Towards Adaptive Deep Brain Stimulation in Parkinson's Disease: A Review

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1.1 Practice Points

- To overcome some of the limitations of deep brain stimulation (DBS) therapy like stimulation induced side effects and limitation of pacemaker battery life, closed loop systems would allow real-time adjustment of therapy according to quantifiable brain response.
- Aside from adaptation through closed-loop DBS, spatial targets can be adapted and this has been found to improve therapeutic benefits.
- Implementation of closed-loop DBS has mainly focussed on computational models, with very little breakthrough made in the transition to clinical trials.
- Neural activity measurements consisting of metabolic and electrical activity are the preferred choice for use as feedback signals.
- The major impediment in the development of fully implantable closed-loop DBS systems has been poor understanding of the underlying workings of DBS.
- The ability to deploy powerful feedback algorithms is limited by the allowable power consumption of fully implantable processors.

1.2 Abstract

Clinical deep brain stimulation (DBS) is now regarded as the therapeutic intervention of choice at the advanced stages of Parkinson's disease (PD). However, some major challenges of DBS are stimulation induced side effects and limited pacemaker battery life. Side effects and shortening of pacemaker battery life are mainly as a result of continuous stimulation and poor stimulation focus. These drawbacks can be mitigated using adaptive DBS (aDBS) schemes. Side effects resulting from continuous stimulation can be reduced through adaptive control using closed-loop feedback, while those due to poor stimulation focus can be

mitigated through spatial adaptation. Other advantages of aDBS include automatic, rather than manual, initial adjustment and programming, and long-term adjustments to maintain stimulation parameters with changes in patient's condition. Both result in improved efficacy.

This review focusses on the major areas that are essential in driving technological advances for the various aDBS schemes. Their challenges, prospects and progress so far are analysed. In addition, important advances and milestones in state of the art aDBS schemes are highlighted – both for closed loop adaption and spatial adaption. With perspectives and future potentials of DBS provided at the end.

Keywords: adaptive stimulation, biosignal processing, closed-loop, directional steering, deep brain stimulation, neural control and Parkinson's disease.

1.3 Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases leading to impairment of both motor and non-motor functions [1]. In the UK, based on the figures from the National Health Service (NHS), it is estimated that there are 127,000 people suffering from PD [2]; these numbers are on the rise. At the advanced stage of PD, clinical deep brain stimulation (DBS) is used to manage the neurological condition and is not a cure, however it provides a therapy to improve the patient's quality of life. DBS has been successfully applied to control other neurological disorders such as essential tremor and dystonia. The development of DBS started over 100 hundred years ago. One of the key milestones was the approval of DBS as a therapy for tremor in 1997 by the Food and Drug Administration (FDA). Approval for PD related symptoms were granted in 2002. Even though underlying mechanisms of DBS are still under debate [3-5], PD is currently the neurological condition most widely treated by DBS [3]. DBS for PD patients is very expensive in terms of life-long maintenance. Its high cost is a result of the progressive nature of PD.

Continuous repetitive stimulation (mostly at 130 Hz) causes some long-term side effects which could result in impaired cognitive abilities and motor functions [6]. The underlying pathophysiology of cognitive decline in PD is reported to be complex and varies across individuals [7]. Kurtis et al. recently obtained level 1 evidence for the effect of DBS on mood and cognition. The reported cognitive decline due to DBS is suggested to have minimal adverse effects on patients. Nevertheless, effective stimulation approaches that are effective towards addressing the accruable side effects may be required. In addition, DBS affects coordinated neuronal communication necessary for cognitive functions [8].

Presently, post-surgery programming of stimulation parameters by trained clinicians can take up to a year or more[9] as stimulation parameters are adjusted heuristically using visual symptoms as the only feedback, after which follow up visits by patients are required to adjust stimulation to changes in patient condition. This makes stimulation parameter setting a very tedious process as every patient has a unique set of stimulation parameters which are required to be adjusted from time to time.

An additional problem with chronic DBS, is the issue of stimulation lead migration [10, 11] Lead migration, involves the unintended displacement of the DBS lead after surgery. Lead migration is reported to constitute 1.6 % of hardware related complications in DBS[10]. DBS leads were reported to migrate by greater than 3 mm in 10% of cases tested in [11]. This may degrade the effectiveness of the stimulation, requiring the need to constantly adjust stimulation to these changes [12]. Both of these can be automatically adjusted using adaptive deep brain stimulation (aDBS) schemes [13]. In addition, aDBS helps with initial programming and adjustment of stimulation parameters as well as long term adjustments of stimulation parameters.

This paper aims to analyse the challenges and advances in the main areas that are essential for aDBS schemes for PD. Several reviews have overlapping content to this paper [14-17]. The work in [14] reviews current techniques in aDBS. The techniques use feedback signals measured through electrical activity. The reviews in [15, 16] present ways in which adaptive stimulation may be delivered based on relevant biomarkers. The review in [17] presents a comprehensive literature on commercial and research-based attempts at closed-loop DBS. However, the pervious reviews do not focus on the control and signal processing techniques that are essential towards the development of effective and computationally efficient aDBS techniques. These aspects are addressed in this review. In addition to electrical activity, other secondary effects are blood flow changes, modulation of neurotransmitters, neurogenesis and many other metabolic activities [18]; these are addressed in the present review. This review also presents the benefits and limitations of directional steering (spatial adaptation) in DBS.

In this context, closed-loop DBS and spatial steering are two forms of DBS adaptation. Closed-loop adaptation is ideally designed to track changes in patient pathophysiology and correspondingly adjust stimulation. This is necessary because continuous stimulation is suggested to result in side effects and shortening of pacemaker battery life [19]. On the other hand, spatial adaptation adjusts to variation in lead position and/or stimulation focus, as poor stimulation focus has been reported to affect therapeutic benefits [12]. In terms of activation time delays, closed-loop DBS may be triggered by PD events in approximately one second. Adaptation due to spatial changes (displacement in lead position) may take months or years.

1.3.1 DBS Fundamentals

The main components of a DBS system are the intracranial electrode and implantable pulse generator (IPG), which are linked through a connecting wire as shown in Figure 1(a). The surgical procedure for DBS implantation involves two stages. The first stage is the DBS lead placement and the second is IPG placement. DBS lead placement begins by defining targets. Common targets include subthalamic nucleus (STN), globus pallidus pars internus (GPi) and the nucleus ventralis intermedius (VIM) of the thalamus, which are shown in Figure 1 (b). Currently, there is only evidence and approval to back the use of DBS in three conditions: PD, dystonia and tremor [20].

DBS leads are implanted through a burr hole ranging from the cortex to the basal ganglia as shown in Figure 1(b). After DBS lead implantation, the optimal stimulation target is identified and patients are assessed for clinical benefits as well as side effects. When the DBS lead is firmly in the target position, the IPG is implanted below the clavicle and connected to the leads through the connecting wires [21]. The three major manufacturers of implantable DBS systems are Medtronic, Boston Scientific and St. Jude. The operating principle for devices produced by all manufacturers is the same; however, there are slight differences in technical features. Table 1 summarises the operating range of the main DBS systems marketed by the major manufacturers. Some of the IPG models in Table 1 have nearly similar lead dimensions. The Vercise neurostimator in Figure 1(a) uses the Boston Scientific lead model 2201 with lead dimensions as follows: diameter (d) is 1.3 mm, interelectrode spacing (s) is 0.5 mm and electrode length (l) 1.5 mm. The Medtronic 3389 compatible with Activa neurostimulator has dimensions, d = 1.27 mm, s = 0.5 mm and l = 1.5 mm. While the St Jude 6149 model has dimensions, d = 1.41 mm, s = 0.5 mm and l = 1.5 mm. DBS lead models produced by the same manufacturer have the same lead diameter – Medtronic models are 1.27 mm; Boston Scientific models are 1.3 mm and St Jude's models are 1.41 mm. The interelectrode pacing and electrode lengths for each model are summarised in Table 1.

1.3.2 Theories and Limitations of DBS

Therapeutic stimulation is rendered ineffective by disease progression, environmental factors, mechanical factors, and behaviourally induced changes in network activity. As a result, additional sessions are required to manually adjust stimulation settings [26]. The procedure can be very costly and time consuming because only a fraction of the stimulation parameter space can be practically explored during each session. Moreover, as PD progresses the dominant symptoms may change which interferes with DBS device programming and there may be a need to modify stimulation settings. Programming is dependent on the target chosen, the orientation of the electrode relative to the target, the disorder being treated, and the symptoms being treated for in a given disorder. In DBS, stimulation

induced side effects are mainly caused by continuous stimulation and stimulation field spread beyond target areas [13]. Stimulation side effects include drooling, flushing dysarthria, and ocular deviation [12].

The choice of the stimulation pattern used has been reported to influence the efficacy of DBS in patients [18]. More knowledge on how stimulation patterns influence efficacy is still gained [27]. There are various theories on how DBS induces beneficial effects in patients. The major mechanisms posited for DBS are 'inhibition', 'excitation' and 'disruption'. The *inhibition* hypothesis is the oldest. After DBS was found to have the same beneficial effect on PD symptoms as lesion therapy [28, 29], STN-DBS and GPi-DBS were believed to inhibit local neuronal activity, by reducing the firing rate of surrounding neurons. This was corroborated by recordings obtained around the stimulation sites of STN-DBS in PD patients and non-human primate models [30, 31]. Based on the firing rate model for movement disorders which claims that parkinsonian impairments result in abnormally increased firing pattern in the STN and/or GPi, DBS mitigates the motor symptoms by reducing this increased firing. However, others point out that it has been possible to treat motor symptoms in situations where the GPi shows low activity [32]. On the contrary, other studies suggest that the most natural explanation for DBS is the *excitation* hypothesis where stimulation depolarises neuronal elements. They believe DBS activates the STN (or GPi) output, thus jamming abnormal pathological activity in basal ganglia circuits resulting from motor impairments [33]. In the *disruption hypothesis* [32], DBS exerts therapeutic influence by dissociating input and output signals, thereby disrupting the flow of abnormal information to the stimulation site. In this theory, therapeutic DBS is allegedly believed to disconnect the abnormal coupling in the basal ganglia as a result of PD. An emerging theory is the *nonexclusive hypothesis* [34]. Since the other theories present exclusive mechanisms for DBS, the nonexclusive theory suggests that DBS is a result of many (nonexclusive) mechanisms including modulation of oscillatory activity, neurogenesis, synaptic plasticity, neurochemical effects and neuroprotection. The mechanisms vary in importance and manifestation, depending on the condition being treated and the brain structure (target) being stimulated.

1.4 Towards Adaptive DBS

This section will focus more on the major areas that are necessary in driving development in aDBS, especially for closed-loop adaptation. Figure 2 shows the typical processing chain for closed-loop DBS adaptation. In Figure 2, the sensed brain signals are sent to a neural activity processor which detects PD events. PD events are decoded by the controller to generate control signals. Depending on how advanced the controller is, control signals can make use of the occurrence

of past PD events as well as current PD events to effect control. The control signal is used to trigger the stimulator (the Medtronic Activa SC is only used as an example). The actuation (stimulation) signals are used to mitigate PD symptoms.

1.4.1 Neural Activity Sensing and Processing

In monitoring changes in sensory, motor and cognitive tasks, neural signals as well as external body signals are potentially useful[35]. A major challenge of closed-loop DBS is the choice of a suitable feedback signal. Below are some of the requirements necessary for feedback signals in PD [40]:

- The signals should be markers that reliably reflect all symptoms of the disease, impairment or disability (such as tremor, bradykinesia and rigidity across patients).
- Relationship between signals and impairment should not just be correlative, but should also be causative.
- Signals should have high response rates such that therapy does not lag impairment.
- Invasiveness of the recording technique should be reduced to the barest minimum.

Based on the above requirements, neural signals are the most advantageous for use as feedback signals. They can be sensed using an implanted custom-integrated chip that allows for measurements, processing and analysis [36]. The same leads can be used both for stimulation as well as measurements. For neural signals, the further the signals are from DBS stimulation sites, the less reliable they are [37], as such signals obtained from deep regions of the brain are more desirable. To obtain neural activity, electrical or metabolic brain activity can be measured.

Electrical activity involves are measured from bioelectrical properties of brain cells and tissues. They involve single neuron activity (spike activity); local field potentials (LFP) recordings; electrocorticorgram (ECoG) recordings and electroencephalogram (EEG) recordings. On the other hand, hemodynamic or neuro-transmitter response could be used in obtaining vital brain information [18]. These are tagged metabolic activity measurements. In the hemodynamic response, blood releases glucose to active neurons at a higher rate than in the area of inactive neurons [38]. The glucose and oxygen released into the blood stream results in an increase in oxyhemoglobin in the veins around the active region. Hemodynamic changes in PD patients can serve as good biomarkers since DBS and PD induce cortical hemodynamic changes in patients [39]. These changes can be detected by methods such as functional magnetic resonance imaging (fMRI),

diffusion magnetic resonance imaging (dMRI) and near-infrared spectroscopy (NIRS). As in hemodynamic responses, the use of techniques that measure neurotransmitter response is pertinent because PD results in degeneration of cells that use dopamine as neurotransmitters [6]. Monitoring dopamine traces from cerebral metabolites have been reported [40], but miniaturisation of implantable systems for chemical analysis is a major barrier.

NIRS measures concentration of oxyhemoglobin based on light attenuation (absorption and scattering) [41]. NIRS was first used in DBS patients by Sakatani and colleagues [42]. The finding suggested that therapeutic benefits were reflected by changes in oxyhemoglobin levels in the prefrontal cortex. Despite its bulkiness, NIRS has been proposed as a suitable measure of neuronal activity due to its ability to accurately quantify neuronal activity which is reflective of symptom severity and has been proposed as a candidate signal to adjust the parameters of DBS in a closed loop configuration [43].

MRI is an emerging technology for observing neural activity in the living brain. It has tremendous potential for use in applications such as blood-oxygen-level-dependent (BOLD) fMRI, which is a non-invasive method for monitoring brain functions [44]. Like NIRS, fMRI is a measurement based on hemodynamic changes, and it offers a spatial resolution in the millimetres range. It has been shown to offer tremendous insights into the underlying dynamics of the human brain [45]. Also, understanding the underlying mechanisms can give more insight as to why different patients' brains respond differently to similar levels of stimulation.

Fast scan cyclic voltammetry (FSCV) is a voltammetry technique that applies a linearly varying potential through a carbon fibre microelectrode (CFM) resulting in redox chemical reactions around the electroactive molecules [46]. The concentration of analytes is measured by the magnitude of evoked current peaks to the redox reaction at the electrode surface. The relationship between the applied voltage and the resulting current provides a chemical signature for the presence of certain neurotransmitters or analytes. FSCV detection is mainly limited to electroactive analytes for example electroactive molecules such as dopamine (a biomarker for PD), adenosine (a biomarker for sleep), and oxygen (which signifies the presence of anoxic brain injuries). The major limitations of FSCV are its bulkiness and that the lifetime of a CFM is a few months, which restricts the application of FSCV detection to intraoperative approaches. For DBS, using anesthetised rat models [48, 49], FSCV was used to regulate stimulation as a proof-of-principle test for closed-loop DBS using neurochemical signals for feedback. Table 2 summarises some of the characteristics of various feedback signals that are suitable for closed-loop DBS.

Neural Activity Sensing: Electrical versus Metabolic Activity

For effective neural recording, cutting edge techniques that access deep and distant regions of the brain are required [50]. These could lead to more insight in brain dynamics. Of equal importance are techniques that have spatial coverage. A major breakthrough in understanding neurophysiological dynamics is dependent on advances in neural signal acquisition [44]. This is the first requirement towards achieving an efficient closed-loop DBS system.

Changes in the bio-chemical environment within the brain can be representative of intended actions and actual actions in patients. These characteristics make metabolic activity sensing suitable for quantifying neural activity. Notable example of techniques that measure bio-chemical activity are, near infrared spectroscopy (NIRS), functional magnetic resonance imaging (fMRI), intracranial dialysis, FSCV and fluorescence measurements. The use of metabolic activity as biomarkers have been investigated in [51]. Their major shortcomings are safety concerns such as MRI compliance and metal artefacts. Other metabolic activity sensors such as NIRS are not affected by metal artefacts, but have relatively poor temporal resolution compared to electrophysiological activity. Their large size is a disadvantage in fully implantable closed-loop DBS systems. Generally, apart from sensitivity to metal artifacts in fMRI, metabolic activity offers many advantages compared to electrical activity recording, notably: absence of electrical noise, simultaneous imaging of a large number of neurons and selective recording from genetically-targeted regions of the brain [52]. Their high signal to noise ratio (SNR), specificity and selectivity can go a long way towards facilitating artefact free closed-loop DBS systems.

For electrical activity, information content is dependent on spatio-temporal resolution, with EEG and single unit activity on the extremes of the spectrum: EEG has the highest spatial scale and the least temporal resolution, while single unit activities have the highest temporal resolution and the least spatial coverage. LFPs offer a compromise in terms spatio-temporal resolution. Combined with their long-term stability at the electrode-tissue interface, this makes them very attractive feedback signals for closed-loop forms of DBS [40]. However, the pertinent question is how informative are they compared to other neuro-electrophysiological signals?

Closed-loop DBS applications can adopt effective paradigms that combine both metabolic and electrical activity sensors for acquiring brain responses in real-time which increases spatio-temporal resolution. This leads to better identification of disease and non-disease states in patients, as the level of information content is strictly dependent on spatio-temporal capabilities of the sensor. This complementary approach takes advantage of the best of both worlds: the fast response rate of electrical activity, and the slower more specific, selective and qualitative sensing offered by metabolic activity. The complementarity of sensing

electrical and metabolic activity has found application in brain machine interfaces (BMI) [44, 53]. In PD, there are no physical symptoms with time course beyond those of tremors. Tremor frequencies in PD are typically in the range of 3 – 8 Hz [54] and biomarkers with temporal resolution less than one second may be required; as such, metabolic and electrical activity are both suitable for detecting PD events.

Challenges of Neural Activity Processing

The development of fully implanted PD detection processors is difficult due to the computationally intensive nature of neural signal processing. This forms a major bottleneck in developing closed-loop implantable DBS systems for clinical intervention. The need for fully implantable PD detection processors is pushing research into the investigation of resource efficient algorithms and techniques. For implantable processors targeting conditions with highly unpredictable physiological signals like PD, high-order algorithms are required. However, for fully implantable systems, the power density for neural tissue damage which is 800 $\mu W/mm^2$ [53], limits the ability to use hardware implementations of complex models that require larger power signatures. Some of the common challenges when dealing with physiological analysis in closed-loop DBS applications are highlighted below.

- *Feedback Algorithms*. Correlations of physiological signals to clinically relevant states are hard to model. High-order data-driven models may be required to distinguish disease states of interest from non-disease states. This makes current feedback algorithms inefficient in tracking patient states.
- *Sensing Devices*. Identifying precise correlations are difficult because the physiological manifestation of disease and non-disease states vary from patient to patient. This imposes a wide range of specifications on sensing devices, hence there is a requirement for personalised systems. Devices susceptible to noise have a tendency to obtain recordings that obfuscate disease states even in conditions with more distinguishable neuronal activity like epilepsy. This can be more challenging in disorders with less distinguishable disease states like PD.
- *Feedback Signals*. These vary with time which makes static feature extraction unreliable. This has led some studies to suggest the possibility of combining more than one neurophysiological signal [40]. Others have proposed the use of multiple features from the same neurophysiological signal [35, 56, 57]. There are also suggestions to complement internal body signals with external body signals which assists consistency in feedback signals.

The ability to assess physiological signals over a large number of channels, features or sensing modalities will be essential to model their correlations to disease states. It is for this reason that data-driven approaches like machine learning are emerging as powerful tools that could be used to handle this challenge [58, 59]. The complexity of brain signals on their own makes closed-loop DBS very difficult to achieve. In closed-loop DBS for PD, having a single feedback signal as the universal biomarker may not be a sustainable approach towards closing the loop.

Prospects of Neural Activity Processing

Due to the complex nature of physiological signals, current laboratory-based closed-loop DBS systems use multiple external computers to process sensed signals. However, clinically viable realisations of closed-loop DBS need to be more robust and autonomous such that all processing is implemented onsite and real-time – this will require high functionality on-chip processing. The shift towards on-chip processing has necessitated the need for simple but efficient processing techniques in order to reduce computational complexity so that processors can be realised in CMOS technology within the power consumption constraints. The bulk of the power consumed in bio-signal sensing and processing for closed-loop DBS is incurred at the processing stage which is currently shifting towards the use of machine learning models. Less computationally intensive machine learning frameworks can be adopted if more accurate biomarkers for PD are identified.

Current bio-signal processing approaches use supervised machine learning methods which require the use of labelled data for training. In the future, bio-signal analysis for closed-loop DBS has the potential of utilising unsupervised machine learning techniques, which will create more dynamic algorithms that can handle the complex nature of neuronal signals. Online unsupervised machine learning techniques have been pioneered in spike sorting and other BMI applications [60]. The shift towards unsupervised learning techniques will eliminate the need for time-stamped measurements, thus eliminating the intervention of trained operators (or clinicians). The prospects of bio-signal processing in closed-loop DBS depends on power consumption constraints and the available insights into DBS and brain mechanisms. Better control over these will facilitate the implementation of effective, autonomous and efficient processing techniques that can be used to adapt stimulation. To overcome the high efficiency and efficacy demands required to close the DBS loop, clever control strategies can satisfy the imposed resource constraints necessary for implantation.

1.4.2 Neural Systems Control Strategies

It has been widely established that closed-loop systems achieve better efficacy and efficiency than their open-loop counterparts. At present, many of the systems are proof-of-principle, and transition to clinically approved interventions are still hampered by such issues as: establishing the relationship between acquired signal and patient condition, invasiveness of recording devices and how chronic implantation can be sustained in invasive devices. To circumvent this, most studies have opted to use models with limited detail to describe the basal ganglia, central nervous system (CNS) and so on. This is understandable because of the inconsistent theories describing the mechanisms of PD and DBS [30 – 34, 61]. The first step in closing the loop is to identify, acquire and analyse biomarkers

so that they can be used as controller inputs. This is necessary because the efficacy of a controller is partly dependent on the quality of its control input. The following sections describe the most prominent control techniques that have been adopted in neural systems and Table 3 summarises their advantages and disadvantages.

Manual Feedback Approach

This uses a manually adjusted feedback approach. It is implemented by manual adjustments. The programmer uses visual feedback signals to manually adjust stimulation. After manually programming the DBS system, it is assumed that the system has enough knowledge to provide corresponding output with specific input signals. This assumption is faulty and misleading and may not hold in complex and unpredictable systems like PD. Nevertheless, a manual feedback approach is always the first step in feedback controller design. All of the currently marketed DBS devices for PD use manual feedback approach.

Simple Feedback Approach

Simple feedback approach uses control techniques that switch between two levels (on-off controller) or responds in a scalar or proportional approach. An on–off controller (or hysteresis controller), is a feedback controller that switches abruptly between two levels. The on-off controller approach adopts a closed-loop control technique that uses threshold crossing to directly generate the control signal to the controller without prior pre-processing. The scalar or proportional approach uses the difference between a set-point and current state, such that a larger difference results in a larger stimulation value.

Simple feedback systems are normally used in low complexity systems. In closed-loop DBS applications, they have mostly been used as the main control strategy in many experimental studies [13, 62, 63, 65 – 70]. This approach may be sub-optimal considering how PD consists of various underlying symptoms including bradykinesia, rigidity and tremor. The on-off approach uses a one-dimensional feedback signal. Many studies in closed-loop DBS have focussed only on the beta-band activity as input to the closed-loop controller. Using more discrete levels as well as multi-dimensional feedback signals presents a more advanced feedback approach than the simple feedback control.

Internal Model-Driven Approach

This is a feedback control approach that incorporates a model of the system, typically a black box model which is defined based on the monitored input-output relationship of the system. An example is the use of system identification techniques to establish input-output relationships for a system that may be difficult to model. At every instant, before providing control commands the model provides a prediction of the system behaviour and the controller inputs are determined

based on a cost function that determines optimum parameters. Examples of these include recursive autoregressive models and Kalman filter methods. For DBS, some computational models have implemented closed loop control using these methods [71, 72].

Classifier-Driven Approach

This uses a feedback control approach that relies on mapping between discrete states to determine input signal to controller [73]. When used with a controller, it is typically used like the on-off controller approach (but with prior pre-processing and multidimensional feedback signals) since it has binary classes representing healthy and unhealthy states. Unlike the on-off controller, it uses multi-dimensional feedback signals to cater for a number of symptoms [75]. It has found wide application in epileptic seizure detection [75, 78]. For epilepsy, an FDA approved closed-loop system, the 'Responsive Neurostimulator System' (RNS), marketed by NeuroPace Inc. uses this approach for modulating therapy for drug-resistant epilepsy [79].

Actor-Critic Approach

The actor-critic approach models the relationship between the physician and the automated neuromodulation system. The critic (like the 'trained clinician') assesses the state of the system based on a cost function and provides the information to the actor. The critic learns about the system by studying its input and resulting output responses. The actor, unlike the error signal of other control techniques provides control signal based on evaluation from the 'informed critic'. This method has been adopted for neural control in [35], and is gaining wide-spread acceptance for controlling non-linear systems because it adopts a technique that resembles real-life clinical interventions.

1.4.3 Neural Tissue Stimulation Techniques

Therapeutic stimulation has been in existence for several centuries. It has been used to mitigate sensory deficits such as blindness, deafness, chronic pain, urinary incontinence, paralysis, PD, ET among others [82]. In therapeutic brain stimulation, the resulting effects depend on the stimulation site, stimulation parameters and other uncontrolled biological effects [9]. To ensure that stimulation is safe, a biphasic stimulation protocol needs to be adopted so that zero charge is injected during stimulation to avoid irreversible phenomena, like tissue damage and electrode corrosion, that result from charge accumulation [83]. Biphasic stimulus paradigms have become the adopted standard. They provide stimulation using a sequence of two cycles of different polarity so that the charge injected during the first cycle is removed during the second cycle. Additionally, the maximum safe electrode charge density must not be exceeded. Conventional DBS electrodes made of platinum-iridium have an electrode charge density of 30 $\mu C/cm^2$/phase [85]. Nonetheless, basic knowledge regarding the responses

evoked by various stimulation modalities is needed in order to adopt a technique that optimises therapy, minimises side effects and maximises battery life. The common stimulation techniques are voltage controlled (VCS), current controlled (CCS) and charge controlled stimulation (ChgCS). Efficiency and safety are the key factors that result in the selection of one of these stimulation techniques.

VCS has been found to be a very efficient method due to its long battery life span. However, its safety has been questionable, due to the fact that constant voltage excitation is delivered to an electrode-tissue interface (ETI) with a variable impedance. This variation will lead to the accumulation of charge at the ETI. Generally, the charge at the stimulation site is desired to be within a safe limit known as the water window [8]. If the charge exceeds this limit, irreversible tissue damage or electrode corrosion may occur. CCS offers better control over injected charge than VCS. However, extra power consumption is incurred in the conditioning circuit used in producing constant current excitation, which impedes efficiency. As a trade-off between efficiency and safety, ChgCS has been introduced using switched capacitor based stimulators [84]. Table 4 summarises the various stimulation techniques and their characteristics.

Clinical DBS design is tending towards current controlled stimulation due to its safety. This has resulted in a surge in the design and development of current neuro-stimulators, although their therapeutic benefits over VCS are yet to be clinically proven [86]. The choice of the stimulation technique impacts on the lifespan of the battery. With the advent of rechargeable batteries, the emphasis on power consumption has reduced [19]. Nevertheless, some patients are unsuited to rechargeable IPG systems [87]. Even patients who can tolerate the use of rechargeable batteries, would want to recharge as infrequently as possible. The charging process is tedious and patients may be required to recharge the system every week. If the battery is allowed to completely run down three times, then replacements may be required, and further surgery [88]. The need for low power stimulation techniques is ever more important considering the demand for cranially mounted IPGs where patients undergo only a single procedure, compared with the current two stage procedure for electrode and IPG placement [48, 49]. Thus, therapeutic stimulation techniques are selected based on trade-offs between efficacy, safety and power consumption.

1.5 Closed-loop DBS

Current DBS systems are poorly suited to cope with the dynamic nature of PD. This has led to growing interest in the design of closed-loop systems for adapting DBS. In order to implement closed loop systems, existing open loop systems can be optimised by incorporating feedback schemes. However, the current dilemma has been the poor correlation between feedback signals and the motor score measured through the Unified Parkinson's Disease Rating Scale (UPDRS), even though some correlations between motor states and certain feedback signals have been identified.

Closed-loop DBS involves adjusting stimulation parameters to characteristic changes in biomarkers. Biomarkers for closed-loop DBS are mainly neurophysiological signals and external body signals. Neurophysiological signals consist of electrical and metabolic activity recordings. External signals are mainly from electromyography (EMG) and accelerometer signals. Recently, various studies of closed-loop DBS have focused on computational models. However, very little work has led to clinical studies. Below is a brief overview of different attempts at closed-loop DBS for PD patients.

1.5.1 Experimental Studies

Clinical studies of closed-loop DBS have been carried out using Parkinsonism induced animal models and patients (with informed consent). These studies have used neurophysiological and external signals as biomarkers; in particular LFP and spike activity, with some others using neurochemical signals have been used as feedback signals.

The work in [70] investigated closed-loop DBS employing spike activity and using 1-methyl-4-phenyl-1,2,3,6tetrahydropyridine (MPTP) induced primate model of PD. The results showed that stimulation triggered by spikes from primary motor cortex (M1) and GPi, led to a reduction in GPi firing rates, which were representative of improved condition. The stimulation was triggered based on a predefined delay of 80 ms. The study presented results that bettered those of continuous stimulation. This provided an interesting proof of principle; however it is not clear how the technique will fare across patients and over time. Also, Brittain et al. [62], proposed another approach of delayed-stimulation, however, alternating current transcranial stimulation was used instead. An extension of this technique using external body signals was presented by Cagnan et al. [63]. It uses a unique stimulation approach that selectively controls neural synchrony by delivering stimulation to the ventrolateral thalamus. This was timed according to the patient's tremor rhythm. The study claimed that DBS can be precisely timed to disrupt disease pathophysiology. It worked on the premise that stimulation selectively regulates neural synchrony through phase-specific stimulation [69]. It attained promising results in six of the nine subjects used. DBS delivered with personalized frequencies has been reported to effectively reduce UPDRS motor scores [90].

A different study [13], uses the beta band local field potentials (LFP) to trigger stimulation on threshold crossing in eight patients. A 56% reduction in stimulation time and a reduction in the energy requirement of the closed-loop DBS compared to its open-loop counterpart were reported. In a follow-up study to overcome the shortcoming of the previous study (short sessions of 10 minutes and unilateral stimulation); Little et al. [66], used 4 PD patients with bilaterally implanted DBS for sessions lasting 2 hours. There was a marked improvement in motor score compared to the open loop approach as in [13]. The major limitations of

both studies were that the thresholds were set heuristically, this meant provisions were not made to adapt them to changes in patient conditions, which is necessary since feedback signals are reported to be inconsistent across time and patient [40]. This static threshold adopted does not adapt to drift in neuronal characteristics. In another study, LFP's were also used as biomarkers for detecting seizure like activity [35]. Seizures were induced by high amplitude current stimulation in ovine models, and seizure like activity was detected using LFP power from pre-defined frequency bands. These power measurements were classified with a Fisher discriminant and an actor-critic control policy was used to regulate stimulation. This approach does not make adequate provision for the dynamic nature of the LFP signals. Similarly [64], illustrated the promising utility of closed-loop DBS for PD based on STN beta LFP levels. Stimulation was delivered only when STN LFP beta activity was elevated. The study used a female rhesus macaque monkey induced by MPTP. However, it concluded that closed-loop DBS systems may need alternate and complementary biomarkers and/or algorithms to reach their full therapeutic potential [64]. LFP's were used in [77] for tremor detection in PD patients using a multi-layer neural network for classification. This method presents a good concept that could be used for demand driven stimulation. However, its use of a static detection scheme coupled with additional complexity introduced by multi-layer neural networks, since the neural-networks are trained offline, could make it difficult for full implantation. The drift in characteristics of neuronal signals over time and across patients, necessitates the use of a tracking paradigm that will adapt to this changes in biomarkers. Using microelectrode recordings (MER), Kostoglou and colleagues [76], proposed a random forest approach for identifying UPDRS improvement in PD patients undergoing DBS – off dopaminergic medications. The results suggested that electrophysiological signals had a strong correlation to improvements in the UPDRS score, and they could be used to predict the UPDRS score. Major breakthrough in DBS adaptation can be achieved if a relationship between motor improvement and electrophysiological signals were to be achieved.

Alternatively, using external body signals, the work in [74] used a combination of surface EMG (sEMG) and accelerometer signals to predict tremors in PD patients. Even though the study predicts tremor with substantial accuracy, patient distress in PD precedes symptoms manifestation; which makes the technique unsuitable for adaptive DBS therapy. Generally, feedback using external body signals has an accompanying delay in detecting PD coupled with the discomfort associated with externally attached sensors. This makes them not very viable for use as biomarkers.

Attempts using neurochemical biomarkers have been made. Grahn et al. [49], describes a rat model that uses FSCV to determine evoked dopamine in the striatum, after which stimulation is regulated accordingly. Another study that uses neurochemical responses from rat models is the Mayo Investigational Neuromodulation Control System (MINCS) [48], it is designed to interface with FSCV. The system recorded striatal dopamine release in anesthetised rats and stimulation was wirelessly regulated in response to evoked neurochemical signals. Studies using neurochemical changes offer improved selectivity, sensitivity

and specificity; however, they are not suitable for real time applications due to the poor temporal resolution associated with neurochemical sensing. Although they tend to have a better consistency across patients compared to other biomarkers. Also, the need to miniaturise implantable devices makes its use unsuitable, as neurochemical sensors tend to be bulky. Table 5 summarises the various studies based on the experimental subjects used, the closed-loop stimulation paradigm and experimental outcome.

1.5.2 In-silico Studies

Even though the underlying principle of DBS and PD are still under debate, various computational studies have been based on neuronal models. Notable among these are the phase dynamics model, firing rate models and the stochastic models. Table 6 summarises the various studies that have implemented computational models for DBS and the merit and demerits of each of the models. Generally, computational studies assess the possibility of implementing real life closed-loop DBS. Nevertheless, they incorporate many model assumptions whose validity might vary across patients. This makes their use limited, nevertheless they assist in providing insight into how algorithms for adapting DBS can be implemented

1.5.3 Peripheral Devices and Integrated Circuit Implementations

Current implementations of closed-loop DBS use software programs for signal analysis [35, 47]. They have high energy demands that could make them impractical and not portable for use. Incorporating low-power hardware or integrated circuit (IC) recording and processing can reduce some of the limitations associated with practicability and portability [98], which is necessary for fully implantable closed-loop systems. IC implementations have mainly focused on neural recording and stimulation stages that can be incorporated into a closed-loop DBS system. Several microchip implementations of closed-loop DBS systems using neuro-electrophysiological features and incorporating stimulation have been reported for various applications. Table 7 summarises those published between 2014 to date. All the systems are proof-of-concept implementations using mostly offline processing and were mostly used for closed-loop DBS control of epileptic seizures [99 – 104]. From Table 7, it is clear that applications using signals with low spatial scale (and high temporal resolution) e.g spikes (unit activity) employ less processing area and power than applications with larger spatial scale (and low temporal resolution) like ECoG and EEG. These confirm the view expressed in [105] that event-related potentials have shown to be more effective in BMI applications compared to spontaneous signals such as EEG because they do not require large storage requirements and lengthy training periods. The requirements for chronically implanted microchips are becoming more

and more stringent to avoid neural tissue damage. This makes the need for minimising power in state-of-the-art microprocessors ever more important. For the most part, very little effort has been put in the design of application specific IC (ASIC) for closed-loop DBS. This has largely been due to the insufficient empirical evidence on the behaviour of the DBS mechanism.

1.5.4 Limitations and Future Directions

Experimental studies in closed-loop DBS are normally carried out within 2 to 7 days after electrode implantation [19]. During this period, patients may experience substantial improvement in PD symptoms, which may not be attributable to the new therapeutic regimes but to 'stun effect'. The stun effect results in a temporary reduction in parkinsonian symptoms and an unresponsiveness in LFP signals after electrode implantation [107]. It is one of the reasons that post-operative programming is delayed [108]. Experimental studies may not easily bypass the stun effect since its exact duration is still yet to be established [19]. Additionally, closed-loop DBS may need to be tested in a chronic setting because the efficacy of conventional DBS has been reported to fall with time, which is primarily as a result of the habituation effect [109, 110]. Longer trials are necessary to determine if this is also the case for closed-loop DBS.

Most of the experimental studies have used a simple feedback control approach and have mainly focused on monitoring beta band LFPs only [13, 64, 111]. However, using only beta band activity and setting heuristically obtained (static) thresholds may be ineffective and suboptimal, as there are serious questions regarding their ability to track fluctuations across time and patients [13, 112]. They have been reported to correlate with symptoms in bradykinesia and rigidity; however, this is not the case for tremor. In tremor dominant PD, gamma [40, 113, 114], and tremor [54] band activities have been found to correlate with PD symptoms. These further questions the use of one-dimensional feedback signals in a simple feedback approach. Multidimensional feedback signals using a simple but effective control approach may be more viable for closing the loop. The main limitation of advanced feedback algorithms is their computational power needs. This could be offset by the less frequent stimulation required resulting from closing the loop.

A major challenge in the development of closed-loop DBS systems, is the continuous and accurate measurement of PD symptoms – tremor, bradykinesia and rigidity. Of the symptoms, tremor can be accurately measured using instruments like accelerometers as demonstrated in [115]. On the other hand, it is difficult to accurately measure bradykinesia and rigidity. Hence, developing techniques for measuring bradykinesia and rigidity, could lead to major breakthroughs in closed-loop DBS.

So far, closed-loop DBS has been hindered by the poor understanding of the underlying mechanisms that result in improved patient conditions. Better understanding of the underlying mechanism will create a more accurate mapping between disease states and stimulation parameters making improved computational models attainable. It is important to have realistic computational models, which will significantly improve the performance of advanced closed-loop systems by incorporating multiple functionalities. These will in turn lead to the development of thorough clinical studies aimed at investigating techniques that optimise clinical benefits that are tailored to patient's needs. Tailoring therapy to patients' needs could be advanced by adopting a similar technique as is used in cardiac defibrillators, which uses a combination of dual sensor technology. This technology combines a short-term sensor and a long-term sensor, in which the short-term sensors track immediate changes from a selected biomarker, and the long-term sensor tracks biomarkers with a slow response rate. Nonetheless, combining sensors with different rate responses requires adequate blending of respective sensor activities. Irrespective of the developments in closed-loop DBS, significant advancement can only be achieved if there are strong multi-disciplinary collaborations between clinicians, engineers, statisticians, health care professionals, computer scientists, regulatory experts and most importantly, end-users.

1.6 Spatial Adaptation

Spatial adaptation allows for the variation of stimulation focus without a corresponding change in lead position. It is a form of aDBS that adapts to changes or inaccuracies related to lead position and/or poor stimulation focus in relation to targeted neural structures [88]. Poor stimulation focus has often affected the therapeutic benefits of DBS [12]. Directional steering of stimulation is the main form of spatial adaptation, and it offers a new dimension to DBS therapy by directional control of stimulation, in addition to the control of normal stimulation parameters like amplitude, pulse width and frequency.

1.6.1 Advances in Spatial Adaptation

Precise neural targeting has been reported to improve the therapeutic window of DBS by reducing the threshold for beneficial effect and increasing the threshold for side effects [116]. This reduces the need for high amplitude stimulation. Figure 3 depicts how current steering can be used in providing stimulation focus in inaccurately placed or age-related lead migration [117]. While the deviations appear to be small they can result in drastic reductions in therapeutic benefits accruable [118]. It is for this reason that the prospects of directional steering have led to the commercial development of current steering systems. Conventional DBS uses cylindrical electrodes which provide poor neural selectivity, since the stimulation distributes symmetrically around the electrode, thus targeting both

intended and unintended areas. In order to overcome this, novel lead designs with electrodes having high contact resolution were modelled in [117]. The novel lead design uses 64 segmented electrodes which offer a larger electrode combination necessary for accurate field shaping and directional steering. In addition, output stages having multipolar current steering in DBS have been developed towards the realisation of better spatial targeting. The first was implemented in [119]. It uses a voltage controlled resistor (VCR) stimulation circuit and tri-polar current steering. The adopted tri-polar configuration can be scaled for use with higher number of electrodes. In another work, a CMOS circuit for current steering using multipolar and multisite current steering was also presented [120, 121]. So far, very little effort has been devoted to the development of output stages for current steering which are necessary to enable power management in directional steering.

1.6.2 Benefits of Spatial Adaptation

The cylindrical electrodes for conventional DBS were designed when there was very little or no scientific understanding of the mechanisms of DBS and neurodegenerative (and neuropsychiatric) disorders. However, the more insights gained have led to more explicit definition of spatial targets for DBS. This has resulted in a surge in the development of electrodes and leads for DBS [47, 117, 122]. These electrode designs have mainly focussed on two strategies for spatial adaptation [89]: 1) employing a number of small segmented electrodes which could be independently activated in response to issues like electrode migration in chronic DBS, or 2) customising a number of the cylindrical electrodes to improve stimulation of brain targets, especially in the more problematic regions. A typical example is in the stimulation of the Vim for ET patients. It has been established that stimulating the ventral caudal (Vc) nucleus of the thalamus induces parathesia [47]. Due to the proximity of the Vc to the Vim, there is the possibility that electric field spread could induce paraesthesia in patients [47]. This is why the major DBS device manufacturers are aggressively exploring the practicality of leads with provision for spatial adaptation. For instance, Boston scientific developed “Vercise”, a 16-electrode array current steering DBS system. Sapiens marketed the “SureSTIM” which has a 32-electrode lead (Sapiens has now been acquired by Medtronic, Inc). And, Aleva Neurotherapeutics developed the “DirectSTIM” which has 8-electrodes.

Using segmented electrodes provides more flexibility in administering stimulation but increases the cost and complexity of the device. In addition, it imposes lower charge injection limits for safety and creates an impractical parameter search space for clinical DBS programming. These are the major issues of contention in deciding which of the two possible routes (either using segmented or cylindrical electrodes) to follow in terms of spatial adaptation. Nevertheless, both techniques have shown that the benefits of accurate targeting and precise field control outweigh its shortcomings [89, 122].

The optimised stimulation offered by customised directional steering will go a long way in conserving energy, therefore increasing pacemaker battery life. As has been highlighted, there are two main ways that advances in spatial adaptation can be made: 1) novel lead designs and 2) output stages for interfacing to multiple electrodes. The manoeuvrability introduced by spatial adaptation can lead to the exploration of potentially beneficial stimulation sites that were previously inaccessible by surgical techniques.

LFP has been reported to predict the most suitable stimulation contacts [123], which provides an efficient tool to expedite the selection of the optimal DBS contacts. This type of approaches uses the spatial distribution of LFPs power spectral densities across the contacts [39]. The spatio-temporal information related to the STN is used to provide confirmation of adequate DBS lead placement. The viability of this approach for optimizing stimulation contacts using LFPs recorded from implanted directional DBS electrodes was tested in [124]. It corroborated the premise that the level of beta activity can be an indicator for determining the optimal directional contact for improving parkinsonian symptoms. The ability to predict the most suitable contacts for mitigating PD symptoms using LFP beta ban activity presents an interesting prospect for spatial adaptation. Considering the effects of neuroplasticity, electrode migration and other extraneous effects, spatial adaptation of DBS has the potential to offer maximum therapeutic benefits without sacrificing efficiency.

1.7 Future Perspective

Research activity in the field of DBS has stagnated over the last few years [98]. Table 8 summarises the evolution and history of DBS and suggests possible future advances. The major innovations in current DBS technology have mainly resulted in broadening the operating ranges of stimulation parameters; it is still not clear how this will increase clinical benefits. Nevertheless, it gives clinicians an increased flexibility and more degrees of freedom (DOF) to search for patient specific DBS parameters. On the other hand, increased flexibility also increases the economic cost of stimulation parameter programming due to the time-consuming trial-and-error process. Other innovations have been the introduction of rechargeable batteries and the concept of stimulation field shaping. Having rechargeable batteries is essential because the economic costs associated with DBS have been reported to be largely dominated by battery replacement cost [125]. As is normally the case in other therapeutic fields, not every innovation brings about considerable changes that may influence patients' quality of life, but many can improve safety, efficiency and flexibility both for patients and clinicians. Aside from incorporating additional functionality, technological advancements could manifest in the form of increased computing capability per chip at a reduced cost. Due to the short market cycle of electronic devices, continuous innovations are required to maintain market relevance even if they may have little or no benefit towards improving patients’ quality of life.

DBS is becoming more appealing due to the growing evidence pointing to the benefits of DBS at the early stages of PD [126]. Another contributing factor is the growing number of PD patients expected to reach 8.7 million people worldwide by 2030 [127]. These could drive unit costs down as manufacturers achieve economies of scale. Low cost devices can translate to better market penetration particularly in developing countries. Currently, the annual sales estimates of DBS devices for PD is approximately $200 million to $300 million worldwide, but the coming years promise a further surge in sales [121]. It is estimated that more than 100 000 patients suffering from PD, pathological tremor and dystonia have been treated with DBS all over the world [129].

With the increase in the number of patients requiring DBS therapy, there is a need for smarter DBS programming strategies that can be self-optimising and autonomous. The thinking is that adaptive or smart DBS has great potential to keep DBS simpler (both for the patient and caregiver) and more viable. In epilepsy, a closed-loop Vagus Nerve Stimulator, the RNS NeuroPace, has been approved by the FDA for the treatment of refractory epilepsy [130]. Closed loop therapy in epilepsy is easier than that of PD because non-healthy neuronal activity can be easily distinguished from healthy neuronal activity by trained clinicians, which is not the case in PD. Nonetheless, considering that both are closely related neurodegenerative disorders, it may not be long before fully implantable closed-loop systems are trialled. As things currently stand, researchers, entrepreneurs and other stakeholders in the DBS field believe that aDBS will be the silver bullet that will solve the myriad of problems currently associated with conventional DBS for PD.

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1.9 Annotated References

Eight references from the bibliography are chosen based on their level of interest. Four are of considerable interest and the rest are of normal interest. With a brief explanation on the reason for their selection provided.

1.9.1 Of Considerable Interest

Reference 1: Amon A, Alesch F: Systems for deep brain stimulation: review of technical features. *Journal of Neural Transmission*, 1-9 (2017).
Reason: The article outlines aspects regarding the technical features of DBS systems.

Reference 2: Hoang KB, Cassar IR, Grill WM, Turner DA: Biomarkers and Stimulation Algorithms for Adaptive Brain Stimulation. *Front Neuroscience* 11: 564, (2017).
Reason: It details possible biomarkers for use in implanted devices and potential stimulation patterns for adaptive DBS.

Reference 3: Hebb AO, Zhang JJ, Mahoor MH *et al:* Creating the Feedback Loop: closed-loop neuro-stimulation. *Neurosurgery Clinics of North America* 25(1) (2014).
Reason: The review addresses advances in strategies adopting neurophysiological signals to trigger stimulation systems.

Reference 4: Meidahl AC, Tinkhauser G, Herz DM, Cagnan H, Debarros J, Brown P: Adaptive Deep Brain Stimulation for Movement Disorders: The Long Road to Clinical Therapy. *Movement Disorders* 32(6) (2017).
Reason: The review evaluates current aDBS studies and highlights some limitations.

1.9.2 Of Interest

Reference 5: Beudel M, Brown P: Adaptive Deep Brain Stimulation in Parkinson's Disease. *Parkinsonism Relat Disord* 22(1), (2016).
Reason: The paper discusses the feedback signals and stimulation techniques involved in adaptive stimulation in PD.

Reference 6: Gardner J: A history of deep brain stimulation: Technological innovation and the role of clinical assessment tools. *Social Studies of Science* 43(5) (2013).
Reason: The paper gives historical account of deep brain stimulation so as to illustrate the major interests involved in the development of deep brain stimulation technology.

Reference 7: Hariz M, Blomstedt P, Zrinzo L: Future of brain stimulation: New targets, new indications, new technology. *Movement Disorders* 28(13) (2013).
Reason: Details ongoing technological advances that are geared towards the development of hardware systems that facilitate current steering, and other closed-loop concepts.

Reference 8: Little S, Beudel M, Zrinzo L *et al:* Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry* (2015).
Reason: The study employed bilateral aDBS in 4 PD patients undergoing STN DBS. Stimulation was triggered according to beta band LFP activity. Bilateral aDBS improved both axial and limb symptoms.

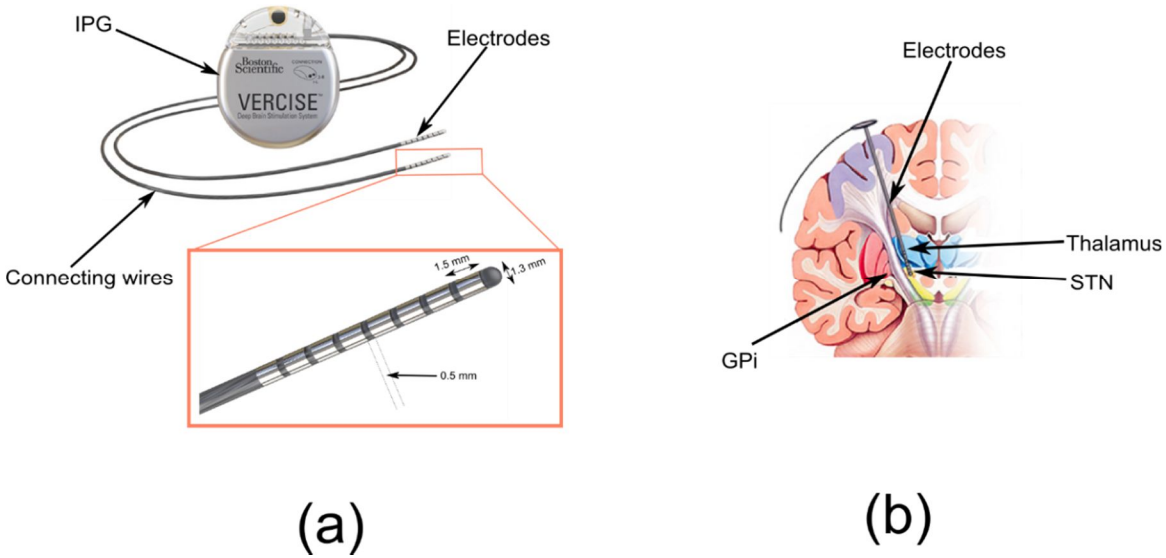

Figure 1. (a) Boston Scientific's Vercise neurostimulator, with electrode and lead dimensions. (b) DBS lead targeting the STN. The diagram shows the thalamus and GPi, which are also major stimulation sites.

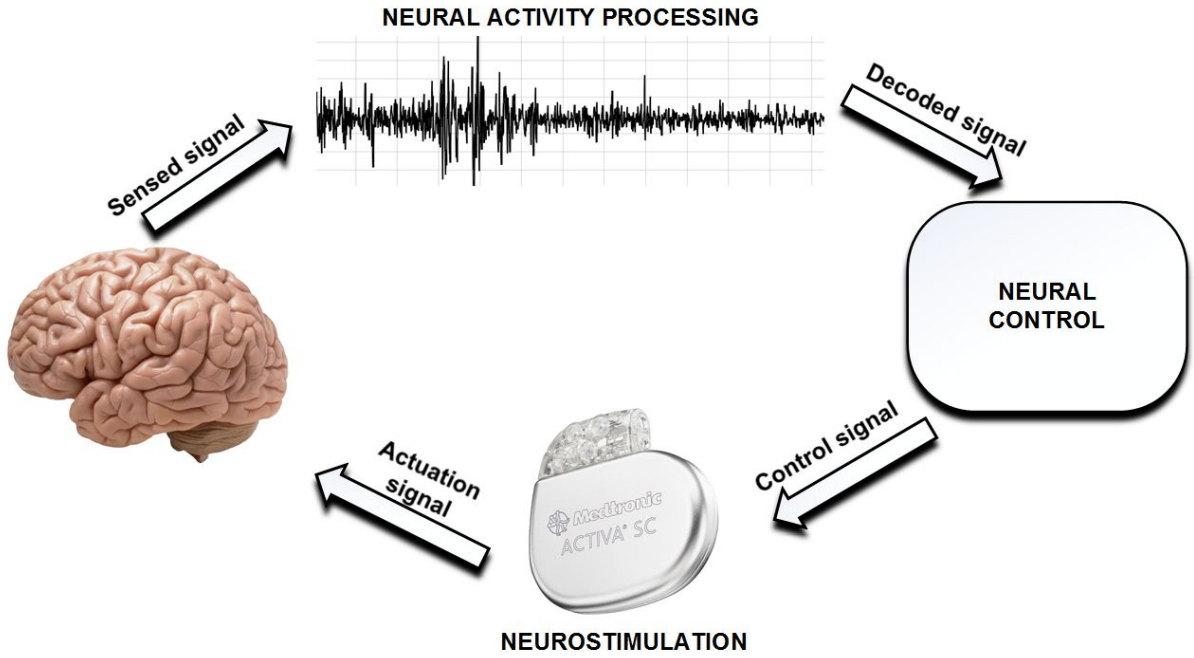

Figure 2. Typical processing chain of a closed-loop DBS system.

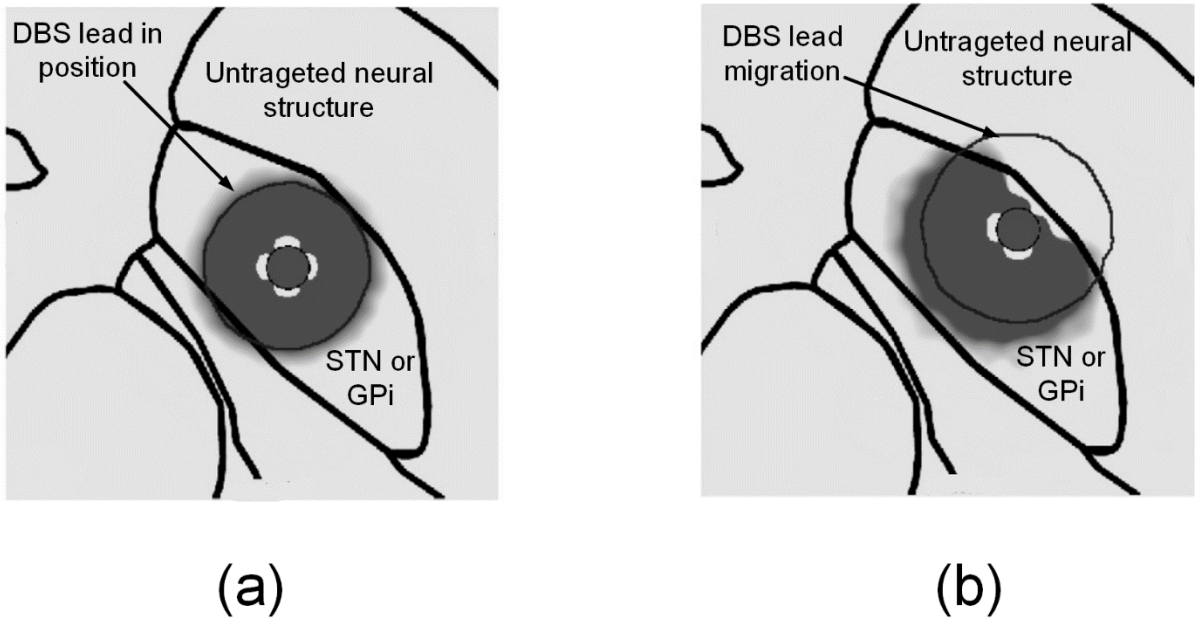

Figure 3. Computational model illustrating the effect of current steering on the volume of tissue activated (VTA). (a) Showing accurately placed lead for STN stimulation. (b) Depicts the use of current steering to control the activation field in inaccurately placed DBS leads for STN stimulation (adapted from [117]).

Table 1. Operating range for different DBS systems [22-25].

Manufacturer	**IPG Model**	**Longevity** [g]	**Lead Technology** [h]	**Stimulation Parameters**		
				Frequency (Hz)	Pulse width (μs)	Amplitude
Medtronic [a, e]	Activa PC [b, i]	Non-rechargeable	Compatible with lead models 3387 (l = 1.5, s = 1.5), 3389 (l = 1.5, s = 0.5) and 3391 (l = 3, s = 4). Models 3387, 3389 and 3391 have 4 electrode leads.	30 – 250	60 - 450	0 – 10.5 V
				2 – 250		0 – 25.5 mA
	Activa RC [b, c, i]	Rechargeable	Compatible with lead models 3387 and 3389.	30 – 250		0 – 10.5 V
				2 – 250		0 – 25.5 mA
	Activa SC [d, i]	Non-rechargeable	Compatible with lead models 3387, 3389 and 3391.	30 – 250		0 – 10.5 V
				2 – 250		0 – 25.5 mA
Boston Scientific [a]	Vercise [d, f, i]	Rechargeable	Compatible with lead models DB-2201-30 AC and DB-2201-45 BC.	2 - 255	10 – 450	0 – 20 mA
	Vercise PC [f, i]	Non-rechargeable	Compatible with lead models DB-2201-30 and DB-2201-45.	2 - 255	20 – 450	
	Vercise Gevia [d, f, i]	Rechargeable	Compatible with lead models DB-2201-30 AC, DB-2201-45 BC, DB-2201-30 and DB-2201-45.	2 - 255	20 - 450	
St Jude Medical [e]	Libra [e, f]	Non-rechargeable	Compatible with models: 6142/6143/6144/6145 (l =1.5, s = 1.5 and 4 electrodes); 6146/6147/6148/6149 (l =1.5, s = 0.5 and 4 electrodes); 6158/6160/6166/6168 (l =1.5, s = 0.5 and 4 electrodes); 6159/6161/6167/6169 (l =1.5, s = 1.5 and 4 electrodes); 6170/6172/6178/6180 (l =1.5, s = 0.5 and 8 electrodes) and 6171/6173/6179/6181 (l =1.5, s = 1.5 and 8 electrodes).	2 - 240	50 - 500	0 – 12.75 mA
	Libra XP [c, e]	Non-rechargeable		2 - 240	52 - 507	
	Brio [c, d]	Rechargeable		2 – 200	52 – 507	
	Infinity [e,]	Non-rechargeable		2 - 240	20 - 500	

[a] Uses both current and voltage sources.
[b] Bilaterally implanted leads with 4 electrode contacts/lead.
[c] Rechargeable battery.
[d] Unilaterally implanted leads with 4 electrode contacts.
[e] Has multipolar configuration. In addition to its polarity, multipolar configuration can be used in uni/bipolar polarity. Medtronic stimulators in current source configuration are limited to only uni/bipolar polarity.
[f] Bilaterally implanted leads with 8 electrode contacts/lead.

[g] Non-rechargeable batteries last between 3 – 5 years, while rechargeable batteries could last for up to 9 years.
[h] Interelectrode spacing is represented by ‘s’ (mm), with electrode length represented by ‘l’ (mm). Boston Scientific leads have 8 electrodes while Medtronic leads have 4 electrodes.
[i] All Boston Scientific leads have dimensions d = 1.3 mm, l =1.5 mm and s = 0.5 mm.

Table 2. Comparison of possible feedback signals and sensing techniques for closed-loop DBS.

Electrical Activity Measurements	**Spike**	**LFP**	**ECoG/iEEG**	**EEG**	
Activity Measured	Unit activity	average potential of a localised neural population	cortical or intracranial activity	Electrical activity from scalp	
Temporal Resolution	< 1 ms	~1 ms	~3 ms	~50 ms	
Spatial Resolution	~ 50 µm	~0.5 mm	~1 mm	~10 mm	
Level of Invasiveness	Invasive	Invasive	Minimally invasive	Non-invasive	
Practicability for use in closed-loop DBS	Implantable	Implantable	Implantable	Bulky, but cheap	
Metabolic Activity Measurements	**Fluorescence Measurements**	**NIRS**	**fMRI**	**FSCV**	**Intracranial dialysis**
Activity Measured	Ca^{2+}, Na^{+} or K^{+} concentration in the brain	Concentration of oxyhemoglobin	blood-oxygen-level and molecular displacement of water	Concentration of neurotransmitter (dopamine)	Concentration of neurotransmitter (dopamine)
Temporal Resolution	~30 ms	< 1 s	~1 s	~1 s	~1 s
Spatial Resolution	~ 10 µm	~ 5mm	~1mm	~ 30 µm	~ 200 µm
Level of Invasiveness	Invasive	Non-invasive	Non-invasive	Invasive	Invasive
Practicability for use in closed-loop DBS	Implantable (with very high data analysis cost)	Bulky	Bulky (a major hindrance is DBS devices are still MR conditional)	Bulky (with high specificity and selectivity)	Bulky (with high specificity and selectivity)

Table 3. Advantages and disadvantages of neural systems control strategies.

Control Strategy	Advantages	Disadvantages	DBS related study
Manual Feedback	It is simple, straightforward and easy to implement.	It is unrealistic and misleading. It cannot correct for errors and cannot compensate for disturbances.	Conventional DBS.
Simple Feedback	It is simple, straightforward and easy to implement.	It can be unstable as it monitors fluctuations between two pre-set levels.	[13, 49, 62-70]
Classifier-Driven	Provides a simple approach for cases with an established relationship between discrete disease states and therapy.	Classification algorithms can be computationally intensive and directly mapping states to therapy may not provide therapeutic benefit due to the non-linearity of the disease/disorder.	[74, 76, 77, 80, 81]
Internal Model Driven	Input-output model may assist in adapting to changes in dynamics of disease or disorder.	Yet to be attempted in any experimental study. They have only been used in computational studies.	[71, 72]
Actor-Critic	Adopts techniques that incorporate real-life clinical diagnostics and intervention.	Requires very accurate sensors that capture and track fluctuations in biomarker in real-time, so that they can be “critiqued” to enable immediate action. State estimates may not be representative of symptom severity.	[35]

Table 4. Benefits and limitations of therapeutic stimulation techniques.

Stimulation Techniques	Benefits	Limitations	Example Commercial Devices
VCS	Provides the longest battery life span compared to other techniques.	Possible accumulation of charge at ETI raises serious safety concerns.	Mainly used by Medtronic devices: Activa PC, Activa RC and Activa SC.
CCS	Offers better control over injected charge than VCS.	Extra power consumption is incurred in the conditioning circuit used in producing constant current excitation	Commercial devices are experiencing a shift towards CCS. Most commercial devices on the market have CCS mode operation.
ChgCS	Offers a trade-off between safety and efficiency.	The need for charging capacitors could make them bulkier than necessary.	Still at infancy. More research is still required before it can be fully deployed.

Table 5. A summary of experimental studies using closed-loop DBS.

Ref.	**[70]**	**[62]**	**[63]**	**[13]**	**[66]**	**[35]**
Experimental subjects	2 African Green Monkeys	12 Patients with tremor dominant PD.	9 patients (6 had ET and 3 had dystonic tremor (DT))	8 PD patients	8 PD patients	An ovine model
Stimulation site and paradigm	Pulse train at 130 Hz delivered to GPi and motor cortex (M1) after 80 ms of detecting single unit neural activity.	Transcranial alternating current stimulation (TACS) delivered to M1 on detecting cortical activity.	Accelerometer triggered stimulation delivered to Ventrolateral thalamus based on the patient's tremor rhythm (3-8 Hz).	Stimulation delivered to STN ramped on threshold crossing of beta-band LFP for each patient.	Bilateral stimulation of STN triggered in response to beta-band LFP threshold crossing.	Network activity in broad beta band (10 – 30 Hz) in Hippocampus (HC) and anterior nucleus (AN) used to trigger stimulation based on an actor-critic control policy.
Outcome	There is more than 50% alleviation in occurrence of tremor in subjects.	Achieves almost 50% average reduction in resting tremor amplitude.	Between 8 % - 51 % tremor suppression in dominant tremor axis for ET patients.	56% reduction in average stimulation time.	The mean improvement in UPDRS scores for unblinded is 66.2% and 49.7% for blinded assessment.	Seizures suppressed within a second. And uses about 10% of nominal power over a period of 15 months.
Ref.	**[65]**	**[77]**	**[74]**	**[76]**	**[49]**	**[48]**
Experimental subjects	A female rhesus macaque (Monkey)	7 PD patients	8 patients with tremor (4 ET and 4 PD)	20 PD patients	Four anesthetized rats	Three anesthetized rats
Stimulation site and paradigm	Stimulation triggered in STN at threshold crossing of LPF beta band.	LFP recorded from STN (No stimulation).	sEMG signals used (No stimulation).	LFP recorded from STN (No stimulation).	A look-up table was used to determine the stimulation parameters based on evoked dopamine (neurotransmitter) release. Sensing through the Striatum (St) and stimulation at the medial forebrain bundle (MFB).	Stimulation wirelessly ramped in response to neurochemical recording. Sensing in St and stimulation at MFB.
Outcome	Stimulator is switched on about 50% of the time but performance comparable to continuous stimulation.	55.2% - 100% tremor detection accuracy.	The predictor achieves an average sensitivity of 100%, with a mean accuracy of 85.7% for all ET trials and 80.2% for all PD trials.	The UPDRS improvement (good or poor) for 19 of the 20 patients were correctly classified.	There is a reported increase in neurotransmitter, which is suggestive of improved motor conditions.	As in [45], there is an increase in striatal dopamine release.

Table 6. The major neuronal models used in computational models for closed-loop DBS.

Type of Model	Merits	Demerits	Ref.
Neuronal phase models	Disrupts self-synchronisation in neuronal population using time-delayed stimulation.	Requires multi-site stimulation in order to disrupt synchronisation. In addition, there is no understanding of the optimal way to keep pathological neurons effectively desynchronised. There are limited experimental studies that verify its efficacy.	[67 – 69, 91, 93, 94]
Stochastic models	Models neuronal dynamics using a range of stochastic processes ranging from regular, irregular, random and bursting neuronal activitiesthat are present within a neural population.	Mostly uses a small neural population. This may be inadequate and unrepresentative of the entire neuronal population.	[71,72]
Firing rate model	Single neuron models of STN, GPe, GPe or thalamo-cortical neurons are connected to represent the basal ganglia network. This makes it more manageable and easy to undertake thorough control analysis.	It is still not clear if conclusions drawn from these models remain true if the number of neurons, their parameters or network connection are changed [85].	[64, 95 - 97]

Table 7. Closed-loop DBS systems with online recording and stimulation.

Ref.	Year	On-chip Stages	Neural Signals	CMOS Technology	Processing	Power (µW)	Area (mm^2)
[102]	2017	Recording, feature extraction and stimulation	EEG/ECoG	0.13 µm	FPGA	1 300	12
[106]	2017	Feature extraction and stimulation	Spike and LFP	0.18 µm	CPU	896	3.7
[101]	2016	Recording and stimulation	ECoG	0.13 µm	FPGA	2 170	16
[99]	2015	Feature extraction, data compression and stimulation.	Spike	65 nm	CPU	626.4	4.8
[104]	2015	Recording and stimulation	ECoG	0.35 µm	FPGA	13 500	12.8
[100]	2014	Recording, seizure detection and stimulation.	iEEG	0.18 µm	Onsite	2 800	13.5
[103]	2014	Recording, feature extraction and stimulation	Spike and LFP	0.18 µm	Partly onsite	468	4

Table 8. Evolution of DBS [3, 70, 131 - 134].

Evolution of DBS		Subperiods (quarters)			
		Q1	Q2	Q3	Q4
Period	1870 - 1969	Direct electric stimulation attempted on animals and then humans. Stereotactic frames to enable access to the brain developed.	–	–	Stereotactic frames are finally used for human surgery. Brain stimulation used to treat chronic pains and neuropsychiatric disorders. Intermittent chronic DBS trialled to reduce tremor in PD.
	1970 - 1989	Stimulation used to treat chronic pain, epilepsy and other movement disorders.	Medtronic trademarks the term 'DBS' for neurostimulation. Stimulation of Periventricular-Periaqueductal Gray is used to treat chronic pain.	Thalamic stimulation is used for treating tremor and dyskinesia.	UPDRS developed as a clinical assesment tool. Thalamic stimulation used for treating depression. Stimulation of the VIM is used for treating PD and tremor.
	1990 - 2004	The efficacy of STN lesion in treating primates induced with movement disordes through 1-methyl-4-phenyl-1, 2,3, 6-tetrahydropyridine (MPTP) is verified. Implantable battery-driven DBS pacemakers are developed.	STN stimulation is used for treatment of PD in first human. DBS therapy to treat motor movement disorder gains FDA approval. Medtronic gains CE mark for DBS device for treating PD.	Approval for bilateral stimulation of GPi and STN for adjunctive therapy in levodopa-responsive Parkinson's disease. DBS for dystonia receives CE Mark and interim FDA approval, called human device exemption (HDE).	The efficacy of pedunculopontine nucleus stimulation is demnstrated using MPTP induced primates.
	2005 – Date	Medtronic introduces the first rechargeable DBS device, called Activa RC. Pacemaker lifespan improved from 3 – 5 years to about 9 years.	First acute trial of on-demand DBS. A non-human primate was used.	Boston Scientific receives CE Mark for their Vercise™ DBS system. The first multiple independent current source system.	–
	Possible future advances (Q4 to be achieved within 10 – 20 years)	DBS approved as a therapy for neuropsychiatric disorders such as medication resistant cases of depression, OCD and TS.	FDA approval for cranially mounted DBS. This could solve the two stage implantation procedure consisting of two separate procedures for lead and pacemaker placement.	Long distance monitoring and adjustment of patient pacemakers, which could reduce the number of face-to-face visits.	Possibility of CE Mark and/or FDA approval for first fully implantable closed-loop DBS system.
		Newer DBS stimulation sites approved.	Development of devices with complete compatability for use with high Tesla MRI for better localisation of targets and improved device safety. Current devices are conditionally safe for MRI.	Robot assisted implantation through frameless stereotaxy.	