Engineering approaches for deep brain stimulation in Parkinson’s disease

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Parkinson’s disease (PD) is a progressive, neurodegenerative disease affecting approximately 12,000 people across Ireland. Most disease diagnoses occur in people aged 60 or older, with the number of cases expected to triple by 2046 as the Irish population ages. The hallmark characteristic of PD is the rapid loss of dopamine-producing neurones within the substantia nigra pars compacta (SNpc), located in the midbrain. Control of voluntary movement becomes compromised after a 60 per cent reduction in SNpc dopaminergic neurones, resulting in motor symptoms such as bradykinesia, resting tremor, and muscle stiffness. At this stage, an 80 per cent decline in putaminal dopamine can be observed. Patients may also suffer from non-motor symptoms including fatigue, anxiety, depression, hypertension, incontinence, and speech and balance problems.

Individuals with PD are most commonly treated with levodopa, a pharmaceutical drug that promotes dopamine production in neurones. However, levodopa efficacy decreases over time, resulting in exacerbated motor fluctuations in advanced disease stages, as well as the development of involuntary movements known as dyskinesias. Dopamine depletion within the SNpc is correlated with increased synchrony between groups of neurones in three areas: the subthalamic nucleus (STN), globus pallidus internus (GPI), and cerebral cortex causing pathological subcortical oscillations in the activity of groups of neurones in the alpha and beta band frequency regions (4-6Hz and 13-30Hz, respectively).

Deep brain stimulation

Deep brain stimulation (DBS) is a functional form of neurosurgery aimed at controlling dysfunctional neural circuits in the brain that promote pathological firing. DBS consists of high frequency electrical stimulation within affected brain regions applied via small, 1.5mm chronically implanted electrodes. The electrodes are connected to a battery powered, pacemaker-like device under the clavicle called a neurostimulator. The clinician can control stimulator parameters such as electrical pulse strength, frequency, and duration externally. Device re-tuning is done on a trial and error basis until an optimal parameter setting is found for the individual patient.

Over the past two decades, DBS has become established as an effective treatment for medically refractory movement disorders including PD, essential tremor and dystonia and is also used to treat chronic pain, obesity, depression, and obsessive-compulsive disorder.

History

The evolution of functional stereotactic neurosurgery techniques led to the first usage of deep brain neurophysiological electrical stimulation in 1952 by Jose M Delgado. Delgado largely performed experiments on animals, but implanted electrodes in 25 subjects having either epilepsy or schizophrenia. Natalia Petrovna Bekthereva carried out the first known usage of DBS to treat motor disorders in 1963, where she showed that high-frequency stimulation was successful in the treatment of hyperkinetic disorders. Other DBS pioneers include Carl Wilhelm Sem-Jacobsen and Irving S Cooper, who showed successful results from chronic cerebellar stimulation in over 200 patients for central palsy, spasticity, and epilepsy.

With the introduction of levodopa in the 1960s, the use of neurosurgical therapy methods for PD declined. However, in the early 1990s two research groups, led by Alim Louis Benabid and Serge Blond, reported positive results using thalamic DBS to treat tremor. Soon after, Lauri V Laitinen published successful results after applying DBS within the GPI. As the success of clinical studies continued, DBS reemerged as a complementary therapy for PD.

Efficacy in Parkinson’s disease

Substantial improvements in motor control in PD are observed following continuous DBS therapy applied to the basal ganglia region of the brain. Stimulation at frequencies greater than 100Hz have led to sustained reduction in muscle rigidity, resting tremor, and dyskinesias when combined with the best medical therapies (BMT). Target areas within the basal ganglia include the STN,
GPi, and the pedunculopontine nucleus, although the latter area is less explored. Greater improvements in clinical scores have been shown when patients are treated with both DBS and BMT, compared to BMT alone. Increased patient quality-of-life and reduced drug dependency are also observed when DBS is used to complement pharmacological treatments.

Potential candidates for DBS are carefully selected, with nearly a third of DBS failures attributed to unsuitable recommendations for surgery. Current recommendations for DBS for PD indicate that candidates should show movement disability despite being extremely responsive to levodopa, as indicated by a 30 per cent increase in their clinical scores post-drug treatment. Other DBS criteria includes little to no cognitive impairment or psychiatric disease, and more preferential candidates are younger, with more advanced PD.

**Therapy in Ireland**

The first DBS clinic in Ireland was created in 2009 by the Dublin Neurological Institute of the Mater University Hospital. While three surgeries have been performed, only pre- and post-DBS care is currently offered to patients. Eligible DBS candidates living in Ireland can travel to the United Kingdom to receive the surgery through the Treatment Abroad Scheme operated by the HSE. Upon their return, there are five accessible PD nurse specialists.

While patients can now travel to Belfast for surgery, current evidence suggests that a DBS centre in the Republic of Ireland would improve patient experience and offer long-term savings. It is predicted that the centre would allow for a 30 per cent increase in residential patients able to receive surgery. Furthermore, a 2016 survey of over 1,000 patients performed by Tallaght Hospital showed that at least 200 patients would benefit from DBS surgery performed nationally.

The results of a cost-effective analysis study for the United Kingdom showed that DBS is more cost-effective than BMT, particularly if introduced at an earlier stage of PD than is currently normal.

**Role of engineering methods**

Despite its clear clinical success and benefit to patients, the exact way in which DBS works is not yet fully understood. Many questions remain regarding how it exerts its therapeutic effects. Programming of stimulators consequently remains a largely empirical process, which is both costly and time consuming. DBS is currently indicated for less than two per cent of patients with PD and is associated with significant side-effects including movement disturbances, paresthesias, depression and speech dysfunction. Half of all patients continue to require medication, and a progressive loss of benefit post-implantation has been reported. The relatively short neurostimulator battery-life can limit programming and usage, and lead to unpredictable expiration and regular battery replacement surgeries, though rechargeable stimulators are now available. A better understanding of how DBS works is needed to improve the control of symptoms and side-effects, and reach a wider patient population.

In recent years, there has been increasing interest among the clinical and scientific communities on the potential that ‘closed-loop’ DBS could offer. Rather than continuously stimulating neurones with a fixed set of parameters in ‘open-loop’ configuration as is the current practice, closed-loop DBS would automatically adjust the stimulation parameters as needed to deliver the correct amount of electrical stimulation to control the patients symptoms at that instant in time. This type of approach offers the potential to alter the stimulation parameters, such as the stimulation strength, to optimise clinical benefit, minimise side-effects, and reduce power consumption. Most recently, simple ‘on-off’ control schemes for DBS have been demonstrated in primates and in patients with PD. Though stimulating for just a number of minutes, these studies demonstrate a proof-of-concept for closed loop DBS, report superior performance when compared to continuous stimulation, and potential savings in battery consumption.

The development of effective control schemes for DBS requires an understanding of the system to be controlled and of the manner in which high frequency stimulation alters its behaviour. An appropriate environment for testing is also required. Trialling of such systems in humans or animal subjects is difficult due to the invasive nature of DBS. An alternative approach is to use computational, or computer, models to design and test suitable closed-loop strategies. The development of models with sufficient physiological accuracy offers the possibility to gain a deeper understanding of the effect of changes in neural activity on motor symptoms and the mechanisms by which DBS works. If sufficiently accurate, these types of models can be used to design and develop new stimulation paradigms which can overcome the limitations of current systems and adaptively respond to changes in the neural system over a range of time scales, before being implemented in patients.

**Current work and future needs**

The Neuromuscular Systems Group at University College Dublin is building a multiscale, computational model of the communication between the basal ganglia region of the brain and the motor units that control muscle to study the mechanisms of action of DBS in PD. In parallel, work is being done to determine potential non-invasive biomarkers of PD using electrical signals recorded from the brain and from muscle.

While substantial progress has been made in the development of models and understanding the processes involved, challenges remain. These include integration of models of different levels of complexity across different scales in space and time, model validation given that much remains to be understood about how the neuromuscular system works and a dependence on data obtained from experiments in patients and different animal models. Computational models to date have focused on the direct effects of DBS within the cortico-basal ganglia regions of the brain, and there remains a disconnect between stimulation parameters, brain dynamics and neuromuscular function. In addition to the instantaneous effects of DBS, incorporation of long-term changes including neuroplasticity will likely be necessary to fully capture the various effects of DBS. As more information becomes available through electrophysiological, imaging and brain connectivity methods, models will evolve enabling hypotheses to be tested in silico and generating new hypotheses, which can be tested in vivo.

**References on request**