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Reengineering deep brain stimulation for movement disorders: Emerging technologies

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Abstract

Deep brain stimulation (DBS) is a neurosurgical technique that consists of continuous delivery of electrical pulses through chronically implanted electrodes connected to a neurostimulator, programmable in amplitude, pulse width, frequency, and stimulation channel. DBS is a promising treatment option for addressing severe and drug-resistant movement disorders. The success of DBS therapy stems from a combination of surgical implantation techniques, device technologies, and clinical programming strategies. Changes in device settings require highly trained and experienced clinicians to achieve maximal therapeutic benefit for each targeted symptom, and optimization of stimulation parameters can take many clinic visits. Thus, the development of innovative DBS technologies that can optimize the clinical implementation of DBS will lead to wider scale utilization. This review aims to present engineering approaches that have the potential to improve clinical outcomes of DBS, focusing on the development novel temporal patterns, innovative electrode designs, computational models to guide stimulation, closed-loop DBS, and remote programming.

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Introduction

Deep brain stimulation (DBS) is a technique used in functional neurosurgery [1], which consists of delivering a deep brain region continuous electrical stimulation through chronically implanted electrodes. The electrodes are inserted using stereotactic methods, which include radiological methods and electrophysiological mapping to localize the target structure. The electrodes are subsequently connected to a subcutaneous neurostimulator. The electrical stimulation consists of a pulse train that can be programmed in frequency, amplitude, and pulse width [2]. Stimulation can be delivered from 4 to 8 cylindrical band contacts at the distal end of the electrode lead. DBS for movement disorders can provide greater than 50% improvement in clinical ratings of motor symptoms in appropriately selected patients [3]. However, clinical programming requires highly trained and experienced clinicians to achieve maximal therapeutic benefit in each patient (~18–36 h [4]). Given the vast size of the parameter space, optimization of stimulation settings can take many visits over several months [5]. Engineering innovations and techniques are likely to deliver better device designs, as well as guided and/or automated programming strategies to improve DBS outcomes. Herein, we discuss the current understanding of the mechanisms of DBS therapy, and we present recent engineering advancements in device design and neuromodulation delivery strategies aimed at improving DBS outcomes.

Current understanding of the therapeutic mechanisms of DBS

Although DBS is now considered an established therapy and is approved by the U.S. Food and Drug Administration (FDA) for the treatment of Parkinson's disease, essential tremor and dystonia, the mechanisms by which it improves symptoms remain debated [6]. This gap in knowledge can hinder our goal of achieving maximal benefits of DBS therapy and minimization of side effects. Historically, high frequency DBS (>100 Hz) was first used in chronically implanted devices in 1987 to address Parkinsonian and essential tremor [7,8]. It was initially thought that DBS causes a temporary reversible lesion effect by inhibiting the target structure and reducing its output [7]. However, several studies have reported contradicting results of excitation of the stimulated structures and increased output at projection nuclei [9,10]. Given that clinical DBS leads are macroscale electrodes, it is likely that DBS non-selectively affects local neurons, afferent inputs, and fibers of passage. This complexity hinders our ability to study the individual roles of activation/inhibition at the cellular level or even the roles of individual structures in the overall mechanism of DBS. Moreover, experimental

studies of DBS modulation of neural activity are hampered by large stimulus artifacts [11].

Overall, it is likely that the therapeutic mechanisms that underlie DBS most likely represent a combination of several phenomena that lead to stimulation-induced modulation of pathologic network activity [12–14]. The pathological neural activity in the basal ganglia-thalamo-cortical motor network is likely generated by increased neuronal synchronization and low-frequency rhythmic oscillations of neurons [15–17]. It is possible that DBS overrides these altered patterns and replaces them with tonic high-frequency output in the target nucleus. A tonic high-frequency signal may be more easily mitigated by the remaining elements of the network as opposed to irregular patterns [11–13]. Moreover, random patterns of DBS in the subthalamic nucleus, even when delivered at a high average frequency that would be considered therapeutic, were not effective in relieving bradykinesia in patients with Parkinson's disease [18]. These findings reinforce the potential importance of regularization of pathological activity in the network for the effectiveness of DBS [19]. This hypothesis would disagree with the idea that DBS acts to randomly interfere with one node in the circuit. Nevertheless, the finding that the temporal patterns of stimulation could affect therapeutic outcomes inspired the testing of novel temporal patterns of DBS.

Novel temporal patterns of stimulation as a therapeutic innovation

The traditional DBS pattern is that of a monophasic cathodic pulse train (with the neurostimulator casing used as the reference electrode) programmable in amplitude, pulse width and frequency, with passive recharge (Figure 1C). Figure 1A demonstrates examples non-regular patterns that have been tested in the literature in Parkinson's disease and essential tremor patients. The dark lines represent the instance of the monophasic pulses. The patterns consist of pulses with short periods of rest (absence of pulses) (Figure 1A, top row), the presence of short bursts of pulses (Figure 1A, second row), highly non-regular pulses with log-uniform distributions of instantaneous pulse frequencies (Figure 1A, third and fourth rows). Brocker et al. [20] applied the absence, presence and log-uniform distribution patterns in the STN of Parkinsonian patients. Their results revealed improved treatment of motor symptoms, or alternatively equivalent treatment of symptoms with a substantial reduction in the required power settings of the device. The latter finding is an important consideration for prolonged battery life of an implanted neurostimulator. Prolonged battery life would result in fewer device replacement surgeries (for non-rechargeable devices) and presumably less infections. A primate study of irregular DBS patterns in the GPi, however, did not result in improved treatment of bradykinesia compared to regular patterns [21].

Akbar et al. [22] applied irregular patterns in Parkinson's disease and essential tremor, as well as biphasic active recharge patterns (see Figure 1D). These biphasic pulse patterns facilitated fast recovery of charge, but increased the amount of power consumed, shortening the battery life. Biphasic active recharge patterns are not required to be delivered symmetrically, and can be programmed with varying parameters including an inter-phase delay (see Figure 1D). While the therapeutic effects of the irregular monophasic patterns were not significantly different than the regular pattern, biphasic active recharge patterns yielded improved clinical scores in many areas. This, however, came at the cost of increased current drain. Ongoing studies are investigating the therapeutic effects of biphasic stimulation patterns with active recharge in dystonia and their potential chronic long term effects [23].

In order to counteract pathological synchronization in the Parkinsonian basal ganglia [24], Tass et al. proposed desynchronizing the target nodes and the network by electrical coordinated reset [25]. Brief high frequency pulse trains delivered across different electrode contacts with varying order in the STN induced significant improvement of motor function by overcoming local and network synchronization [26].

In contrast to the benefits observed in Parkinson's disease, non-regular patterns did not provide therapeutic benefit in treating essential tremor, suggesting that tremor might be better controlled with regular patterns [19]. This result may have been caused by sufficiently long gaps in the stimulation train. These gaps could facilitate pathological activity and lead to undesired propagation through a region [27].

Collectively, these studies demonstrate the utility of temporal patterns as an entirely new dimension in the stimulation parameter space. This added dimension may serve to improve effectiveness and in some cases to increase the efficacy of the therapy, but large and well-powered studies will be needed.

Innovations in DBS lead design

The current standard DBS electrode leads consist of four cylindrical electrode contacts (see Figure 2A), which can only yield symmetrical electrical stimulation fields. The neural tissue that generates action potentials in response to a specific set of stimulation parameters is referred to as the *volume of tissue activation* (VTA). If a lead is sub-optimally implanted, a wider VTA maybe necessary to activate target nucleus or region, at the potential expense of activating other areas prone to side effects [28]. Emerging DBS leads have been engineered to