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Strategies for Real-Time Adjustment of Stimulation Patterns in Closed-Loop Deep Brain Stimulation for Parkinson's Disease: A Comprehensive Review

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Abstract: Parkinson's disease (PD) is a prevalent neurodegenerative disorder that poses significant healthcare challenges worldwide. Deep brain stimulation (DBS) has proven effective for managing PD, particularly for patients with inadequate medication response. However, traditional high-frequency DBS systems lack the capability to adjust stimulation patterns in real time based on patient responses. In contrast, closed-loop DBS systems, which adjust stimulation based on recorded biomarkers, present a promising alternative that allows more flexible, on-demand electrical pulses delivery, offering possibility of achieving better therapeutic outcomes with less invasive stimulus. This review article explored various strategies for real-time adjustment of stimulation parameters in closed-loop DBS primarily based on electrophysiological biomarkers, particularly local field potentials (LFPs). We categorize these strategies into four categories: simple on-demand methods, control methods in systems theory, optimization or machine learning algorithms, and desynchronization approaches. By synthesizing existing literature, we provide a comprehensive overview of these strategies, highlighting contributions from multiple disciplines and the prospect of optimizing treatment for Parkinson's disease using closed-loop approach.

Keywords: Parkinson's Disease, Closed-loop Deep Brain Stimulation, Stimulation Control Strategies.

1. Introduction

Parkinson's disease (PD) is one of the most prevalent neurodegenerative disorders, affecting millions worldwide and costing billions of dollars annually in the United States alone [1]. Characterized by a range of motor symptoms, including rigidity, tremors, and bradykinesia, Parkinson's disease significantly reduces patients' quality of life and could lead to negative psychological effects [2]. As the global population aging, the incidence of PD is increasing faster than any other neurodegenerative disorders, posing increasing challenges for healthcare challenges [3].

Introduced in the 1990s, deep brain stimulation (DBS) has become a widely adopted treatment for PD, pioneered by Alim-Louis Benabid and others [4,5]. Traditional DBS systems involve implanted electrodes that deliver high-frequency stimulation (>100 Hz) to specific brain regions associated with PD symptoms, typically the subthalamic nucleus (STN) [6] and the globus pallidus pars interna (GPi)

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[7]. While effective in symptom relief, these open-loop DBS systems have limitations: they cannot adjust stimulation patterns in real-time based on the patient's condition. This static nature can reduce therapeutic benefits and increase side effects when small deviations in stimulation patterns or targeting occur.

To address these limitations, closed-loop DBS systems have emerged, which adjust the stimulation in real time based on recorded biomarkers. By monitoring electrophysiological signals, such as local field potentials (LFPs), these systems tailor stimulation to the patient's current neural activity, thereby improving treatment efficacy and reducing side effects. Closed-loop DBS typically involves electrodes for stimulation, sensors for recording biomarkers, and processors for analyzing the signals and adjusting the stimulation patterns [8,9]. The sensors, integrated with the electrode array, capture LFPs, which are analyzed by algorithms to determine optimal stimulation patterns. A controller then adjusts the pulse delivery, helping to alleviate symptoms and restore motor function.

Research on closed-loop DBS focused on strategies for adjusting stimulation patterns based on recorded LFPs. Basic strategies adjust stimulation activation or amplitude in response to biomarkers, which have been tested in clinical settings [10-17]. Advanced strategies apply systems theory [18-22], machine learning [23-26], and nonlinear dynamics [19-30], demonstrating effective suppression of parkinsonian neural activity on computational models.

This article seeks to provide a comprehensive review on the proposed strategies for the real-time adjustment of stimulation in closed-loop DBS. By synthesizing existing literature, it highlights contributions across multiple disciplines. The strategies are organized by theoretical motivations, with each section covering relevant principles, technical details, key studies, and a discussion of advantages and limitations. This approach aims to offer a clear and comprehensive overview of current closed-loop DBS strategies.

2. Strategies for Adjusting Stimulation Patterns in Closed-Loop DBS Systems

2.1. Simple On-Demand Strategies

Early DBS involves implanting electrodes to deliver continuous, high-frequency stimulation to the basal ganglia (BG) nuclei associated with PD symptoms [4,5]. Simple closed-loop adapt this approach by activating a predefined stimulation pattern in response to pathological events or by modulating stimulation amplitude based on biomarker levels. The on/off paradigm activates stimulation only when recorded biomarkers exceed certain thresholds, while amplitude modulation adjusts the stimulation intensity to keep biomarkers within a target range.

2.1.1. On/Off Paradigm

In the on/off approach, single-threshold and dual-threshold strategies are commonly used. Single-threshold methods activate stimulation when biomarkers, like beta-band power, exceed a set threshold. Little and colleagues demonstrated this approach by using beta power as a trigger, showing improved motor scores in PD patients compared to conventional DBS [10]. Dual-threshold strategies define upper and lower limits for biomarkers, activating stimulation when values fall outside this range. Gilron et al. [11] used this dual-threshold approach, adjusting stimulation based on LFPs fluctuations from the subthalamic nucleus (STN) and cortex. Similarly, Velisar et al. and Swann et al. demonstrated threshold-based stimulation that targeted specific symptoms such as tremor, bradykinesia, and dyskinesia by modulating voltage or current [12,13].

Machine learning techniques have further advanced on/off strategies by enabling symptom prediction. Trained classifiers detect motor symptoms, such as tremor and bradykinesia, based on non-invasive biomarkers, enabling proactive stimulation. For instance, Khobragade et al. used an artificial neural network to predict tremor onset from surface electromyogram (sMEG) data,

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achieving high sensitivity [14]. Griffiths et al. identified dyskinesia through movements of normal amplitude and acceleration but with shorter periods of stillness [15].

2.1.2. Amplitude Modulation

Amplitude modulation adjust stimulation amplitude in real time to maintain the biomarker levels within a designated range. Rosa et al. tested an adaptive DBS system that modulate voltage according to beta-band LFP power in a PD patient [16]. This adaptive stimulation reduced bradykinesia and minimized side effects compared to traditional open-loop DBS. The team also tested this approach on a larger group of patients, demonstrating reduced side effects and improved motor function through real-time voltage adjustments [17].

2.1.3. Advantages and Limitations of Simple On-Demand Methods

On-demand stimulation offers a straightforward approach for managing specific symptoms, like tremor and bradykinesia, by activating stimulation only when necessary [13]. This method is particularly effective for long-term symptom management, as it can adapt to a patient's daily activities and selectively respond to motor symptoms [11]. However, these strategies rely on fixed thresholds, which may not accommodate fluctuations in symptom-related neural activity across different sessions or patients.

2.2. System Control Methods

Control methods from systems theory offer a structured way to adjust DBS stimulation patterns. In this framework, the basal ganglia (BG) circuit is viewed as a system that receives DBS pulses serves as inputs, and the neural responses, measured as local field potentials (LFPs), act as outputs. The input-output relationship can be modeled with transfer functions, enabling the use of control methods like proportional-integral-derivative (PID) control to adjust stimulation in response to deviations from target neural activity.

2.2.1. Input-Output Models

A crucial first important step is to establish an input-output model that defines how stimulation affects neural activity. The inputs include stimulation parameters, particularly amplitude, while the outputs are LFPs. The relationship can be captured by a transfer function, with system identification techniques employed to estimate the parameters, either from clinical data or BG circuit model.

For example, Liu et al. [18] modeled BG neurons firing rates a function of input stimulation, estimating model parameters by fitting the data from a circuit model of the BG. Similarly, Yang et al. [19] developed a linear state-space model with stimulation parameters as inputs, and the features derived from simulated ECoG data as outputs, summarizing stimulation effects on neural activity are captured by a low-dimension hidden state.

2.2.2. PID Control Methods and Others

Once an input-output model is defined, controllers can be designed to modulate stimulation based on neural responses. PID control is a widely used methods typically based on the LFP. Dunn et al. [20] employed a PID controller based on the LFP of STN neurons, showing that this approach reduced oscillations in a cortico-basal ganglia network. Gorzelic et al. [21] focused on restoring the inhibition of GPi to the thalamus, thus using the spatially averaged synaptic conductance as control signal and its deviation from a reference value as the error.

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Other controller designs have also been explored. Yang et al. [19], for instance, combined a state-space input-output model with a linear-quadratic-Gaussian controller, which minimizes a quadratic under the assumptions of Gaussian noise and linear control-state relationship. Santaniello et al. [22] employed a minimum variance controller that minimized an error term to restore the power spectrum of the LFP to a reference normal profile.

2.2.3. Limitations and Prospects of Control Methods

Most studies primarily utilized simulated data instead of clinically recorded data. On one hand, they demonstrate the feasibility of control methods based on input-output models and provide a framework for clinical applications. On the other hand, clinical research has yet to be conducted for establishing their safety and effectiveness for practical DBS systems. In particular, the mathematical input-output models may not accurately capture the complex neural responses to stimulation, and real-time monitoring of LFPs needs to be integrated into the systems to optimize the control input.

2.3. Optimization Algorithms

Optimization algorithms frame the determination of DBS patterns as an optimization problem, where an objective function is either minimized or maximized. By incorporating recorded biomarkers in the objective function, stimulation patterns can be updated in real time to achieve desired physiological effects. Additionally, including the variance of stimulation signal can lead to constraints on energy consumptions. Two key types of optimization algorithms discussed here are genetic algorithms (GAs) and reinforcement learning (RL), both of which offer promising approaches for closed-loop DBS.

2.3.1. Genetic Algorithms

Genetic algorithms (GAs) are a class of optimization algorithms inspired by genetic variation and natural selection. In GAs, multiple trial solutions are iteratively generated and selected according to their fitness, essentially the value of the objective function, until a satisfactory solution converges. One of the biggest advantages of GAs is their capability to optimize over a large parameter space, making them suitable for identifying effective waveforms based on LFPs.

Feng and colleagues utilized GAs to optimize DBS waveforms by generating trial currents to stimulate target areas like the STN, evaluating each current's effectiveness, and refining patterns through mutation and selection until optimal currents were found [23]. Brocker et al. utilized GAs to identify optimal waveforms in both animal model and human patients, showing that the GA-derived pattern was as effective as standard stimulation while consuming much less energy [24].

2.3.2. Reinforcement Learning

Reinforcement learning (RL) trains an agent to make decisions based on interactions with its environment, guided by rewards. At each iteration, the agent selects actions according to a policy informed by its current state and updates its state accordingly. The agent's goal is to learn to maximize the cumulative reward by updating the policy. In closed-loop DBS, RL allows the training of an intelligent DBS system (the agent) that delivers appropriate stimulus to the basal ganglia-thalamus (BGT) network (the environment). The agent aims to maximize therapeutic outcomes while minimizing side effects and energy use.

In Lu et al. [25] and Cho et al. [26], RL was used to select stimulation amplitudes based on synaptic variables from the GPi to the thalamus. Lu et al. employed an actor-critic agent, while Cho et al. compared four different agents. In Lu et al., the reward function encompassed two components: the deviation of averaged synaptic variables from normal values and the fluctuation of stimulation current,

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aiming to restore normal synaptic dynamics while imposing constraints on energy consumption. In Cho et al., the reward included two terms quantifying therapeutic effects based on thalamic reliability, as well as a term addressing side effects and a term encouraging appropriate switching of DBS to reduce energy consumption.

2.3.3. Limitations and Prospects of Optimization Algorithms

Most research on GAs and RL for DBS is based on simulations rather than clinical data, presenting challenges for real-world application. However, GA and RL frameworks could eventually integrate clinical data, using real-time physiological signals in GAs or replacing BG models in RL with preclinical or clinical data. Compared to simpler on-demand and control-based methods, GAs and RL offer more dynamic and adaptive adjustments without requiring predefined thresholds. While these methods show promise for responsive DBS systems, their complexity and need for extensive clinical validation remain challenges for future implementation.

2.4. Desynchronization Techniques

Motor symptoms in Parkinson's Disease are associated with abnormal synchronized firing of basal ganglia neurons, such as enhanced beta-band oscillations associated with bradykinesia [40]. Consequently, a significant area of research has focused on desynchronizing specific neuronal populations to alleviate parkinsonian symptoms.

Desynchronization methods, rooted in nonlinear dynamic, focus on altering the phases of individual neurons within a network, disrupting their collective firing patterns. Research has investigated the desynchronizing effects of various stimulation patterns applied at different phases of the population.

2.4.1. Phase Resetting Approach

Early development of desynchronization techniques for DBS was informed by phase resetting theories for an ensemble of interacting phase oscillators. Tass's pioneering studies demonstrated that various stimulation patterns, including a single [27] or a double [28] pulse and a double low-frequency pulse trains [29] can desynchronize neural activity. The coordinated reset developed by Tass applies the phase-dependent stimulus is applied at different target sites in a coordinated way [30]. Computational studies showed that coordinated reset can reduce abnormal synaptic weights and therefore produce long-term desynchronizing effects [31].

In clinical applications, phase-resetting patterns like coordinated reset can be administered only when synchronization is detected, a technique known as demand-controlled coordinated reset [30]. Cagnan and colleagues investigated a phase-locked approach, where stimulation timing is determined by the phase of tremor-related oscillations [32,33].

2.4.2. Time-Delayed Feedback Techniques

Another branch of desynchronizing methods is based on feedback control techniques, particularly the time-delayed feedback control, where the stimulation signal depends on the activity of oscillators. Early nonlinear theories suggested that delayed interaction between oscillators can suppress or enhance synchrony [34]. The stimulation signal is based on the activity of oscillators at a previous time, essentially using delayed interaction to suppress synchrony. By applying a stimulus that is out of phase with the oscillators' current activity, synchronization is disrupted.

Researchers such as Hauptmann, Rosenblum, and Pikovsky have extensively studied time-delayed feedback control, demonstrating its effectiveness in suppressing pathological rhythms in neural

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populations [35-39]. Rosenblum and colleagues [35,36,37] investigated a population of coupled neural oscillators receiving time-delayed feedback signals based on the mean field of the population, while Hauptmann and colleagues [38,39] explored coordinated delayed feedback stimulation which involved feedback signals at four different sites with different delays.

2.4.3. Advantages and Limitations of Desynchronization Methods

Desynchronization techniques offer several advantages over conventional high-frequency, continuous stimulation, as they are more precise and use lower frequency and amplitude, reducing energy consumption and minimizing side effects. In particular, the phase-locked stimulation reduces stimulation frequency from the conventional 130 Hz to tremor frequency (4–8 Hz) [33]. This not only allows desynchronizing techniques to operate with lower energy consumption but also reduces side effects caused by current spread in high-frequency stimulation.

However, these methods are primarily based on theoretical models of phase oscillators, which may not fully capture the dynamics of neuronal populations. Additionally, few clinical studies have specifically examined the therapeutic benefits of time-delayed feedback signals, although theoretical frameworks have been outlined and their clinical applications have been discussed in nonlinear dynamics research.

3. Conclusion

This article reviews the strategies for real-time determination of effective stimulation patterns in closed-loop DBS systems, focusing on closed-loop optimization techniques that adjust stimulation patterns based on recorded electrophysiological signals, particularly local field potentials (LFPs) of basal ganglia (BG) neurons. Four categories of strategies are identified in the literature: simple on-demand strategies that activate stimulation or modulate amplitude based on biomarker levels, control methods grounded in systems theory like PID control techniques, optimization algorithms including genetic algorithms (GAs) and reinforcement learning (RL), and methods aimed at desynchronizing the collective firing of BG neurons such as time-delayed feedback techniques. These strategies have drawn upon theories from multiple subject areas, offering unique mechanisms for modulating stimulation patterns.

These strategies have contributed to the management of parkinsonian symptoms by providing theoretical frameworks and practical solutions. Simple on-demand control strategies have been mostly employed in clinical studies for their ability to deliver timely interventions and simplicity of implementation. Control methods introduce a theoretical approach to modulating neuronal dynamics based on models of relevant neuronal populations informed by real-time LFPs. Optimization algorithms, such as GAs and RL, also grounded in computational modeling, may facilitate more adaptive DBS systems with their strong learning ability. Additionally, desynchronization techniques may offer promising approach that can achieve desirable therapeutic effects while reducing energy consumption and side effects.

Several areas may warrant future research to facilitate the applications of closed-loop strategies in DBS systems. An aspect is to investigate more effective while computationally cheaper methods, such as GAs or RL frameworks that are easier to implement clinically, as well as more sensitive biomarkers that indicate symptom onset. Additionally, the integration of real-time data into theoretical approach, such as system control methods and desynchronization techniques, will be a significant issue. Exploring the clinical benefits and side effects of these strategies will also be essential to establish their safety and effectiveness in diverse patient populations.

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