Dynamic DBS & Levodopa Optimization Model:

Predicting and Optimizing Dopaminergic Response from Levodopa Intake

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Abstract

Parkinson's disease (PD) is a progressive hypokinetic movement disorder characterized by motor dysfunction, including tremors, rigidity, and bradykinesia — a primary symptom of PD that refers to slowness of movement (Bologna et al., 2020). The prevalence of PD is increasing, particularly among older adults, with a growing number of diagnoses in younger populations. As a result, research into effective treatment interventions has been a pivotal area of research. Two of the most effective treatments are levodopa therapy and Deep Brain Stimulation (DBS), which are often used in combination to improve motor symptoms. Managing levodopa levels alongside DBS presents a significant challenge: fluctuations in levodopa concentration leads to frequent "on-off" periods and dyskinesias, while manual DBS adjustments are ambiguous in terms of what the optimal level of stimulation is required. This research proposal presents a machine learning model that predicts real-time levodopa levels based on neural firings and patient symptoms. The model also dynamically adjusts DBS stimulation parameters to optimize motor function while minimizing side effects. This model has the potential to enhance the precision and efficacy of Parkinson's disease treatment, providing a more personalized and responsive therapeutic approach alongside already existing therapeutic methods.

Introduction

Deep Brain Stimulation (DBS) is a neuromodulation therapy used for patients with advanced Parkinson's Disease (PD), where two electrodes are implanted in the brain to target primarily the substantia nigra—however this depends on individual differences. This procedure is analogous to a heart pacemaker, allowing users to adjust stimulation levels based on their motor control needs. PD symptoms result from the loss of dopaminergic projections from the substantia nigra pars compacta (SNc). As a result, the subthalamic nucleus (STN) loses inhibition, leading to hyperactivity and increased firing of basal ganglia outputs, such as the globus pallidus interna (GPi) and substantia nigra pars reticulata (SNr). This disruption in firing patterns and lack of synchronization are believed to contribute to PD symptoms.

Levodopa is the primary treatment for managing PD tremors. While it has demonstrated positive effects, its efficacy is limited, particularly when used in combination with DBS. A key challenge remains in determining the optimal stimulation levels and levodopa doses for individual patients (Milosevic, 2018).

Different brain regions require varying levels of stimulation for effective symptom management:

- Subthalamic nucleus (STN): 100 Hz for optimal neuronal inhibition.
- Ventral intermediate nucleus (Vim): 200 Hz due to a higher prevalence of glutamatergic synapses.
- Substantia nigra pars reticulata (SNr): 50 Hz for neuronal inhibition.

Despite advancements in levodopa and DBS, there is still ambiguity regarding the optimal levels of stimulation and medication required to effectively manage tremors. What truly is the *baseline*? How much is *too much or too little*?

We propose a solution to addressing these questions through a machine learning model that learns from neural firing data to optimize treatment levels.

The model will function as a feedback loop:

- Increasing DBS stimulation when levodopa levels are low.
- Decreasing DBS stimulation when levodopa levels are high.

Along with these alerts, the model is able to suggest to the user that they require an increase or decrease in levodopa intake when stimulation levels rise or fall.

Hypothesis

We hypothesize that the model will be able to detect elevated or depleted levodopa levels, and through learning from patient responses, become highly become highly precise in adjusting DBS stimulation and levodopa dosage to optimize treatment outcomes.

Methods

Subjects

To train and test the model, we will use data from both healthy participants (which acts as the control group for the machine learning model to compare neural firing and refine actions) and PD patients who are currently on levodopa and have undergone DBS surgery.

To control for variations in brain regions, we will select participants with electrodes implanted in different areas, such as the STN, GPi, or SNr.

Patient Data

Training the model will require datasets containing neural firing patterns from basal ganglia outputs (e.g., GPi, SNr) alongside corresponding levodopa levels. We attempt to seek additional existing datasets on PD patients that provide information on neural activity and levodopa response for model testing and validation. These datasets may be available from opensource sites such as Kaggle and Github.

Required Libraries and Packages

The model will be built using the Python language, as it allows for access to extensive Python libraries. To build the model, a number of Python packages will be used, and other libraries to analyse and display data.

The proposed model will adopt Reinforcement Learning (RL), which is a branch of machine learning that enables it to learn by trial and error. The model will explore different dosing and stimulation strategies, adjust based on the resulting patient response, and refine its policy to maximize symptom relief while minimizing side effects.

- ***Pandas*** *– Used to display, analyze, and clean patient data. This includes organizing patient data regarding electrode placement location (e.g., Substantia Nigra pars reticulata (SNr), Subthalamic Nucleus (STN), Globus Pallidus interna (GPi)).*
- ***NumPy*** *– Handles numerical data and multi-dimensional arrays related to patient information and neural activity.*
- ***Matplotlib*** *– Visualizes brain regions and neural activity patterns to map electrode placement and patient response.*

- ***Machine Learning Models of Neural Activity (MNE)*** *– Python package for analyzing human neurophysiological data from neurofunctional techniques such as MEG, EEG, sEEG, and ECoG.*
- ***Neo > Spyke Viewer*** *– Spyke Viewer is a Python package for handling and visualizing electrophysiological data (e.g., neuronal firing rates).*
- ***PyTorch*** *– Used to develop and train the RL model, particularly for creating the neural network architecture—which comprises the "meat" of the model.*
- ***TensorFlow*** *– Provides an alternative framework for model development and deployment, especially for handling large-scale datasets.*

By importing these libraries and packages into Python, we can develop a model capable of producing high accuracy levels and widen treatment options for Parkinson's Disease patients.

Discussion

Levodopa, when combined with Deep Brain Stimulation (DBS), serves as an optimal treatment for patients with Parkinson's Disease (PD). However, determining the ideal levodopa dosage is a challenge due to several factors such as individual variability in baseline dopamine levels, differences in DBS electrode placement, and the unique physiological responses of individual patients (Fasano, 2023).

To address this uncertainty, we propose a machine learning model capable of optimizing levodopa dosage and DBS stimulation levels. The model takes input from patient symptoms recorded after exposure to different DBS stimulation levels and employs a reinforcement learning technique to refine its predictions over time. By continuously learning from patient

responses, the model adapts to individual needs, ultimately determining the optimal levodopa dosage and DBS adjustments for each patient.

An example case on how this model performs goes as follows:

Case 1: Increased Stimulation and Levodopa Needed

1. Patient A has been prescribed levodopa alongside undergoing Deep Brain Stimulation.
2. Patient A experiences tremors and slight rigidity.
3. This suggests that both stimulation levels and levodopa dosage should be increased.
4. The model detects a lack of synchronization in neural firing patterns, particularly in the basal ganglia outputs (e.g., GPi, SNr), confirming the need for increased stimulation and levodopa dosage.

Case 2: Decreased Stimulation and Levodopa Needed

1. Patient B has been prescribed levodopa alongside undergoing Deep Brain Stimulation.
2. Patient B exhibits involuntary movements (dyskinesia), a known side effect of excessive levodopa intake.
3. This suggests that both levodopa dosage and DBS stimulation should be reduced to prevent overstimulation.
4. The model identifies hyperactivity in the basal ganglia outputs and abnormal firing patterns, confirming excessive dopaminergic activity.

The implementation of this model holds incredible potential for improving PD treatment. By refining dosage adjustments from trial-and-error outputs of the model, it can enhance patient

outcomes, minimizing side effects such as dyskinesia or rigidity, and provide personalized, data-driven approach to PD management. Future advancements in machine learning and neurotechnology could further enhance this model, leading to greater precision and adaptability in neuromodulation and neuropharmacological therapy.

Works Cited

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