Closed-Loop Deep Brain Stimulation

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***Abstract*—This work aims at providing a wide overview of different approaches of *Brain Medical Stimulation* dedicated to patients afflicted by severe disabling diseases like Parkinson, dystonia, obsessive-compulsive disorder and treatment-resistant depression. The most diffused and accepted concepts found in literature and in the market are presented and analyzed. The main open issues and future directions are investigated.**

I. Introduction

Over the last two decades a brand new high-frequency therapy for the treatment of some neurological movement-related disorders had evolved, the so-called *Deep Brain Stimulation* (DBS).

Despite of the huge interest in this field, DBS can still be considered in its infancy and much work remains to be done in order for it to be considered as a mass-scale therapy. In this paper we are going to present the DBS therapy, looking at its main aspects and their clinical applications, outlining the main issues of this approach and some possible improvements.

Nowadays more than 70 thousands different patients, mainly afflicted by *essential tremor*, *Parkinson Disease* (PD) and *dystonia*, have undergone DBS surgery, but the very first reported experiment for PD patient dates back to 1994 [1], employing a basic version of open-loop (i.e. uncontrolled) DBS. Starting from there many developments and tests have been conducted, up to the recent concept of closed-loop DBS as suggested in [2], [3] and [4].

In Section II the main neurological diseases that can be treated through DBS are reviewed and a comparison between open and closed loop techniques is reported. In Section III we're going to underline the medical equipments and the clinical setup needed to provide this kind of procedure discussing some results present in literature. Finally Section IV concludes the report giving a brief overview about the main open issues and possible future directions.

II. Related Work

In order to deliver DBS some electrodes need to be implanted into specific areas of the brain, targeted through MRI or computed tomography. Then stimulation could be useful for many mental disorders, aiming at relieving the pain of the patient or improve motor-functional capabilities.
The rationale behind DBS is to deliver high-frequency stimulation, typically over the beta band, i.e. the frequency range of about $[15 - 35]$ Hz. In this way, for example in PD, DBS is able to reduce the overly synchronized activity of the motor cortex, which controls the body's skeletal muscles [5]. Actually the reason why DBS works is that high-frequency stimulation induces a regularization of neuronal patterns which decreases the output from the stimulated site. The transmission of pathological bursts and oscillatory activities within the neural network are prevented; this results into an improved processing of sensorimotor information and reduction of disease symptoms. The underlying physiological causes, however, are likely multiple and a complete explanation is still missing although many contributions are already present in literature [6] and [4].

A. Treatments

Although treatments for thalamic DBS for essential tremor and PD-related tremor were already been granted in 1997 [6], the specific Parkinson-focused procedure had been approved by the *Food and Drug Administration* only in 2002 [7].

DBS is nowadays an attractive alternative to surgery for the management of tremor and can be deployed via many different techniques, some of them are presented in the next sections.

A common main aspect of those approaches is the selection of the optimal target region to be stimulated, for which several possibilities have been proposed in literature. In the past few years the preferred target has become the SubThalamic Nucleus (STN), which has been proven to provide a robust and well-performing outcome over time [6], relieving all the features of PD,

including also resting tremors [8], [9].
Another sensible target region is the *Globus Pallidus Pars Interna (GPi)*, which is preferable for patients whose symptoms regard speech, cognitive and mood disturbances [6], whether focusing on *Bilateral Thalatomy* often is not well tolerated because of the swallowing deficits.
Moreover several studies suggested that the *posterior subthalamic* area is a better stimulation region due to the fact that patients may be incidentally benefiting from electrode contacts located outside of the thalamus [10].

Surely it has to be taken into account that patients suffering from such invasive and problematic diseases like Obsessive-Compulsive Disorder, Epilepsy, Parkinson and Tourette Syndrome accept to undergo surgery and join DBS trials, although managing severe side affects due to the stimulation like paresthesias, headache, dysarthria, paresis, gait disturbance and ataxia.

As we have already stated the use of DBS has been adopted in tremor-related disease therapies as for example *distonya* and *Parkinson*. However, DBS has been also proved to be successful, although in a more limited way, for psychatric syndromes like *Tourette*'s one, *obsessive-compulsive disorder* and *cronical treatment-resistant depression* (TRD) [6]. This latter is a severely disabling disorder with still nowadays almost no proven treatment options that could be proposed to the patient once multiple medications, psychotherapy, and electroconvulsive therapy have previously failed [11].

Since so far no therapy could be considered an ultimate cure for those diseases, the adjustment of stimulation parameters is crucial to make receiving treatments much more beneficial for patients.

B. Closed vs Open Loop DBS

At the present time a shift of paradigm from open-loop to closed-loop DBS is in progress. In particular open-loop DBS was designed to continuously (cDBS) or randomly (rDBS) deliver high-frequency stimulation to the patient whose pattern and intensity are adjusted manually [12], [13]. Their widespread adoption has been, however, limited by costs, side effects and partial efficacy; hence all recent implementations are trying to *close the loop* in response to physiological changes. The rationale behind those implementation is that an adaptive control allows to automatically adapt to the dynamics of the disease having less undesirable effects and more clinical benefits than standard paradigms, as carefully proven by [2].

The most important aspect is to find a robust feedback signal to track over time the fluctuations of symptoms due to various cognitive and physic factors, while minimizing the surgical intervention impact [14]: so far *Local Field Potential* (LFP) [15] [16] or *Action Potentials* (APs) have been successfully employed [17], [18]. Another aspect towards which there is a lot of interest is the power consumption [19] and [20], although there are many implementations capable of even reducing the power consumption delivering about the half of electrical energy than open-loop counterpart (thus extending the lifetime of implanted battery systems) and at the same time achieving many improvements [4].

Another fundamental technical challenge when dealing with closed-loop system is the need of simultaneous sensing and stimulation system without influencing each other. Hence to remove stimulation artifacts are generally used: differential sensing, a front-end low-pass filter and a spectral bandpower processor. Stimulation should be designed taking care of sampling rate and stimulation frequency, trying to minimize the interference. Furthermore a suitable detection algorithm should be implemented for classification between stimulation signal and signal of interest, e.g. through Support Vector Machines (SVMs) [3].

III. Clinical Trial and Results

For this Section we decided to focus on the paper by Little S. et al. [4] being one of the most complete and precise works found in literature. The authors proposed a comparison among an adaptive DBS (aDBS), a continuous DBS (cDBS) and a random DBS (rDBS), the latter one in order to exclude the possibility that intermittency itself was the factor that influenciates the results of aDBS.

A. Patients and Methods

In the mentioned study, the authors analyzed aDBS, cDBS and rDBS in 8 PD patients (also referred to as *cases*) with severe dysfunctions as motor fluctuations and/or dyskinesias, as described in Table I.

Patients underwent DBS surgery to get the electrodes be implanted on the *subthalamic nucleus* (STN) as described in [21].

Each patient defined a case and has different parameters such as age, disease duration, Unified Parkinson's Disease Rating Scale (UPDRS) on and off stimulation, DBS indications and the most meaningful stimulation parameters of the implanted technology.

The correct locations of the permanent quadripolar macroelectrode were then confirmed with post-operative fast spin-echo T2-weighted magnetic resonance imaging (MRI) and Computed Tomography (CT).

The experiment performed was set in phases, the first of which required to record bipolar LFP activity of the electrodes in the STN after overnight withdrawal of antiparkinsonian medication. This procedure was carried out before the final surgical intervention in order to establish the correct electrodes placement.

Patients were clinically tested off stimulation through cDBS, aDBS and random bursts of stimulation not triggered by beta amplitude rise (rDBS). In this study the authors used a random approach to assign every experimental conditions to each patients.
About 5 minutes rest without stimulation was given before each experimental condition being provided. Thus the mean amplitude threshold for triggering stimulation was set to $3.9 \pm 3.8\%$ above the mean beta amplitude of the LFP, which corresponds to a peak-to-peak amplitude of the beta filtered signal of 2.6 ± 0.6 μV.
The mean duration at rest of aDBS, cDBS and random blocks was respectively 629 ± 102 s, 640 ± 143 s, 507 ± 37 s and 512 ± 32 s and 300 s occurs to assess clinical parameters in each condition.

B. Experimental Setup

An important role in DBS studies is played by the new technologies supported by the Neurologic Division of Medtronic (Minneapolis, MN). Little et. al., indeed, used a permanent quadripolar macroelectrode (model 3389) featuring 4 platinum-iridium cylindrical surfaces, which contacts were numbered between 0 to 3 from the most caudal position they represent to the most cranial one.

The scenario we are about to describe is shown in Figure 1 where the main blocks are highlighted.

The LFPs were acquired from the contacts 0-2 and 1-3, then the first block (*StimRecord Amp* in Figure) performs on those signals a band-pass filtering in the frequency range $[3 - 37]$ Hz and an amplification of a factor $(\mathrm{X}9, 100)$ using a 3-stage common mode rejection amplifier. This operation allowed to record a robust signal of beta oscillations from the STN, which have been proven to correlate with motor tasks, as already mentioned [17].

The choice of the optimal pair of contacts of the macroelectrode (either 0-2 or 1-3) has been made by estimating which pair reaches the greater beta amplitude in patients at rest, unstimulated and off medication. After this procedure the frequency of the beta peak can be determined through the frequency spectrum of the LFP relative to the selected bipole and the signal is then filtered in real time around this values.

On the other hand, they test the goodness of adaptive stimulation effects and benefits by implementing also a continuous DBS (cDBS) at high frequency (130 Hz). This allows to discover the correct voltage for the stimulation. The selected contact for the stimulation is assigned on the basis of the bipolar ones used in the previous phase (contact 1 if pair 0-2 had been previously chosen, 2 if 1-3).

Stimulation started at 0.5 V and increased by 0.5 V every 3 to 4 minutes until clinical benefits were seen and as long as no side effects were shown by the patient, such as paresthesia or excessive increased heartbeat. This voltage was fixed across subsequent test conditions and the stimulation trigger threshold was heuristically determined based on the best achieved reduction of stimulation time while maintaining the majority of visible clinical benefits.

The analog output recorded and amplified in the first block was then passed to a low-cost data acquisition unit (model 1401) which converts it into a digital signal, subsequently displayed on a portable computer using *Spike2* software interface, both provided by *Cambridge Electronic Design* (CED), Cambridge, UK.

This software is also responsible for the digital filtering and thresholding of the LFPs as described in the following. LFPs were rectified and smoothed using a moving average (MA) filter of 400 ms that provides an online value of beta amplitude and allows to control triggering stimulation via a user-defined threshold selected by an external portable device. The trigger output was passed via an opto-isolated input to the stimulator and, although the time for the stimulation to cross the threshold depends on LFP amplitude, the perceived delay from the crossing event and the start of stimulation has been fixed from 30 to 40 ms.

The third block of the experimental setup consists of an ad-hoc custom-built stimulator device battery-powered (± 9) V which uses an embedded microprocessor and a digital-to-analog converter (DAC) for stimulation control, delivering as output a biphasic charge balanced symmetrical pulse waveform with no nominal distortion at 0.5 kΩ and linear input-output voltage function. To provide a higher level of safety during this process the stimulator provided a continuous readout of the stimulation voltage: the harmful charge densities were constrained below 30 μ Q/cm^2 and the DC currents were blocked with a DC-blocking capacitor. All connec-

tions to the patient were required to be optically isolated, following EN60601-1 for medical safety standard rules [22].

Stimulation, once triggered by bursts of variable-duration beta peaks, was sustained until beta amplitude fell below the selected threshold and was delivered monopolarly at 130 Hz with a pulse duration of 100 μs after being ramped up and down over 250 ms onset and offset, in order to avoid typical paresthesias switching on and off the stimulation.

C. Results

The main results of such a stimulation device (aDBS) are presented and briefly discussed in this Section.
First let's mention that physiological analysis were performed in Matlab via wavelet convolution, statistical analysis were conducted with SPSS Statistics and clinical data were normally distributed. Hence mean, standard error of the mean (defined as $\mathrm{SEM} = \sigma/\sqrt{N}$, being σ the standard deviation and N the size of the sample space, 8 in the considered case) and parametric statistic analysis (p) are shown as last rows of Table I.

Combining both blinded and unblinded UPDRS clear benefits of mean reduction in motor scores have been shown of about 58% for aDBS, 42.5% for cDBS and 20.2% for rDBS. This already proves that intermittent stimulation not based on beta bursts is not very effective. Indeed, the study also contributes at proving that motor deficits have their counterpart effect in the beta synchronization.

Then the total electrical energy delivered per unit time assuming 0.5 kΩ was calculated. The aDBS delivered 132 ± 21 μW, which is much less than cDBS 270 ± 7 μW.
On-time period was $44.2 \pm 2.4\%$ of the time for aDBS, well matched by $43.3 \pm 1.5\%$ of the time for rDBS. Also it is noticeable that on-time periods tend to progressively drop during aDBS because beta bursts tend to become less frequent in this mode.
Thus aDBS revealed to be more clinically effective than other traditional techniques, by lowering the side effects and the battery-lifetime of the implanted system. More in detail considering the mean decrease in total electrical energy delivered together with the requirements of the low-energy circuits for the feedback-controlled stimulation and the ramping system, the battery life resulted to be doubled from about 4 years of cDBS to 8 years of aDBS. This also allows to limit the number of surgical interventions thus reducing risks and costs (both hardware and clinical), and improving at the same time the patients quality of life since they are subject to less complete anesthesias and less side effects.

In addition these results were confirmed by Temperli et. al. studies [24], which showed that the change in tremor, rigidity and bradykinesia following the onset or offset of STN DBS follows an approximately exponential course. They inquired the sequential pattern of return of parkinsonian signs, highlighting the worsening trend of symptons like tremor (within minutes), bradykinesia and rigidity (over half an hour to an hour), axial signs (few hours), until the 90% of the UPDRS motor score worsening was reached (after about 2 hours). The important discovery was made switching STN DBS "on" again when all motor UPDRS subscores improved with a similar pattern, but faster than their rate of worsening, especially for axial signs.

All the provided results also suggest that the LFP signal directly acquired from STN is robust and also allowed simultaneous sensing and high-frequency stimulation.

IV. Conclusions and Future Work

The aDBS device discussed in this paper addresses many challenges and critical issues of the traditional devices. Overall aDBS is able to have significantly high clinical improvements (and could be even greater if longer periods are considered) and simultaneously significantly reduce the stimulation time and the power consumption. This allows to double the battery-lifetime and also likely reflects into a reduction of side effects.
Moreover the paper by Little et. al. [4] could also be considered as a proof-of-concept that the LFP signal is an effective biomarker robust over time and can also be acquired from the same site of stimulation, thus the surgical procedure has not been complicated using aDBS because a single brain target is still used.

In a more general view many open issues are still present because the problem is very complex and any setting can be tuned with many parameters. New techniques should aim at minimizing risks for the patients while optimizing the physiological marker or changes to detect for every specific symptom and locating the anatomical target where to sense and stimulate in response to those detected events. Moreover the level of smoothing to be applied to the beta activity and the on-stimulation time remain to be optimized. The applied algorithms should be real-time, lightweight but complex enough. The optogenetic technique is very promising allowing to select activation of neurons using light rather than

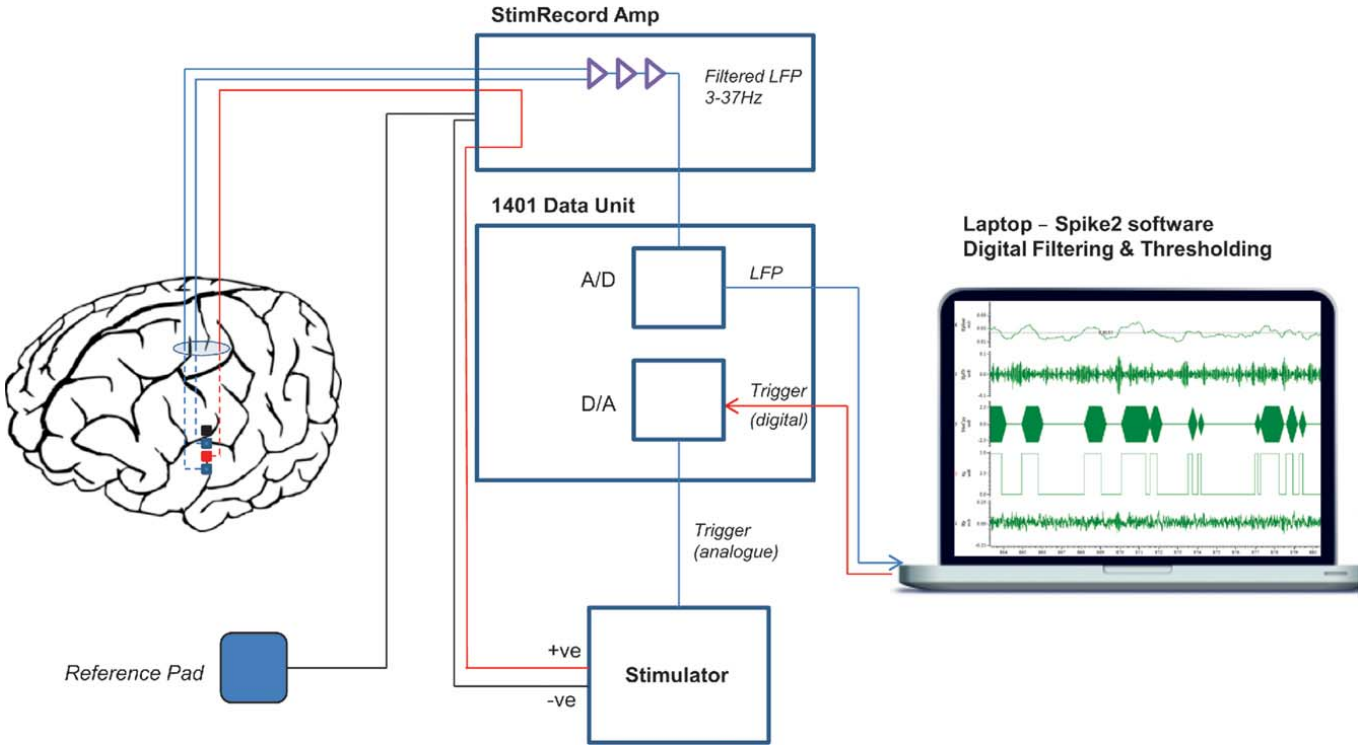

Figure 1. Experimental scenario of [4], similar setup also in [23].

	Age - Disease Duration (yr)	UPDRS		DBS Indications	Online Filter Range (Hz)	Stimulation			Time on Stimulation %		Time between Stimulation Bursts (s)	
		Off	On			V	Site	Contact	aDBS	Random	aDBS	Random
Case1	59 - 12	42	20	On/Off fluctuations, tremor bradykinesia	16 - 22	2.7	L	1	44.2	44.5	1.09	1.19
Case2	62 - 10	20	8	On/Off fluctuations, tremor	19 - 25	1.8	R	1	35.5	34.1	0.64	0.75
Case3	67 - 7	43	14	On/Off fluctuations, dyskinesias	23 - 29	1.8	R	2	43.4	42.6	0.47	0.69
Case4	49 - 10	42	6	Tremor	17 - 24	1.6	L	2	46.4	46.5	0.45	0.50
Case5	49 - 10	58	23	On/Off fluctuations, tremor	16 - 18	2.1	L	1	42.1	45.2	0.94	0.86
Case6	63 - 3	18	8	Tremor/Bradykinesia	28 - 34	2.6	R	1	57.7	45.8	0.73	0.64
Case7	67 - 14	63	24	On/Off fluctuations	17 - 22	2.4	R	2	37.1	40.8	0.64	0.65
Case8	57 - 8	43	17	Severe Off periods, On/Off fluctuations	16 - 20	2.7	R	1	47.6	46.7	1.75	1.53
Mean	59.1 - 9.4	41.1	15		22	2.1			44.3	43.3	0.84	0.85
SEM	2.5 - 1.3	5.6	2.5		1.8	0.2			2.4	1.5	0.2	0.1
p										0.58		0.81

Table I
CLINICAL AND STIMULATION DETAILS, TAKEN AND REARRANGED FROM [4].

electricity [25]. The applicability of those devices should be possibly extended to other neurological disorders.

Finally, for sure the gain in term of efficiency and efficacy can be deeply improved over time also providing a multiple LFP-based mechanism or a multiple biomarker selection to track medical state and implementing a

more specific setting for each subject based on personal parameters of the patients and on their pathological rhythms of dysfunction.

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