18 shows the rate of change in median symptom score during a behaviorally triggered change in stimulation for Session B of the experiment. Stimulation changes reflected selective changes in stimulation amplitude from 0-100% therapeutic voltage within a 0.5 second window. Distributions show transitional states going from the DBS Off condition to the DBS On condition and its reverse. Color is used to reflect changes in symptomatic state determined by our classifier, where red represents the symptomatic state and green reflects the opposite. Across subjects, changes from the DBS Off condition to the DBS On condition cause a negative deflection from preceding epochs whereas the transition from DBS On to DBS Off show a positive deflection.

Delivering random patterns of stimulation was found to be significantly different in going from DBS Off to DBS On ($p<0.01$) but not from DBS On to DBS Off.

Closed-Loop Behavioral Changes in Frequency

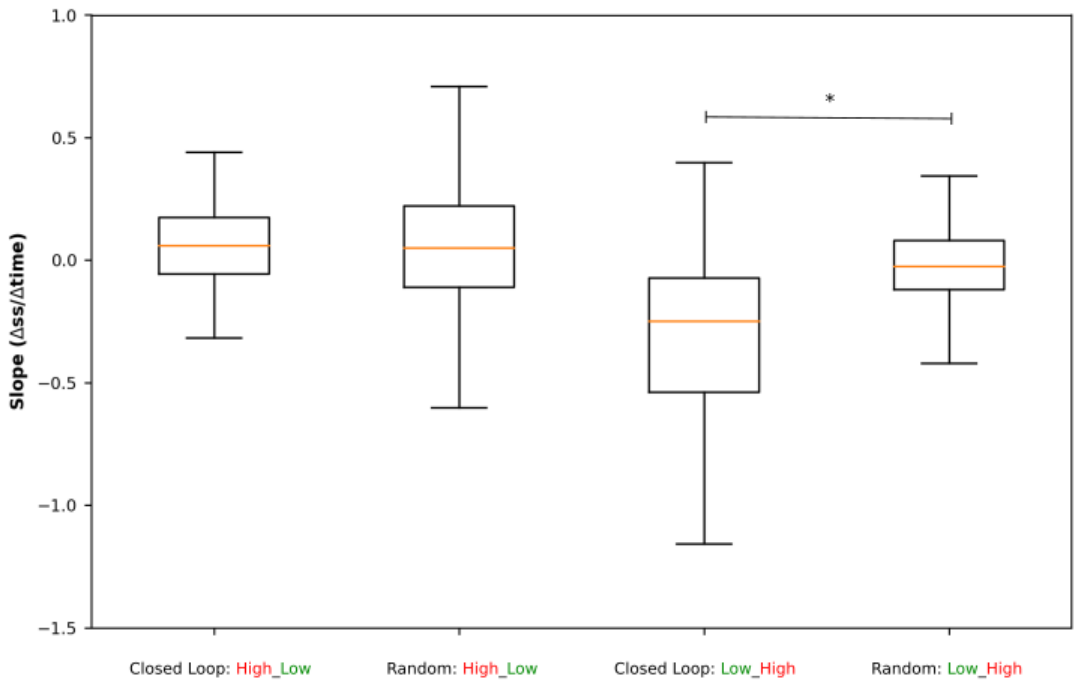


Figure 19: Rate of change in median symptom score during a behaviorally triggered changed in stimulation. Stimulation patterns are defined in the x-labels of each boxplot, but follow the general trend of showing a transition between using high frequency stimulation or low frequency stimulation. Labels colored green signify an SVM classification of not being symptomatic whereas red represent the opposite. See text for further detail.

Figure 19 shows the rate of change in median symptom score during a behaviorally triggered change in stimulation for Session C of the experiment. Stimulation changes reflected selective changes in stimulation frequency from Low (20 Hz) to High (130 Hz). Distributions show transitional states from the "High Frequency" condition to the "Low Frequency" condition and its reverse. Color is used to reflect

changes in symptomatic state determined by our classifier, where red represents the symptomatic state and green reflects the opposite. Across subjects closed-loop changes from the high frequency condition to the low frequency condition cause a negative deflection from preceding epochs whereas the transition from low to high showed a slight positive deflection. Delivering random patterns of stimulation was found to be significantly different in going from high to low frequency only ($p<0.01$).

Closed-Loop Behavioral Changes in Frequency and Location

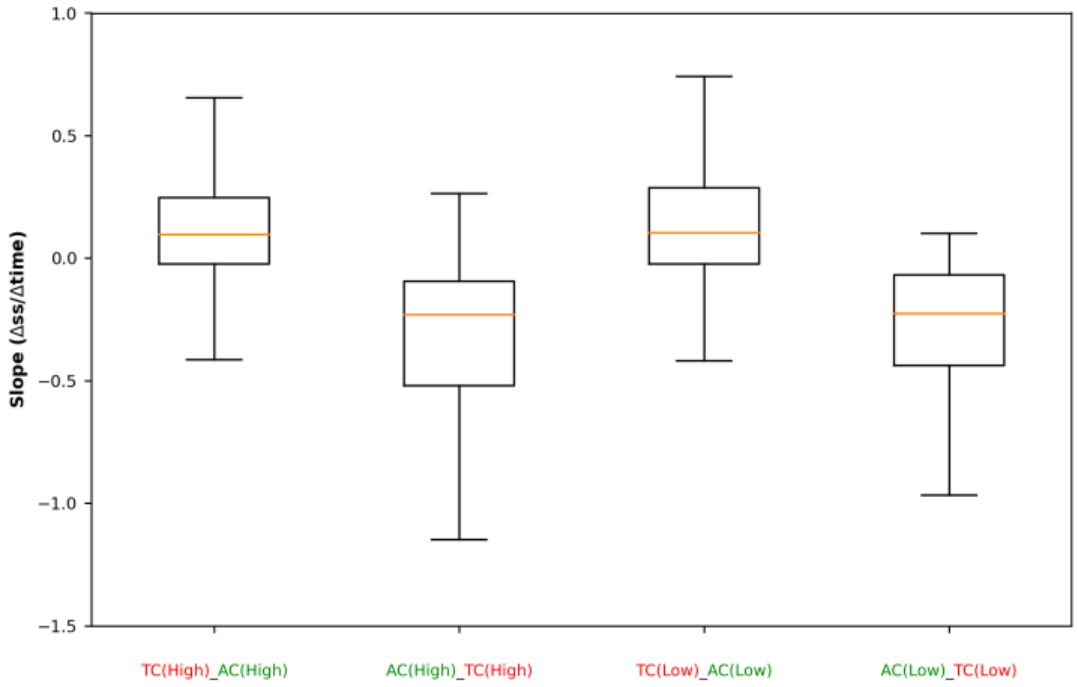


Figure 20: Rate of change in median symptom score during a behaviorally triggered changed in stimulation. Stimulation patterns are defined in the x-labels of each boxplot, but follow the general trend of showing a transition between using therapeutic contact stimulation vs. alternate contact stimulation. Frequency was kept fixed in these trials during stimulation changes. Labels colored green signify an SVM classification of not being symptomatic whereas red represent the opposite. See text for further detail.

Figure 20 shows the rate of change in median symptom score during a behaviorally triggered change in stimulation for Session D of the experiment. Stimulation changes reflected selective changes in stimulation location, switching between the therapeutic contact and the alternate contact. Frequency was kept fixed during these changes. Distributions show transitional states going from the therapeutic contact to the alternate contact and its reverse. Color is used to reflect changes in symptomatic state determined by our classifier, where red represents the symptomatic state and green reflects the opposite. Closed-loop changes from the therapeutic contact to the alternate contact, fixed at a high frequency of 130 Hz, cause a positive deflection from preceding epochs whereas the transition from the alternate contact to the therapeutic shows a negative deflection. This behavior was consistent across the two tested frequencies. There were no random patterns of stimulation tested in this paradigm.

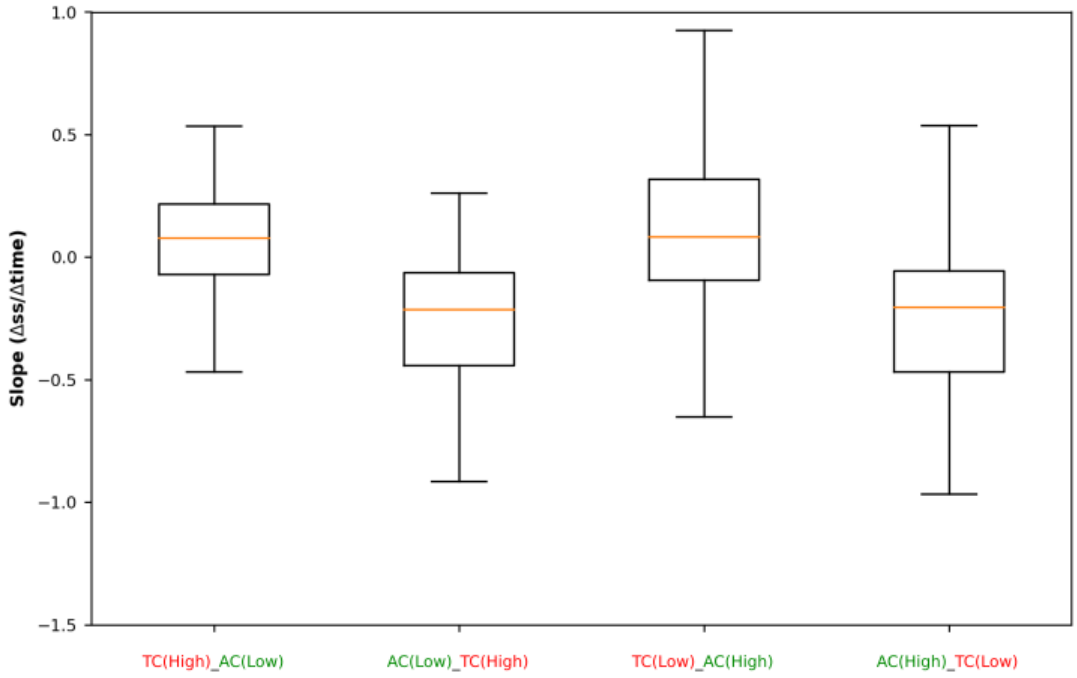


Figure 21: Rate of change in median symptom score during a behaviorally triggered changed in stimulation. Stimulation patterns are defined in the x-labels of each subplot, but follow the general trend of showing a transition between using the therapeutic contact vs alternate contact stimulation. Frequency was not kept fixed during stimulation changes and is labeled as low or high depending on the condition. Labels colored green signify an SVM classification of not being symptomatic whereas red represent the opposite. See text for further detail.

Figure 21 shows the rate of change in median symptom score during a behaviorally triggered change in stimulation within Session D of the experiment. Stimulation changes reflected selective changes in stimulation location, switching between the therapeutic contact (TC) and the alternate contact (AC). Frequency was not kept fixed during these changes. Distributions show transitional states going from the TC to the AC utilizing opposing frequencies as well as their reverse. Color is used to reflect changes in symptomatic state determined by our classifier, where red represents the symptomatic state and green reflects the opposite. Closed-loop changes from the TC at

130 Hz to the AC at 20 Hz show a positive deflection from preceding stimulatory epochs whereas the transition from the AC at 20 Hz to the TC at 130 Hz shows a negative deflection. Testing the opposite stimulatory pattern shows that changes from the TC at 20 Hz to the AC at 130 Hz show the same positive deflection from preceding stimulatory epochs whereas the transition from the AC at 130 Hz to the TC at 20 Hz shows a negative deflection. There were no random patterns of stimulation tested in this paradigm.

Discussion

The purpose of the work presented in this section was to investigate aim 2 of this dissertation, which was to develop and test a closed loop system using dynamic temporal modulation driven by real-time rapid symptom assessment. Previous sections examined the ability of symptom scores to detect and quantify symptom severity in short time-scales within PD subjects, and the results from that section showed that symptom scores (SS) were a reliable metric of the subjects symptomatic state and could reliably be used to distinguish these symptomatic states from normal behavior. Therefore, to complete investigation of this aim, symptom scores were used as a feedback signal for closed-loop stimulation changes.

Open-Loop Stimulatory Effects

In order to properly evaluate the stimulation effects of any closed-loop stimulation pattern we needed to first establish the effects of any singular change to stimulation that a subject may experience. This evaluation explored two separate paths within the Open-Loop patterns of stimulation. These patterns served as stimulatory

controls in our experiment. The first category was an evaluation of subject performance in comparison to their DBS Off state for each Open-Loop condition. Comparisons of these conditions could justify any particular trends in behavior that were witnessed in our closed-loop patterns. The second category of analysis was the ability of these stimulation changes to dissipate in the time allotted for each subject.

Subjects performed significantly better than their DBS Off session in all open-loop conditions. Seeing significant improvement within the DBS On condition was expected, as this condition was essentially a copy of the subject's clinically derived stimulation parameters. This meant that at the very minimum that their normal DBS system was working as intended. This same logic applied to another condition (TC High) where the same contact location and frequency parameters were the same as the clinically determined versions, the only difference being the amplitude of stimulation received. As mentioned in our methods (see Methods), voltages across contacts used in the frequency and location manipulation sessions were kept constant in order to apply the same amount stimulatory power to each contact. This diminished amount of amplitude may explain the decrease in subject performance as stimulation amplitude has been implicated in graded therapeutic responses in previous work [41-42].

Other open-loop conditions were somewhat surprising to see how effective they were in altering subject performance. Based on investigatory work of stimulation parameters and their effects on STN-targeted DBS [42-43], low frequency stimulation should theoretically drive subject behavior towards a symptomatic state, yet as shown in our results (Figure 16), low frequency at the therapeutic and alternate contact showed significant improvement in comparison to DBS Off, and were very similar in

performance to normal DBS On. One particular difference in our study compared to the work done in [43] is that the range of frequency being delivered is vastly different. Their study showed that subject's experiencing ~5 Hz of stimulation at the therapeutic contact would experience an increased state of akinesia involved with that frequency of stimulation. Given that hardware limitations of the Medtronic DBS system prevented anything lower than 20 Hz stimulation, it could be that this experiment was incapable of pushing behavior in a symptomatic direction. Additionally, our task design is quite different in comparison to previous work. Due to the large library of symptoms we can capture in our task it may be that lower frequencies do not affect all symptoms equally within PD patients leading some patients to still exhibit decent performance despite the lower frequency stimulation.

One final analysis of Open-Loop conditions investigated the time allotment for each subject to "washout" the stimulatory behavioral changes induced by Open-loop stimulation. Considering that in most cases subjects were able to cross the Median symptom score threshold within the first couple seconds of the washout trial, it should suggest that our task design allows for sufficient separation of stimulatory patterns from one condition to the next.

Closed-Loop Stimulatory Effects

Our approach to closed-loop stimulation in this experiment is based on the notion that PD symptoms may be explained by aberrant neuroplasticity. Specifically, activation of the direct pathway reinforces ongoing motor behaviors, while activation of the indirect pathway discourages those behaviors. Open-loop DBS has been used effectively to

alleviate PD symptomology by possibly disrupting the indirect pathway of the basal ganglia, but DBS in general has yet to harness the "push-pull" capabilities of the circuit via substantia nigral stimulation. We predicted that selective transitions of stimulation to the substantia nigra would drive behavior in certain directions as shown in previous work in non-human models [7][44].

Closed-loop pattern analysis was performed in a limited time-locked fashion in order to view particular changes in behavior due to specific changes in stimulation. This required us to look specifically across average changes in behavior in response to a particular change in stimulation. Based on SS traces during a stimulation change the rate of change in median SS was calculated after a change to stimulation was delivered. From our findings, there is a slight hint at some bidirectional control utilizing a closed-loop pattern. Taken from our amplitude manipulation session Figure 18 showed a larger distribution of slopes when transitioning between DBS On vs. DBS Off, hinting at the fact that behaviorally responsive therapeutic stimulation can reduce the symptomatic state of a particular subject.

Based on our open-loop results we found that lower frequency stimulation of the therapeutic contact was nearly equivalent in alleviating symptoms when compared to higher frequencies. The belief behind low frequency stimulation is that it should push subjects to perform worse at our task. In open-loop conditions this was not the case, as we believe our frequency range was insufficient to replicate such behavior as well as the fact that our task may have introduced noise from multiple sources. Figure 19 however shows that selective transitions between low frequency stimulation and high frequency stimulation may hint at some opponent behavior. While the figure shows that stimulation

at low frequencies does not cause a major positive deflection in SS, it does show that transitioning from low to high frequency improves behavioral performance, falling in line with the notion that higher frequency stimulation is thought to be better at alleviating symptoms in the sub-thalamic nucleus [43].

Our final session leads us to the mixed combination of contact location and frequency manipulations. This session required to be split into two separate figures to allow for separate analysis of changes in contact location and changes in frequency. In this investigation we expected to see the "push-pull" reaction from stimulating the substantia nigra and subthalamic nucleus in an alternating fashion. Figure 20 hints at the behavioral pull of utilizing the alternate contact. Based on the distributions in Figure 20, using alternate contact stimulation would make the subject perform worse. Despite frequency changes, switching from the alternate contact to the subject's therapeutic contact always caused an improvement in behavioral performance. Based on the average contact location calculated in Figure 13, alternate contact stimulation could have been activating the direct pathway of the basal ganglia possibly reinforcing periods of bad behavior right after stimulation of their therapeutic contact. Additionally, altering changes in frequency from one contact to another as seen in Figure 21 shows improvement when stimulation was performed at the therapeutic contact and was pulled towards the symptomatic state when utilizing the alternate contact. Despite seeing differences in alternate contact stimulation at high and low frequencies during our open-loop conditions, we do not see a significant difference in our closed-loop design. In general, low frequency stimulation of the alternate contact has a slightly tighter distribution than higher frequencies but on average the two showed to be very similar.

Summary

The aim of the work presented in this section was to develop and test a closed-loop system for the treatment of PD. Subject performance was used as a feedback signal for controlling stimulation, and machine-learning was used to develop subject-specific models relating motor performance and symptom assessment. These models were used in real time to detect and modulate stimulation based on the pattern of investigation. Based on our findings, open-loop stimulation at the alternate contact using lower frequencies showed a weak improvement to its high frequency counterpart. Lastly, closed-loop stimulation between the alternate and therapeutic contacts hints at some opposing behavioral skew in motor performance.

Conclusion

The closed-loop stimulation paradigm in deep brain stimulation (DBS) is still a relatively novel approach to improving stimulation-based therapy. It shows promise as the next step in advancing technology but still requires a bit investigation before it can be fully integrated into the platform. The purpose of this dissertation has been to contribute novel groundwork for closed-loop systems in the treatment of Parkinson's Disease real-time measurement of symptoms. Our results hopefully will contribute to the ongoing investigation of closed-loop stimulation.

Specific Aims

At the beginning of this dissertation two separate aims were detailed as guidelines for this experiment to follow. They aims are as follows:

Aim 1: Investigate real-time motor assessment on short-timescales as a measurement of symptom severity.

The purpose of this aim was to lay the groundwork for all symptom assessment to be based on for our closed-loop system. In order to investigate this aim, 2D spatial transformations taken from a graphics tablet sampled at 200 Hz. We then applied our metrics library to their behavioral performance and averaged them into 1-second epochs. Machine learning was then used to determine how symptomatic the subject performed during their training session by calculating their individual symptom score distributions. The classifier created during the training session was then utilized in subsequent sessions to detect and quantify all future sessions as being symptomatic or not.

Aim 2: Develop and test a closed loop system using dynamic temporal modulation driven by real-time rapid symptom assessment.

After determining that symptom score signals were accurate in detecting and quantifying the symptomatic state of a PD subject, these same signals were then used to modulate stimulatory patterns during a closed-loop session. Classification was determined in a binary fashion where the threshold of classification was defined as the median symptom score point during the subject's SVM training session. Each subsequent session then followed a novel stimulatory pattern to investigate. Open-loop patterns showed significant improvement in the alternate contact whereas closed-loop patterns showed a hint of bidirectional control of behavior.

Future Work

There still remains much investigation in order to improve upon the current closed-loop DBS therapy. It will be up to both clinical investigators and device manufacturers to work in tandem in order to bring actual changes to the therapeutics devices currently in market.

The emphasis of this thesis has been to develop and test a closed-loop system using machine learning as a binary classifier. This was done in the simple case where our symptom score feedback signal was a direct measure of behavioral performance. Future iterations of closed-loop DBS systems may implement an internal measure of symptoms such as the use of beta-band frequencies to detect tremor. Extraction of neural features to train and test a linear classifier would prove to be a major step in correct direction of

closed-loop as in that implementation symptom detection would all be internal and not require the subject to engage in a 10 minute video-game. While the device used in this dissertation was only utilized for the purpose of interfacing stimulation changes; in the future, data could be extracted and analyzed in real-time to outperform our tested system.

In reference to the algorithm used to modulate stimulation parameters, the most critical part of this classifier is the ability to discern/distinguish symptomatic epochs from non-symptomatic ones. Essentially, the need for this classifier to perform a binary classification of symptom scores is a vital part of this experiments closed-loop validation. For experiments done in this dissertation stimulation modulations were determined in a simple binary fashion; if the subject was being symptomatic a new stimulatory command would be sent and vice versa if symptoms were not detected. A major novelty of our design was our ability to test and analyze the effects of multiple stimulatory patterns across 3 separate sessions. Typically in previous closed-loop paradigms only a singular parameter was altered to show the basic response to newer stimulation, but in our design other parameters, such as frequency, pulse width, electrode contacts could be altered with relative ease. Future work would leverage the command interfacing capabilities used in our design to pair with extracted neural features and make the overall changes in stimulation completely predictive of subject performance instead of being responsive.

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