# Feedback control for deep brain stimulation for motor disorders

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Deep brain stimulation (DBS) is an effective treatment for many people living with Parkinson's disease (PD). Although the primary treatment for PD is based on medications, disease progression eventually leads to inadequate symptom control. DBS provides benefits by alleviating motor dysfunctions such as muscle rigidity and tremor. DBS devices deliver electric pulse trains into specific brain regions via implanted electrodes. Existing DBS systems usually provide continuous stimulation with constant settings of parameters such as the amount of charge delivered per pulse. However, PD is characterised by fluctuations in the severity and frequency of impairments. DBS would be improved if stimulation settings were adjusted automatically in response to each patient's ever-changing needs. This requires a device incorporating sensing of signals that estimate the severity of motor impairment linked to an adaptive control algorithm that optimises therapeutic stimulation. Several types of signals are candidates for this function. Spontaneous local field potentials recorded by the DBS electrodes have shown promise in some experimental studies of adaptive DBS. More recently, DBS-evoked potentials have been reported. In particular, evoked resonant neural activity has properties including a larger amplitude than spontaneous potentials, suggesting it may be a suitable feedback signal to control adaptive DBS.

**1. Introduction:** Deep brain stimulation (DBS) is an established therapy applied to treat a range of challenging health conditions. DBS systems comprise several components implanted in the body and function by delivering electric pulses to selected neural targets in the brain. The implanted components include electrode arrays and a battery-powered stimulator that is usually placed in the patient's chest. Typical electrode arrays in today's DBS systems provide 4–8 discrete sites of stimulation and are connected to the stimulator by subcutaneous cables. In most cases, two electrode arrays are implanted so that the corresponding neural targets in both brain hemispheres receive stimulation. After implantation, the stimulator is programmed to deliver electric charge pulses with specified parameters to selected electrodes on each array. As discussed further below, both optimal adjustment of these parameters and appropriate selection of electrodes are required to maximise the therapeutic benefit of DBS for each patient.

Most current users of DBS are people living with movement disorders, particularly Parkinson's disease (PD). PD is a chronic, degenerative condition characterised by debilitating motor symptoms of muscle rigidity, bradykinesia (slowness of movement), and tremor. Although at first these problems are usually addressed adequately with medications, the underlying disease progresses inexorably. As the motor disorders worsen and the medications become less effective, implantation of a DBS device is often recommended. At present, there are over 6 million people living with PD worldwide, of whom ~150,000 are users of DBS [1].

Although DBS improves the quality of life for PD patients [2–4], conventional devices have limitations that diminish outcomes. The main limitation is that today's DBS provides constant stimulation regardless of each patient's continually changing needs. PD symptoms fluctuate due to factors such as voluntary activity, medication cycles, circadian rhythms, and disease progression. Thus, conventional DBS can at different times be insufficient or excessive. Under-stimulation can allow disabling motor symptoms to increase, while over-stimulation can cause side effects including cognitive-motor disturbances (e.g. problems with speech articulation) and psychiatric issues (e.g. depression) [5, 6]. Consequently, current users of DBS systems require frequent adjustment of DBS settings because of poor symptom alleviation or intolerable side-effects. Such adjustments, which are performed manually by skilled and experienced clinicians, have been shown to improve patient outcomes [7]. Unfortunately, however, it is infeasible for clinicians to explore all available combinations of DBS parameters, so the optimum benefit is often not achieved [7, 8]. Sometimes a small change to DBS settings can suddenly liberate a patient from an extended period of severe motor disability [9, 10]. These problems have spurred research into adaptive DBS systems that can adjust stimulation settings automatically for each patient at any time.

**2. Feedback control of DBS:** An ideal DBS system would incorporate sensing of signals that indicate the patient's symptom state so that stimulation parameters can be adjusted to optimise therapy while minimising adverse side-effects. In principle, there are two broad categories of signals that can be utilised for this purpose. First, transducers could be applied to monitor the patient's movements and provide signals indicating the type and severity of motor dysfunction. For example, accelerometers attached to the patient's limbs can quantify motion related to tremor and generate feedback signals to control DBS parameters such as the level and timing of pulses [11]. At present, such techniques are not available in commercial DBS systems. Although they offer potential benefits including the ability to monitor the patient's motor disorders directly and with fine time resolution, they also have serious disadvantages. In particular, they require components (accelerometers or other transducers) to be attached to the patient or surgically implanted in addition to the DBS device. A system with multiple transducers would be more expensive and complex than conventional DBS systems and probably more difficult to deploy in a typical clinical setting.

The second category of feedback signal comprises bioelectric potentials including those that can be measured from the electrodes implanted to deliver DBS chronically. While it is feasible to record useful bioelectric potentials from various brain regions using additional electrodes [8, 11, 12], the simplest configuration for an adaptive DBS system would record from the same electrodes used for stimulation, as they are already positioned within or close to the neural circuits of interest.

The block diagram shown in Fig. 1 illustrates the signal processing generally required to implement automatically adaptive DBS using potentials recorded from the brain. Two types of potentials

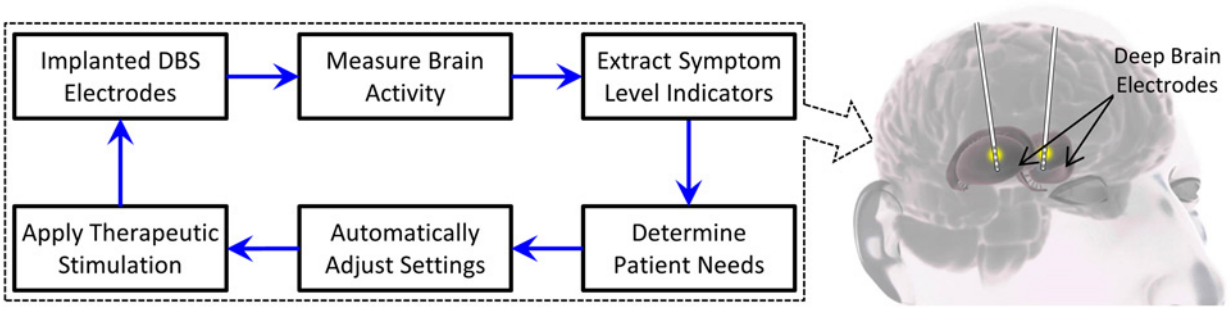


**Fig. 1** *Principal blocks of an adaptive DBS system. Electrode arrays implanted into the target structures of the brain are used both to deliver therapeutic stimulation and to record neuronal activity in the brain. These bioelectric potentials are processed to extract features indicating the type and severity of the patient's symptoms. This information is related to the desired symptom state and DBS parameter settings are adjusted accordingly*

are relevant: (i) spontaneous signals, particularly local field potentials (LFPs); and (ii) evoked potentials. LFPs are signals that can be recorded from a chronically implanted DBS electrode and represent the aggregate activity of a neuronal population in the vicinity of the electrode. Although this activity contains measurable components up to ∼1000 Hz, it is dominated by low-frequency components. In particular, a frequency band encompassing approximately 13–30 Hz, known as the beta band, contains signals that have been shown to correlate broadly with the occurrence of motor dysfunction, particularly bradykinesia and rigidity, in PD [12]. Accordingly, as discussed below, beta signals are practical candidates for the automatic feedback control of DBS.

In contrast to LFPs, evoked potentials are signals generated by neuronal populations in response to brief stimuli delivered via a DBS electrode. Such signals can be recorded from the stimulating electrode or another, typically proximate, electrode. One recently reported DBS-evoked potential has the form of a decaying oscillation following a stimulating pulse train, and is therefore described as evoked resonant neural activity (ERNA) [13, 14]. The fundamental frequency of ERNA is generally far above the range of the LFP beta frequency band, encompassing approximately 250–400 Hz. ERNA has properties that suggest it may be preferable to beta signals for feedback control of DBS, as discussed later.

As shown in Fig. 1, adaptive DBS systems that utilise bioelectric potentials to control stimulation comprise six main functional blocks: (i) electrodes chronically implanted in the brain that both deliver therapeutic stimuli and record potentials; (ii) amplification and signal conditioning that enable electrode potentials to be recorded and processed within the implanted electronic unit; (iii) signal processing that extracts information from the potentials indicating the patient's motor state (i.e. the type and severity of symptoms); (iv) an algorithm that determines whether or how stimulation should be adjusted by comparing the patient's current motor state with an optimum state; (v) adjustment of appropriate DBS parameters (e.g. amplitude or frequency of stimulation); and (vi) application of DBS to the electrodes with the selected parameter settings. Different signal recording and processing techniques have been adopted depending on whether the potentials used to control DBS are spontaneous (e.g. beta-band LFPs) or evoked (e.g. ERNA).

**3. DBS controlled by beta signals:** Numerous studies have reported that beta-band LFPs contain spectral features that correlate with symptoms of bradykinesia and rigidity in patients with PD [12]. One commonly observed characteristic of beta signals is that they typically have higher levels when Parkinsonian impairments are present than when symptoms are alleviated. In particular, the level of a discrete spectral peak within the beta band seems to vary consistently in accordance with clinically observed motor disability. One experimental adaptive DBS system based on this observation has been evaluated clinically with a small group of participants [15]. That system detected a spectral peak within the 13–35 Hz band and compared the averaged amplitude of that peak to a predetermined threshold. Whenever the peak exceeded the threshold, stimulation was enabled; otherwise, stimulation was disabled. This simple control scheme resulted in a 56% reduction in stimulation time in comparison with therapeutically effective continuous DBS. To evaluate benefits to patients, a standard assessment, the unified PD rating scale (UPDRS), was used. Averaged across the eight PD patients who participated in the experiments, the improvement in UPDRS for adaptive DBS compared to conventional continuous DBS was ∼28%; this was a statistically significant difference.

Although these experimental findings provide strong support for the clinical utility of an adaptive DBS system based on beta-band LFPs, several factors have slowed the commercial emergence of an implantable device enabling adaptive DBS as a routine therapy to alleviate symptoms of PD. One problem is that the LFP is a small signal and its electrical characteristics vary considerably among patients implanted with DBS electrodes. For example, in the above study, the filtered LFP signal containing the beta peak was found to have an amplitude of only approximately 1–2 μV [15]. Such small signals are difficult to record reliably given the technical constraints applicable to a low-power device implanted in the body.

**4. DBS controlled by evoked potentials:** A promising alternative to the use of spontaneous signals is to record bioelectric potentials generated in response to the stimulation delivered via the DBS electrodes. Such evoked potentials are time-locked to the causative stimuli and can be recorded directly from the DBS electrode array. In particular, ERNA is an evoked potential having several characteristics that suggest it is suitable for use as a feedback signal for controlling adaptive DBS therapy [13]. As shown in Fig. 2, the ERNA waveform consists of an oscillatory response commencing several milliseconds after the occurrence of each stimulus pulse (Fig. 2*a*). The amplitude and morphology of ERNA change across the delivery of multiple stimulus pulses in a contiguous burst (Fig. 2*b*). On average, ERNA is orders of magnitude larger than beta-band spontaneous LFPs. Immediately after the end of a DBS pulse train, the ERNA signal decreases in magnitude while continuing the oscillatory morphology. The frequency of ERNA can be estimated as the inverse of the time period between successive peaks in the oscillation. Recordings of ERNA obtained during experiments with patients undergoing implantation of DBS devices for the alleviation of PD symptoms show that the ERNA frequency decreases systematically with increases in DBS current (Fig. 2*c*). At DBS levels that are therapeutically effective (2.25 mA and above), the frequency of ERNA was found to remain relatively constant, averaging ∼260 Hz.

For any proposed bioelectric potential to be useful as a control signal for DBS, it is essential that it has one or more features demonstrating a consistent relationship with the varying symptom state

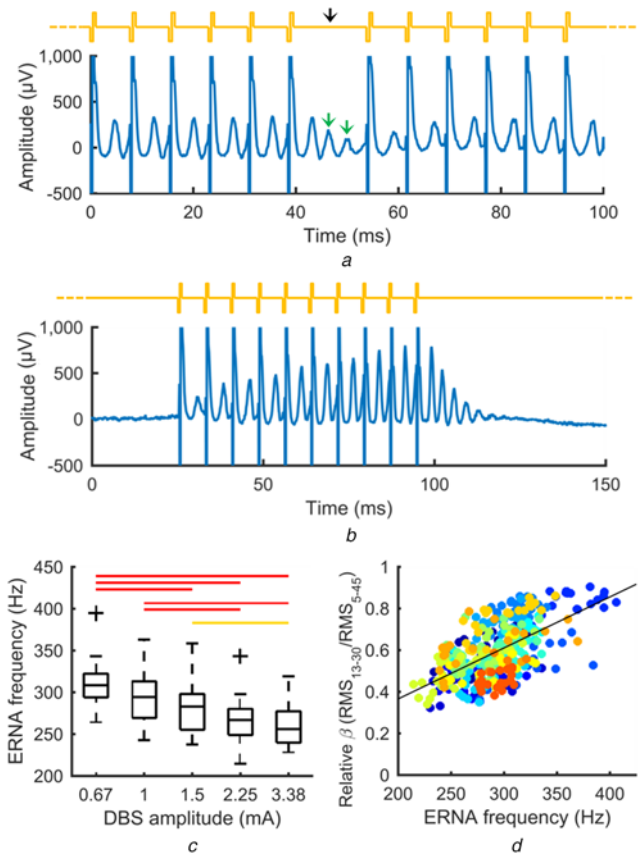


**Fig. 2** *Representative waveforms showing ERNA and significant features of ERNA recordings obtained from DBS electrodes implanted in patients with Parkinson's disease. This figure is reproduced in part from [14], with permission*

*a* The top waveform (yellow) represents a DBS pulse train delivered at 130 Hz; one pulse in the train was omitted (black arrow) enabling the ERNA waveform to be captured within an interval of ~14 ms. The green arrows indicate two peaks of ERNA following the initial peak and illustrate the typical ERNA morphology of a decaying oscillation (blue)

*b* A burst of ten consecutive DBS pulses (yellow) applied to record ERNA (blue) as an alternative to continuous DBS. This stimulus type enables ERNA to be monitored without applying therapeutically effective continuous DBS

*c* ERNA frequency (estimated as the inverse of the period between consecutive waveform peaks) decreases as DBS amplitude increases. In the ten PD patients from whom these data were recorded, levels of 2.25 mA and above were found to be therapeutically effective, on average. At those levels, the ERNA frequency reached a minimum of ~260 Hz and did not differ significantly between levels of 2.25 and 3.38 mA. Horizontal lines indicate statistically significant differences in ERNA frequency (red: $p \leq 0.001$; yellow: $p < 0.05$)

*d* Relation between ERNA frequency and bioelectric activity in the beta frequency band for the same ten PD patients. The correlation shows that the relative beta-band amplitude decreased with decreasing ERNA frequency ($\rho = 0.58$, $p < 0.001$); the colours indicate the different brain hemispheres tested. As clinical studies have established that lower beta levels correspond to better alleviation of Parkinsonian symptoms, these data suggest that lower ERNA frequencies are associated with therapeutic benefit from DBS

of each PD patient. Evidence that ERNA frequency is related to the severity of PD motor dysfunction is presented in Fig. 2*d*. In that graph, the level of the beta-band LFP is used as an indicator of motor state in accordance with the established findings of previous studies as outlined briefly above. The data show that ERNA frequency was lower, on average, in conditions where the beta level was reduced, corresponding to the alleviation of PD symptoms. Therefore, adjusting the DBS level automatically such that the ERNA frequency is minimised may be an effective and straightforward technique for implementing adaptive DBS.

**5. Conclusion:** For many years, it has been a goal of researchers and DBS device manufacturers to develop an implantable stimulator capable of controlling DBS automatically in response to the continually fluctuating therapeutic requirements of people with Parkinson's disease. Although commercialisation of such adaptive systems has been slow to emerge, several techniques are being developed and evaluated that show promise in meeting this need. Signals derived from the beta frequency band of LFPs have been demonstrated to enable clinically effective control of DBS in some studies [15, 16]. However, beta signals are relatively small and may be difficult to monitor reliably in every patient given the presence of electrical noise arising from the electrode-neural interface and interfering signals associated with voluntary movement. In contrast, potentials evoked by DBS are generally free from these problems as they have large amplitudes and are temporally synchronised to the causative stimulation pulses. ERNA is an evoked potential that appears particularly suitable for use as a feedback signal. Preliminary clinical evidence suggests that a simple estimate of the ERNA frequency could be used to control DBS. Further research is being conducted to develop and evaluate an ERNA-based adaptive DBS system that optimises therapy while minimising unwanted side-effects.

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The authors declare the following potential conflicts of interest. We are named inventors on patents relating to ERNA, which are assigned to DBS Technologies Pty Ltd., and also hold shares or options in that company.

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