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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, which consists of continuous delivery of an electrical pulse 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 is a combination of surgical implantation techniques, device technology, 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 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.

Keywords

Deep brain stimulation; DBS; Movement disorders; Neurostimulator; Neuromodulation

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Conflict of interest

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Introduction

Deep brain stimulation (DBS) is a technique used in functional neurosurgery, 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. 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 [1]. However, clinical programming requires highly trained and experienced clinicians to achieve maximal therapeutic benefit in each patient. Given the vast size of the parameter space, optimization of stimulation settings can take many visits over several months [2]. 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 [3]. 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 1987 to address Parkinsonian and essential tremor [4,5]. It was initially thought that DBS causes a temporary reversible lesion effect by inhibiting the target structure and reducing its output [4]. However, several studies have reported contradicting results of excitation of the stimulated structures and increased output at projection nuclei [6,7]. 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 [6].

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 [8–10]. 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 [11–13]. It is possible that DBS overrides these altered patterns and replaces them with tonic high-frequency output in the target nucleus, which may be more easily compensated by the remaining elements of the network [6,8,9]. 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 [14]. These findings reinforce the potential importance of regularization of pathological activity in the network for the effectiveness of DBS [15]. This hypothesis would disagree with the idea that DBS acts to randomly interfere 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 monopolar cathodic pulse train (with the neurostimulator casing used as the reference electrode) programmable in amplitude, pulse width and frequency. Fig. 1A demonstrates examples non-regular patterns that have been tested in the literature in Parkinson's disease and essential tremor patients. These patterns consist of pulses with short periods of rest (absent of a pulse) (Fig. 1A, top row), the presence of short bursts of pulses (Fig. 1A, second row), highly non-regular pulses with log-normal distribution of instantaneous pulse frequencies (Fig. 1A, fourth row), and pulses consisting of the same average stimulation frequency as the clinically-optimal settings but with an overall 20% coefficient of variance (Fig. 1A, bottom row). Brocker et al. [16] applied the absence, presence and log-normal distribution patterns in 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.

Akbar et al. [17] applied patterns with 20% CV in Parkinson's disease and essential tremor, as well as charge balanced regular biphasic patterns (see Fig. 1C). Biphasic pulse patterns facilitated recovery of charge, but increased the amount of power consumed, shortening the battery life. Biphasic patterns are not required to be delivered symmetrically, and can be programmed with varying parameters including an inter-phase delay (see Fig. 1D). While the therapeutic effects of the 20% CV pattern were not significantly different than the regular pattern, biphasic 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 in dystonia and their potential chronic long term effects [18].

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 [15]. 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 [19].

Collectively, these studies demonstrate the utility 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 Fig. 2A). These contacts can only yield symmetrical electrical stimulation fields. The tissue that lies within the stimulation field is referred to as the *volume of tissue activation* (VTA). If a lead is sub-optimally implanted, a wider VTA may be necessary to extend the stimulation field to the target nucleus or region, at the potential expense of activating other areas prone to side effects [20]. Emerging DBS leads have been engineered to provide control over the shape of the VTA, and to personalize therapy by combining the lead location with structural images. Fig. 2B presents four novel lead designs that are currently undergoing preclinical and clinical trials [21–23]. Three of these designs (from Aleva, Boston Scientific, and Abbott-St. Jude Medical) have 3-segments across two of the cylindrical contacts. The collective idea behind the novel designs is to steer currents in the direction of therapeutic targets and to avoid stimulating areas prone to side effects. The fourth design (from Medtronic-Sapiens) has 10 rows of 4 electrodes per row, and with alternating rows offset by 45° facilitating stimulation in 8 radial directions. This design allows the VTA to be shaped by choosing various combinations of independently active electrodes. However, an increased number of channel options would further complicate clinical programming. Visualization of the VTA based on patient specific imaging via computational modeling may reduce this burden.

Imaging and computational tools for personalized DBS

Clinical DBS programming is typically performed without the opportunity to visualize the spread of stimulation, or the VTA, relative to the surrounding anatomy. This can be problematic if electrodes are suboptimally placed, or if the VTA spreads across non-target areas without overt clinical signs. This situation may result in unintended side effects following a programming session. An engineering solution to the problem is the development of software systems that would enable the 3D visualization of the VTA as a function of the stimulation parameters and electrode location within the brain [24,25]. Fig. 3A shows the electrode location on a patient's MRI, and from this image, 3D subcortical structures can be extracted by utilizing a brain atlas. Fig. 3B shows the electrode location with respect to the subthalamic nucleus and the thalamus (shown in green and yellow, respectively). However, the effect of DBS is not limited to the region targeted and DBS can propagate through anatomical connections, which can influence distributed neural networks in the brain. Fig. 3C depicts anatomical fiber tracts extracted through diffusion tensor imaging (DTI) that have been overlaid onto the subcortical nuclei. Finite element models of the DBS electrode and the electric field can be transmitted to the brain with the tissue conductivity properties derived from diffusion tensor imaging. These yield the VTA as a function of stimulation contact, amplitude, pulse width, frequency, electrode shape and impedance (see Fig. 3D). These models will be indispensable in guiding the clinical programming of high-density electrode leads, such as the Medtronic-Sapiens lead discussed above. Moreover, these models can also aid in guiding the design of novel temporal patterns, which can be delivered in a more precise way. In a recent study, Brocker et al. used model-based computational evolution to optimize the temporal stimulation pattern and his

group showed improved efficacy and power efficiency in humans with Parkinson's disease [26].

Overall, it will be important as DBS technology advances to develop easy to use tools for clinicians who lack access to specialized movement disorders care. One danger in the field is to develop solutions that are too complex to implement on a large scale.

Development of closed-loop DBS systems

While DBS is an effective treatment for movement disorders, traditional DBS systems deliver constant stimulation without adjusting the therapy for the patient's individual symptom(s), medication status, or side effects. It may be possible to achieve improved patient outcomes and increased battery life by utilizing a biomarker approach to monitor a patient's disease state, and to adapt the delivery and parameters of stimulation. Such a system is called a "closed-loop DBS" system and Fig. 4 shows how the system functions.

A crucial first step in the development of closed-loop DBS is the characterization of biomarkers associated with the patient pathophysiology. Next generation neurostimulators, such as NeuroPace RNS [27] and the Medtronic Activa PC + S [28] devices, allow for the chronic recording of brain signals directly from the implanted leads. These devices will enable the translation of disease biomarkers and they can be studied acutely during DBS surgery as well as in chronic systems. The most extensively investigated DBS biomarker in surgery is the parkinsonian beta-band (12–30 Hz) power in the local field potentials (LFPs) drawn from the subthalamic nucleus region. Increased power in beta activity has been correlated with PD motor symptoms and this exaggerated beta power can be reduced with medication (levodopa) and with DBS [29]. Little et al. (2013) [30] have shown intra-operatively that closed-loop DBS is possible by increasing stimulation amplitude with increased beta power. Other groups are working towards chronic implementation of this approach [31,32]. Chronic closed-loop DBS for the treatment of Tourette syndrome, a hyperkinetic disorder, has been shown in a case study with bilateral responsive stimulation of the centromedian thalamus [33].

Recording and stimulating from the same electrode, however, injects stimulation artifacts into the neural signals that confound the detection of biomarkers. Implantation of additional electrodes in other nodes of the pathological network can overcome this shortcoming. Subdural electrocorticography (ECoG) strips can be placed on the surface of the primary motor cortex through the same surgical burr hole in order to extract biomarkers of movement disorders. These strips add minimal risk to DBS surgery and to brain tissue, as they are not penetrative. Moreover, ECoG electrodes yield signals with much greater amplitudes. This advantage and their distance from the stimulation area will yield high quality signals. In addition, cortical electrodes enable the network study of basal ganglia-or thalamo-cortical interactions. Recent studies have shown that motor cortex ECoG signals in Parkinson's disease exhibit exaggerated cross-frequency coupling compared to other indications (such as epilepsy and dystonia). This exaggerated biomarker could be suppressed with optimal DBS modulation of the subthalamic nucleus [34,35]. Moreover, the ECoG signals yielded a biomarker for dyskinesia in Parkinson's disease [36]. Dyskinesias occur when medication

and stimulation levels cannot be regulated, and the clinical manifestation is in hyperkinetic activity in multiple body regions. This marker could potentially be used to decrease stimulation and to prevent dyskinesias in a closed-loop system.

Finally, motor symptoms can be potentially captured from wearable sensors, such as tremor. Case studies in Parkinson's disease [37] and essential tremor [38] suggest the feasibility of using wearable sensors. One downside of this approach is that the system will only be able to suppress symptoms after they manifest, and neural signals would be likely to neuromodulate prior to a clinical manifestation. Also a technical challenge will be establishing the communication between external sensors and the implanted devices. Sensors also need energy and may drain centrally implanted devices of precious battery. Nevertheless, there is a significant utility for wearable sensor technology in the movement disorders field. There has been an explosion of ongoing investigations in wearable sensors for the development of objective measures that can be used to record long-term changes [39]. Current clinical scales are assessed by scoring a video recording (examination by a specialist), who then assigns a categorical rating to each item. This approach is highly subjective and can only be implemented completely during patient visits. The use of wearable technologies could yield continuous scoring of hypokinetic or hyperkinetic symptoms. It will also be important to create telemedicine solutions that will make it easier for patients to obtain DBS devices, and to be programmed and managed from remote locations.

Conclusion

Today's advances in scientific knowledge and technology are laying the groundwork for the realization and potential of DBS therapy. These advances will better serve patients and clinicians. There is a window of opportunity for technical development in DBS, and ongoing engineering efforts should be focused on the development and testing of (i) novel temporal patterns, (ii) innovative electrode designs, (iii) computational models to visualize VTA, and (iv) closed-loop DBS. Efforts in these areas have the potential to lead to transformative, not just incremental change in DBS therapy. Modifying the temporal pattern of DBS stimulation has offered a new dimension to the therapy, whereas novel electrode designs will allow steering and shaping of the current to target the optimal structures (nuclei and fiber pathways). This steering can be accomplished with the guidance of computational models. These changes will enable greater specificity in brain circuit targeting and will improve the benefit-side effect ratio of DBS therapy. The near term future will likely see a rapid increase in pilot clinical studies on closed-loop DBS for a wide range of symptoms enabled by next generation DBS devices capable of chronic recordings in real-time. Recordings from these devices will facilitate improved scientific understanding of the pathophysiology of movement disorders. The collective knowledge will inform the DBS mechanisms of action and guide the path for new design goals in future devices.

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Highlights

- Deep brain stimulation has emerged a promising therapeutic option for movement disorders.
- Collaborations between medicine and engineering will shape the future of DBS devices and delivery.
- Novel temporal stimulation patterns, electrode designs, personalized computational models are reviewed.
- Closed-loop DBS systems which adapt to the patients' symptoms are discussed.

Figure 1.

(A) Novel temporal patterns compared to regular pattern (middle row). Top row: Patterns with short periods of absence. Second row: Patterns with the presence of short bursts of pulses. Fourth row: Highly non-regular pulses with log-normal distribution of instantaneous pulse frequencies. Bottom row: Pulses consisting of the same average stimulation frequency as the regular pattern but with an overall 20% coefficient of variance (CV). (B) A monophasic pulse. (C) A balanced biphasic pulse. (D) Parameter space of biphasic pulse design. Adapted from Refs. [16] and [17].

Figure 2. (A) Current clinical DBS leads (Adapted from St. Jude DBS Brochure 2010, St. Jude DBS Product Catalog 2011, Medtronic DBS 3387/3389 Lead Kit Manual). (B) Emerging DBS electrode lead designs (Adapted from Rossi et al., 2016). BSN: Boston Scientific Neuromodulation; SJM: Abbott-St. Jude Medical; MDT: Medtronic. Adapted from Ref. [40].

Figure 3.

(A) Implanted electrode overlaid on patient MRI. (B) Extracted 3D thalamus and subthalamic nuclei (in yellow and green, respectively). (C) Fiber trajectories within created using DTI tractography. (D) The voltage distribution in the tissue medium determined from a finite element model with the total current amplitude divided between adjacent electrode contacts. Adapted from Refs. [25,41].

Figure 4.

A closed-loop DBS system that is utilizing biomarkers from the DBS leads, from additional subdural ECoG strips, and/or from wearable sensors. A controller adaptively changes the stimulation parameters based on the extracted biomarkers.