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Engineering the Next Generation of Clinical Deep Brain Stimulation Technology

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Abstract

Deep brain stimulation (DBS) has evolved into a powerful clinical therapy for a range of neurological disorders, but even with impressive clinical growth, DBS technology has been relatively stagnant over its history. However, enhanced collaborations between neural engineers, neuroscientists, physicists, neurologists, and neurosurgeons are beginning to address some of the limitations of current DBS technology. These interactions have helped to develop novel ideas for the next generation of clinical DBS systems. This review attempts collate some of that progress and with two goals in mind. First, provide a general description of current clinical DBS practices, geared toward educating biomedical engineers and computer scientists on a field that needs their expertise and attention. Second, describe some of the technological developments that are currently underway in surgical targeting, stimulation parameter selection, stimulation protocols, and stimulation hardware that are being directly evaluated for near term clinical application.

Keywords

Neuromodulation; Parkinson's Disease; Essential Tremor; Dystonia; Epilepsy; Obsessive Compulsive Disorder; Depression

Introduction

Deep brain stimulation (DBS) is an effective clinical technology, positively impacting the lives of tens of thousands of patients worldwide, directly quantified by Medtronic announcing that their 100,000th DBS patient was implanted in 2012. DBS has FDA approval for the treatment of essential tremor (ET) [Benabid et al., 1991], Parkinson's disease (PD) [Obeso et al., 2001], dystonia [Vidailhet et al., 2005], and obsessive-compulsive disorder

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(OCD) [Greenberg et al., 2010]. In addition, numerous clinical trials are currently underway or recently completed to evaluate its efficacy for other disorders, most notably epilepsy [Fisher et al., 2010; Morrell et al., 2011] and treatment refractory depression (TRD) [Malone et al., 2009; Holtzheimer et al., 2012].

The clinical outcomes achieved with DBS are a testament to the efficacy of the current device technology, surgical implantation techniques, and clinical programming strategies. For example, DBS for movement disorders can commonly provide greater than 50% improvement in clinical ratings of motor symptoms in appropriately selected patients [Miočinović et al., 2013]. However, DBS typically requires highly trained and experienced clinical oversight to achieve maximal therapeutic benefit in each patient [Moro et al., 2006]. In turn, an important and necessary step forward for wider scale use of DBS therapies is the development of assistive technologies that optimize its clinical implementation.

The inception of modern DBS is credited to Benabid et al. [1991], but the basic concepts date back to the 1960s [e.g. Hassler et al., 1960; Fessard et al., 1963]. The most common clinical DBS hardware in use today is the Medtronic Activa system. However, competitive systems are currently available in Europe from St. Jude Medical (Libra system) and Boston Scientific (Vercise system). All of these clinical DBS systems consist of an implanted pulse generator (IPG) connected to a lead with multiple (4-8) cylindrical band electrode contacts at the distal end of the lead. A commonly used lead used in clinical practice is the Medtronic 3389 model which has four platinum-iridium contacts separated by 0.5 mm spacing. Each electrode contact is 1.5 mm in length and 1.27 mm in diameter resulting in a surface area of $\sim 6 \text{ mm}^2$.

DBS Surgery

Each DBS implant center follows their own specific surgical protocol, but the fundamental steps of the surgery consist of pre-operative target planning, electrode placement, and IPG placement [Abosch et al., 2013]. Currently, the most common DBS procedure is to implant electrodes into the subthalamic region of the diencephalon for the treatment of PD (Fig. 1). The exact physiological mechanisms of this therapy, as well as the directly stimulated neural pathways explicitly responsible for therapeutic benefit, remain unknown [McIntyre and Hahn, 2010].

The brain target location for electrode implantation in each hemisphere of each patient is initially determined using anatomical MRI data. These targeting scans are typically acquired in an outpatient visit prior to the DBS surgery. However, to identify a target point in the brain, the neurosurgeon must define a coordinate system that is compatible with their surgical instruments. To do this they rely on a stereotactic frame. The most common frame systems are made by Elekta (Leksell) or Integra (Radionics CRW). The frame is placed on the patients head, the morning before the surgery, and they are taken to get a CT and/or MRI with the frame in place. Fiducial markers associated with the frame allow for definition of common coordinate system used for all subsequent surgical steps (Fig. 1A). The head image with the frame is then co-registered with the anatomical MRI using a commercial neurosurgical navigation software package. The most common targeting software systems

are made by Medtronic (StealthStation) or BrainLab (iPlan). These software systems enable interactive definition of the target point within the context of the MRI, as well as the surgical trajectory used to reach that point (Fig. 1B). Selection of these parameters enables the surgeon to adjust the mechanical features of the frame system such that the target can be reached during the operation.

The DBS electrode implantation surgery is typically performed with the patient awake. A burr hole is drilled in the skull, a guide canula is inserted into the brain, and a microdrive is used to advance the electrode to the target. The majority of DBS centers also perform microelectrode recording (MER) based physiological confirmation of the target prior to permanent placement of the DBS electrode (Fig. 1C). In addition, test stimulation through the implanted DBS electrode is typically performed to evaluate therapeutic benefit and possible side effects prior to fixing the lead in place. Final lead placement is commonly verified intraoperatively using fluoroscopy and/or post-operatively using CT. The IPG is then implanted in the subclavicular region and connected to the DBS electrode(s), typically in a follow-up procedure. Duration of the total DBS implant process is estimated at 4.5 hours for a unilateral implant, and 6 hours for a bilateral procedure [Abosch et al., 2013].

A wide range of research efforts are currently underway to improve the surgical targeting of DBS electrodes. These efforts focus on alternative frame systems, improved imaging protocols, and advanced MER signal processing strategies. Traditional stereotactic frames represent the standard in DBS surgery; however, so called “frameless” systems have also been developed. Commercial versions of these systems are made available by Medtronic (Nexframe) and FHC (microTargeting). The primary benefit of using a frameless system is patient comfort. The mechanical accuracy of frame-based and frameless systems is the same (~1.5 mm error) [Holloway et al., 2005], and clinical outcomes from frameless procedures are comparable to those achieved with traditional frame systems [Bronte-Stewart et al., 2010; Konrad et al., 2011].

One of the more dramatic alternative surgical strategies currently under development is the concept of using intraoperative (a.k.a interventional) MRI to guide placement of the DBS electrode [Starr et al., 2010; Larson et al., 2012]. These procedures require a frameless MRI compatible aiming device and use direct visualization on the patient imaging data to verify lead placement. This facilitates the use of general anesthesia for the patient, which would be desired by most people, and can speed up the overall procedure. However, this requires a specially equipped OR with an interventional MRI, and small (or low contrast) anatomical targets can sometimes be difficult to visualize on the MRI. Commercialization of this concept is being spearheaded by MRI Interventions (ClearPoint).

High-field MRI (7T) is also beginning to make inroads into DBS surgical targeting [Abosch et al., 2010; Lenglet et al., 2012]. The superior signal-to-noise ratio and image contrast that can be obtained at 7T can improve anatomic delineation of the target brain region for DBS electrode placement. Preliminary analyses suggest that 7T images have comparable distortions to that observed on traditional 1.5T surgical targeting images [Duchin et al., 2012]. Therefore, 7T datasets are beginning to be used to augment traditional surgical planning strategies.

While imaging technologies continue to evolve to provide improved predictions of the target location for DBS electrodes, the gold standard for clinical verification of electrode placement decisions remains intraoperative MER. Historically, single microelectrode passes were performed in a serial manner to develop a neurophysiological map of the target region. However, modern commercial MER systems enable simultaneous collection of multiple recording channels and sophisticated real-time analysis of the neural activity. Commonly used clinical systems are manufactured by Alpha Omega (MicroGuide) and FHC (Guideline). Similar to the brain-machine interface research field, intraoperative DBS neurophysiologists can be faced with an overload of recording data to process. Therefore, a number of innovative signal processing concepts are currently under development using artificial intelligence to help identify the target depth for electrode placement [Wong et al., 2009; Shamir et al., 2012]. In addition, brain atlas representations of the target region of often used to help visualize the surrounding anatomical nuclei and automated fitting algorithms have been developed to fit atlases to the MER data [Lujan et al., 2009]. MER information can also be used to develop probabilistic databases that can assist in DBS surgical targeting and visualization [Finnis et al., 2003; D'Haese et al., 2012].

DBS Programming

Once the DBS system is implanted, therapeutic stimulation parameter settings for the patient need to be defined (Fig. 1E). The fundamental purpose of DBS is to modulate pathological neural activity with applied electric fields. However, the clinical personnel that typically perform the DBS programming do not necessarily have a scientific understanding of the underlying neural response to adjustments in the various stimulation parameters. Instead, they base their decisions on the observable behavioral responses to the stimuli. Fortunately, guidelines do exist for general stimulation parameter selection strategies that are typically effective [Volkman et al., 2006], but it is infeasible to clinically evaluate each of the thousands of individual stimulation parameter combinations that may be useful to a given patient. As a result, the therapeutic benefit currently achievable with DBS is strongly dependent on the surgical placement accuracy of the DBS electrode and the intuitive skill of the clinician performing the stimulation parameter selection [Moro et al., 2006].

The traditional method for selecting therapeutic settings in a patient starts with what is called a “monopolar review”. Each electrode contact is individually stimulated as a cathode (with the IPG case as a return electrode), starting at low amplitudes, gradually increasing the stimulus strength until a therapeutic effect is noted or a side effect is generated. This process is repeated for each individual contact, and the contact with the largest “therapeutic window” or stimulus amplitude range between beneficial effect and side effect, is typically selected for further refinement and customization of the stimulation parameters. The monopolar review is typically performed during a half day patient visit, and subsequent follow-up visits are often required to fine tune the settings and balance medications with stimulation. Overall the DBS programming process is estimated to require a total of ~20 hours per patient [Hunka et al., 2005].

Our group identified the DBS programming process as a logical opportunity for neural engineering intervention into a clinically relevant problem. The approach we pursued was

the creation of patient-specific DBS computer models to assist in the clinical programming process (Fig. 1). These models integrate the surgical targeting imaging data with quantitative estimates of the volume of tissue activated as a function of the stimulation parameter settings [Butson et al., 2007]. The results are then imbedded into a 3D graphical user interface that can run on a tablet computer; thereby providing interactive visualization of DBS in each patient [McIntyre et al., 2007]. Head-to-head comparison of DBS outcomes generated by model-defined vs. clinically-defined stimulation parameter settings has shown that model settings perform as well as, and in some measures better than, clinical settings [Frankemolle et al., 2010]. This concept was commercialized under the name GUIDE DBS, which is now owned by Boston Scientific.

New Developments in DBS Devices

The core components of the clinical DBS IPG and electrode have remained basically unchanged for decades. However, improved scientific understanding on the effects of DBS is enabling more explicit definitions for design goals in future devices. This is opening a new window of opportunity for technical development in DBS, which is made possible by new advances in IPG circuit designs and electrode manufacturing processes. These ongoing engineering efforts are focused in four general areas: 1) electrode design, 2) current-steering, 3) novel stimulus protocols, and 4) closed-loop DBS.

The basic design of the current clinical DBS electrode (stereotypical cylindrical contacts in a linear array) was defined at a time when very little scientific guidance on the underlying neural response to stimulation was available. However, improved understanding of the anatomical and electrical constraints of the specific brain target regions used to treat different disorders is now enabling the invention alternative electrode designs [Butson and McIntyre, 2006; Vasques et al., 2010; Martens et al., 2011; Keane et al., 2012; Pollo et al., 2014]. These alternative electrode design concepts focus on two general strategies: 1) customizing the size and shape of a small number of large electrode contacts to better stimulate a specified brain target, or 2) employ a large number of small electrode contacts which can be independently activated to match the specific brain target. While option 2 may represent the optimal engineering solution, option 1 may be more applicable to clinical use. For example, using arrays of small contacts provides greater overall flexibility for stimulation customization, but it comes at the cost of increased device complexity, lower charge injection limits for safe stimulation, and a greatly expanded parameter search space for clinical DBS programming. These pros and cons are currently being explored by all of the major DBS device manufactures, as well as start-up companies like Sapiens Steering Brain Stimulation and Aleva Neurotherapeutics.

In addition to sculpting the electrode design to the target, the concept of current steering between different electrode contacts also has great potential to expand our ability to control the size and shape of the stimulation volume. Computational models have provided motivation for the integration of current steering technology into clinical DBS systems [Butson and McIntyre, 2008; Martens et al., 2011; Chaturvedi et al., 2012]. Theoretically, coupled integration of advanced electrode designs (i.e. brain target specific) with multiple independent current sources could provide unparalleled flexibility to customize the

stimulation to the patient and possibly overcome small errors in surgical placement. However, once again these technological advances must provide simplistic paths for clinical implementation and optimization, or they run the risk of making the DBS programming process even more daunting than it already is for the clinical users.

A great deal of engineering effort has been focused on characterizing the spatial extent of stimulation, which is primarily dictated by the electrode design, active contacts, and parameters of the stimulus pulse (i.e. amplitude and duration). However, the temporal pattern of the applied stimulus pulses can also have a profound effect on the neural response and network integration of the artificially induced signals generated by DBS. For example when treating tremor, it appears that DBS pulses should be applied without variability in the inter-stimulus interval to maximize therapeutic benefit (e.g. temporally regular DBS) [Birdno et al., 2012]. However, bradykinesia might be better controlled with temporally non-regular patterns of stimulation [Brocker et al., 2013]. Other attempts to define alternative stimulation protocols have pursued the concept of desynchronizing coupled oscillators using coordinated reset (CR) stimulation, where temporal bursts of stimulation are applied through multiple electrode contacts [Tass, 2003]. Recent experimental testing of this concept has demonstrated that both acute therapeutic effects, as expected from traditional DBS, as well as sustained long lasting improvements in motor function are possible after the CR stimulation had ceased [Tass et al., 2012].

Increasing the energy efficiency of the individual stimulus pulses generated by the IPG also represents an active area of engineering research in DBS. Both theoretical and experimental evidence now support the concept that non-rectangular “centered” (e.g. triangular or Gaussian) pulses represent the most energy efficient stimulus waveform shape for activating neural tissue [Wongsarnpigoon and Grill, 2010; Foutz et al., 2010]. However, to realize the energy saving potential of these alternative stimulus pulses, the circuitry of the IPG will need to be customized to the pulse design. This will require implementation of current-controlled stimulators with a variable (or dynamic) compliance voltage that follows the shape of the non-rectangular pulse [Foutz et al., 2012].

Traditional DBS systems function without a physiologically recorded control signal and apply continuous stimulation regardless of a patient's pathological state. It may be possible to achieve increased battery life as well as optimized patient outcomes with closed-loop DBS systems that utilize a biomarker to monitor a patient's disease state and modulate the delivery of stimulus pulses (Fig. 2). Closed-loop DBS systems that rely on electrophysiology-based biomarkers have actually already been used in humans for over a decade in the treatment of epilepsy with the NeuroPace RNS system [Morrell et al., 2011]. Unfortunately, results from those studies have thus far failed to demonstrate substantial superiority over traditional “open-loop” systems [Fisher et al., 2010]. One hypothesis for this shortcoming of currently available closed-loop systems is that we do not yet have an adequate understanding of the brain network activity patterns we are attempting to modulate. This reinforces the need for advanced disease-specific (and patient-specific) brain network models to better decipher the neural activity patterns generated within.

The most extensively investigated DBS biomarker, especially in the context of PD, is beta-band (13-30 Hz) power in the local field potential (LFP) recorded from the subthalamic region (Fig. 2). Increased power in beta activity has been correlated with PD motor symptoms and this hypersynchrony can be reduced with DBS [Kuhn et al., 2008; Bronte-Stewart et al., 2009]. However, understanding of the pathological mechanisms responsible for the exaggerated oscillations remains limited. Computational models of subthalamic LFPs suggest the spatial reach of the recorded signals can span several millimeters, but these signals are highly dependent upon correlated synaptic input to the subthalamic nucleus [Lempka and McIntyre, 2013]. Historically, coupled oscillation between globus pallidus and the subthalamic nucleus was thought to drive the beta hypersynchrony in PD [Terman et al., 2002]; however, recent hypotheses are more focused on the interaction between motor cortex and the subthalamic nucleus [Whitmer et al., 2012].

Proof of concept studies have generated encouraging results supporting the potential for closed-loop DBS systems explicitly designed to control PD symptoms. Pre-clinical studies in non-human primates have demonstrated the utility of coupling globus pallidus DBS with a biomarker control signal based on cortical beta power [Rosin et al., 2011]. Pilot clinical studies have generated successful results using beta power in the subthalamic LFP as a DBS control signal [Little et al., 2013]. In addition, efforts are underway to define alternative biomarkers based on the concept of cross-frequency coupling. Intraoperative recordings have shown that amplitude modulation of gamma activity by the phase of the beta oscillations in the primary motor cortex is exaggerated in PD patients, and this excessive coupling is reduced by DBS [de Hemptinne et al., 2013]. Therefore, either the subthalamic nucleus and/or motor cortex appear to be clinically viable candidates for providing closed-loop control signals in PD. In turn, key engineering developments for the future will be the development of advanced recording technologies that are customized to the anatomical and electrophysiological needs of the specific disease and optimal biomarker signal for specific symptoms.

The near term future will see an explosion of pilot clinical studies on closed-loop DBS biomarker identification analyses for a wide range of disorders. This avalanche of chronically recorded human electrophysiological data is being enabled by the numerous Medtronic Activa PC+S systems implanted around the world [Afshar et al., 2013]. These results, as well as the ever growing database of human brain recordings amassed by NeuroPace and their collaborators, represent treasure troves of data holding untold riches. However, as the world of brain machine interfacing (BMI) knows all too well, collecting the data is only the first step in a very long process of analysis and interpretation. We propose that the DBS community will need to build bridges to the worlds “Big Data” computer science and BMI to leverage their best practices and lessons learned to actually realize the true potential of DBS technology.

Conclusions

DBS is a powerful clinical technology that allows for customization of the therapy to the individual patient needs over time via alteration of the stimulation parameters. Furthermore, DBS does not destroy tissue, allowing patients to potentially benefit from emerging

restorative therapies. However, defining the optimal surgical placement for the DBS electrode and programming DBS devices for maximal therapeutic benefit can be a difficult and time consuming process. In addition, current clinical DBS electrode designs and stimulation pulsing paradigms were derived empirically and are probably not optimal. New DBS technical developments have been vetted in computational models, as well as pre-clinical animal experiments, and are beginning to enter wide scale clinical testing. In turn, advances in scientific knowledge and technology are laying the groundwork for the re-engineering of DBS technology to better serve clinicians and patients.

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HIGHLIGHTS

Enhanced collaborations between neural engineers, neuroscientists, physicists, neurologists, and neurosurgeons are beginning to address some of the limitations of current DBS technology.

Describe technological developments in surgical targeting, stimulation parameter selection, stimulation protocols, and stimulation hardware.

Figure 1.

Deep brain stimulation. A) Stereotactic coordinate system is defined relative to the patient imaging data using the fiducial markers displayed in green. B) Atlas representations of anatomical nuclei are used to help identify the target (yellow volume - thalamus; green volume -subthalamic nucleus (STN)). The blue line represents the intended surgical trajectory. C) Stereotactic location of microelectrode recording data (thalamic cells - yellow dots; STN cells -green dots; substantia nigra cells - red dots). D) DBS electrode placement. Purple cylinders represent the electrode contacts. E) Red volume simulates the volume of tissue activated during therapeutic DBS.

Figure 2.

Closed-loop DBS. Electrophysiological biomarker signals are derived from the synchronous activity of large populations of neurons (and their synaptic inputs) surrounding the implanted recording electrodes. These signals summate into a local field potential (LFP) which can be analyzed as time series data. Typical closed-loop control systems convert the data into the frequency domain, monitor power in a specific frequency band (pink box), and trigger stimulation when that power exceeds a threshold (red dashed line).