Option to Provide the Necessary Feedback for Closed-Loop neuroStimulation

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Abstract — Recent developments in Deep Brain Stimulation (DBS) and computer technology have resulted in dramatically new and effective surgical treatments for Parkinson's disease and other movement disorders. From the DBS, by research, the concept has evolved to Closed-Loop neuroStimulation (CLnS) which is the brain target point electric stimulation linked to the patient's body and brain response.

One delicate CLnS difficulty in rising concept functionality is contoured by the need of a feedback source.

Regarding Parkinson's disease, the Subthalamic Nucleus (at target point) generates a modulated signal by Parkinson's tremor. The amplitude values of the modulated signal envelope are far most variable during the day.

By neurostimulating with a signal linked to the differences between maximum and minimum values of modulated signal envelope provided, the patient will receive the exact values required for Parkinson symptoms suppression.

Index Terms — Biomedical measurements, Closed-Loop neuroStimulation, Deep Brain Stimulation, DBS process, Neurostimulation

I. INTRODUCTION

Parkinson's disease is a progressive brain disorder characterized by tremor, muscular rigidity and slowness of movement (bradykinesia). Around 1945’s, the surgery treatment has came to be a very good version characteristic of Parkinson symptoms suppression.

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Recent developments in DBS and computer technology have resulted in dramatically new and effective surgical treatments for Parkinson's disease and other movement disorders. From the DBS, by research, the concept has evolved to Closed-Loop neuroStimulation (CLnS). This new CLnS concept is a highly active research area in neuromodulation science.

Still, DBS is the base application that lies below the CLnS, that safely and effectively manages some of the most disabling motor symptoms of Parkinson's disease, Essential Tremor, Dystonias and Epilepsy.

DBS concept is defined as a medical device needed to be surgically implanted, aiming to provide highly controlled electrical signals and those transmissions to the brain. The electrically stimulation is accomplished towards certain brain structures that control muscular activity. For Parkinson's disease, those structures are the STN or GPi. Symptoms avoidance should occur by neurostimulation at amplitudes between 1 and 4V, pulse widths of 60 to 120μsec, and rates of 130 to 180Hz.

The CLnS concept of integrating the stimulator into the natural regulation system, instead of mimicking the behavior, is expected to yield various clinical benefits.

In Parkinson's disease case, the closed-loop stimulation process starts by implantation of an electrodes array (2 to 5 unipolar/bipolar/quadripolar leads) that is intended to strongly localize the final target.

The implantation of the leads requires stereotactic neurosurgical techniques for the initial implant and ongoing postoperative patient supervision.

Stereotactic surgery or stereotaxy is a minimally-invasive form of surgical intervention that makes use of a three-dimensional coordinates system to locate small targets inside the body and to perform on them actions such as...
ablation (removal), biopsy, stimulation, implantation, radiosurgery (SRS) etc.

The three dimensions are latero-lateral (x), dorso-ventral (y) and rostro-caudal (z).

This technique uses images of the brain to guide the surgeon to a target within the brain. A colorful term for this surgery is neuro-navigation. An external frame attached to the head (frame-based) or imaging markers attached to the scalp (frameless or image-guided surgery) are being used to orient the surgeon in his approach (Fig. 1, San Diego, Neurosurgical Medical Clinic, Inc.).

Figure 1. Stereotactic frame-based, patient's fixation - left image, lead track positioning - right image.

Target localization for stereotactic implantation of the DBS lead is performed with the use of CT and/or MRI scans. For further localization of the target, test stimulation or mapping electrode may be used afterwards. Neurosurgeons who use microelectrode recording in stimulation techniques may choose commercially available microelectrodes such as Medtronic, Radionics, MicroNeurode, FHC and microTargeting electrodes. Even on its benefits, it must also be taken into consideration that it is not recommended for the DBS lead to be used for mapping.

II. BACKGROUND

There are three commonly used surgical techniques for motor diseases:

a) Ablation surgery is the minimally invasive mechanical unwished tissue removal. Represents the medical procedure that neutralizes and eliminates the harmful tissue making use of laser or high radio frequencies causing heat, coagulation and tissue death. Failure tissue removal procedure will cause infection.

b) Deep brain stimulation offers many advantages against ablative technique. The procedure is also minimally invasive and there is no tissue removal. The afterwards body response may be modified considering that this technique is based on an electronic stimulator system implant with subsequent control. Bilateral STN stimulation can give the maximum desired effect with minimal side effects, opposite bilateral thalamus ablation which may cause undesirable results.

c) Gamma Knife is a non-invasive technique that uses radiation to brain treatment and is often called radiosurgery. The device aims gamma radiation focus directly through a target point.

The present case study is DBS leading to CLnS, the two concepts will be individually detailed to reveal elements and conclusions throughout this research.

A. Indications.

Bilateral brain neurostimulation is a Parkinson’s control therapy if the tremor together with all disease symptoms are an advanced daily events disability problems and work life limitation. The GPi or the STN is the target for this process.

Stimulation may also be considered as ancillary or compensatory option against patient inadequate drug treatment response of L-dopa, also adding the unwanted appearance of body habits joined with raising medication dose levels.

Unilateral thalamic neurostimulation is indicated for the upper area body tremor avoidance. This course is chosen for patients who were diagnosed with Parkinsonian tremor or Essential Tremor.

B. Contraindications.

Diathermy exposure (use of high-frequency electric current for deep heating of tissues in physical therapy, all now referred to as diathermy). Shortwave, ultrasound and microwave diathermy will heat the tissues at different depths for different purposes. These may cause molecules in deep tissue to vibrate, heating the tissues and increasing blood flow to them. Low heat warms tissue and higher degrees will destroy tissue. Further, the diathermy therapy becomes energy conveyance to the implanted system, causing tissue damage to implanted electrodes area, leading to serious trauma until death. Diathermy exposure it is also restricted causing additional neurostimulation system components failure, forcing a new surgery to replace them, reducing the proper evolution of the patient. Injury of patient and/or implanted system can occur during diathermy exposure whether the neurostimulation system is running or not.

Magnetic Resonance Imaging (MRI) on the upper patient’s body area wherein the impulse generator is usually located, advancing to brain where the lead electrodes are implanted.

Transcranial magnetic stimulation (TMS) is also a restricted medical application.

CLnS is not recommended for (Medtronic, et al.):

- patients with neurological disease origins other than idiopathic;
- patients with a previous surgical ablation procedure;
- patients under 18 years age;
- patients beyond 75 years age;
- patients with dementia, coagulopathies, other psychiatric or neurologic disorders, including but not limited to Tourette syndrome, depression, obsessive compulsive disorder.

C. Location of stimulation.

For Parkinson’s disease, stimulation settings for leads implanted in the GPi may be higher than stimulation settings for systems implanted in the Subthalamic Nucleus (STN). Consequently, systems implanted in the GPi may have shorter battery life than systems implanted in the STN.\(^3\)

Target sites for Tremor Control Therapy and Parkinson’s

\(^3\) Clinical studies in neurostimulation for advanced Parkinson’s disease, at least 58% of all subjects had identical rates bilaterally at all follow-up visits.
Control Therapy include the ventral intermediate nucleus of the thalamus (Vim), and the STN or the GPI respectively.

For further highlighting of Parkinson's disease brain areas, table 1 below (Medtronic, 2008) offers target sites and indication related.

<table>
<thead>
<tr>
<th>Target Site</th>
<th>Indication</th>
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<tbody>
<tr>
<td>STN/GPi</td>
<td>Bilateral stimulation of the GPI or the STN is indicated for adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson’s disease that are not adequately controlled with medication.</td>
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<tr>
<td>Vim</td>
<td>Unilateral thalamic stimulation is indicated for the suppression of tremor in the upper extremity. The system is intended for use in patients who are diagnosed with Essential Tremor or Parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability.</td>
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If the Vim is the targeted nucleus, the desired stimulation effect is an obvious suppression of tremor. Other stimulation effects that may aid in placement of the lead, but may not be desirable, include paresthesia, especially in the hand and around the mouth (Medtronic, et al. 2008).

III. OUTCOME OF COMPETITION

For more than a decade, doctors have been implanting devices called deep-brain stimulators into patients with Parkinson’s disease and stimulating a small area of their brains with low-voltage electrical pulses.

The devices electrically stimulate the GPi or STN, a structure deep inside the brain, through four electrodes (Morgen E. Peck, et al. 2008). When electrical impulses hit the targeted cells, the tremors associated with Parkinson’s disease subside.

There are three hypotheses to explain the mechanisms of DBS:

- Depolarization blockade. Electrical currents block the neuronal output at or near the electrode site;
- Synaptic inhibition. This causes an indirect regulation of the neuronal output by activating axon terminals with synaptic connections to neurons near the stimulating electrode;
- De-synchronization of abnormal oscillatory activity of neurons.

However, the quality of treatment greatly depends on how well surgeons implant these electrodes. A misplaced lead could stimulate surrounding tissue and cause changes in the patient’s mood and cognition.

Such a positioning error was recently found to be a leading cause of the therapy’s failure. Even with a perfect implant (Fig. 2, M. Cook, 2009), patients have only one control parameter: open-loop device "on " or "off ."

Afer days to weeks, after implantation, the stimulator is programmed using a small computer which communicates with the implanted stimulator by an external antenna. Usually several hours of programming are needed, requiring close cooperation of the neurologist or neurophysiologist, with the patient and family.

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So what we have (Fig. 3) is an inflexible system that is trying to control a highly variable as the brain like it is a plastic organ.

IV. DATA SETS AND SELF-REGULATION OF CLOSED-LOOP NEUROSTIMULATION

Leads are implanted as in DBS lead implanting procedure, using frame-based stereotactic surgery, a lightweight frame that is attached to the patient's head using local anesthesia. The head is CT and/or MRI4 scanned to identify the target area in relationship with the external frame.

Since both the frame-based and the target area are "seen" in the images, the distance of the target from reference points on the frame-based can be measured in three dimensions. Surgical apparatus attached to the head frame-based can be adjusted to the 3D coordinates of the target, and can be accurately approached by the surgeon (Fig. 1).

For an accurate approach a CT and MRI image fusion is also needed. This fusion is required to be made due to the difference of resolution and information density that can be

4 The use of MRI is done before the CLnS system implantation, MRI procedures being necessary for stereotaxy. After implantation, as 2.1 b) mentioned, MRI will not be allowed.
The CT scan is the best procedure to use when visualizing bones or cancer, while the MRI is best used when examining the ligaments, tendons, tumors, blood vessels or hemorrhages. Since MRI yields more contrast than CT, when differentiating the bone, cartilages and the soft tissues, it will give more precise delineation of normal critical structures and more accurate definition of tissue volumes.

Knowing that almost all types of tissue are present in the patient’s head, both CT and MRI scans are recommended. The fusion between them is the ideal way to localize target with equally important aspect of defining the lead track for to reach the target point.

In order to improve the route to the target point, two other coordinates are established in the calculation resulted from CT and MRI fusion, namely ARC and RING. These two coordinates express the amount of coronal and sagittal arc, giving surgeon a safe and accurate advance of the lead electrodes to the target, without crossing certain brain volumes and by avoiding intersection with any blood vessels.

However we must have consideration that imaging data from MRI introduces some geometric distortion because all magnetic fields possess inhomogeneities of the main field and non-linearities of magnetic field gradients and current effects. In general, system distortion is particularly important for larger fields of view as this distortion tends to increase with growing distance from the centre of the magnet. Also MRI does not provide the necessary geometric accuracy and physical information required in CT based 3D treatment planning systems, such as electron density of body tissues. Nor can MR image complex bone/air heterogeneity. This information is essential for patient dose calculation and for designing compensators and modulators to shape the beam profile. Therefore, the unique information provided by MRI studies must be registered to and then integrated with CT treatment planning data set (e.g. G. Sannazzari, 2002).

Physicians must take into account that fusion of the two CT and MRI images offers all necessary data regarding target location as well as the lead route to target point, therefore, the corporate researchers have build a dedicated software program for this issue.

Giving attention to inner stimulating system, looking into the past, there’s been only one way to tell how patients are taking to the treatment: by monitoring behavior outcomes. But a better way to evaluate treatment is to ask the brain giving attention to inner stimulating system, looking into the past, there’s been only one way to tell how patients are taking to the treatment: by monitoring behavior outcomes. But a better way to evaluate treatment is to ask the brain activity which can provide the data necessary to adjust the new signal values of stimulation.

A system that integrates neural recordings from implanted electrodes for DBS, and uses it to program the amplitude, repetition rate, and duration of pulse generation of the CLnS stimulator. Another goal is to have a final component of the design, including the amplifier that connects to the implanted electrodes, the data circuits, digital filters and microprocessor that decides if, how, and when to stimulate.

The technical system designed by several neural engineers (Fig. 5) must have a feedback from the brain activity which can provide the data necessary to adjust the new signal values of stimulation.

In general, closed-loop control is preferred over open-loop control for both physiological and technological reasons. For example, there is a highly nonlinear relationship between the open-loop stimulation parameters and the resulting behavior produced by stimulating.

Moreover, the relationship between electrical stimulation and the resulting patient's adaptive reaction is a time-dependent relationship. In open-loop systems the patient must visually monitor the body changes produced by the stimulation and adjust the command signal accordingly, but making these adjustments is both difficult and tedious. With closed-loop feedback control however, the relationship between the input and output parameters can be automatically regulated to provide a linear relationship and to compensate for those effects which vary over time.

The biggest problem is precisely this aspect. To close the circuit and make the whole system work according to the patients’ feedback. Several ideas have been studied and discussed (e.g. Neural Interfaces Workshop, Bethesda, 2005), bottom-line being feedback control system that was not only if acceptance has been given by the physician in order to adjust the patient’s stimulator actions/parameters.

Only if the DBS system manufacturer provides patient's directly parameters adjustments.
identified as one of the major challenges confronting the DBS industry in years to come.

Knowing that one of the means to detect the target point is associated with signal analysis obtained during electrode advancing to target point, its path must be a way to get information on what interests us.

We must consider that the implanted leads normally used for DBS implant are in contact with the target point. In surgery, one of the ways to know that the target point is reached is to monitor the signal collected from the implanted lead. The entire lead implantation process is made with a micromotor device added to patient's head mounted stereotactic frame-based and carefully physician's real time signal monitoring during lead advance. The signal of the lead on the way to target point is a linear sampled signal which does not give any dates on the patient's Parkinson's disease or his condition regarding this issue.

Exact time of arrival of the lead on target point forces dissimilar signal receiving unlike any up to that moment. The STN gave forth a modulated signal in 90 up to 95% of the cases a modulated signal. Having the lead to target point, the signal provided by it can be used as feedback information to functionally close the CLnS system.

The carrier signal can difference between 200Hz to surprisingly high frequencies around 300Hz. This signal is modulated in amplitude by Parkinson's tremor frequency. The modulation signal (i.e. Parkinson's tremor) has mostly 3Hz to 6Hz frequency value, with occasionally peak to 7-8Hz.

If the carrier signal modulated by Parkinson's tremor signal is converted to an envelope signal, we can easily further obtain the minimum and maximum values of the modulation amplitude.

The amplitude values of the modulated signal envelope are variable during the day, related to patient's psychological condition and its body composition given by nutrition, temperature, etc. The STN signal provided through the lead electrodes is shown below, in Figure 6.

Giving the fact that the difference of maximum and minimum amplitude value is variable, this variation is the key required to adapt the stimulation signal parameters on CLnS in reaction to patient's brain response.

Closed-Loop neuroStimulation concept is the ideal solution, but having present research treated irregular aspect. The elementary source of feedback information from the body that may be part of this wonderful neuro solution, responds to the entire package of variables. Regarding this option to provide the necessary parameters for CLnS, the technical system can give maximum applied efficiency as intended.

Using as feedback source the modulated carrier signal envelope, the information provided by it can be used as functionality feedback to successfully close the CLnS system.

VI. BENEFITS

It eliminates the patient interaction with the neurostimulation control system.

It prevents adverse reactions and bad condition of the patient when the neurostimulator generates same linearly identical values when the disease has temporarily fallen reactions.

It gives an optimal stimulation closely connected to the patient's brain response.

It avoids the potential risk of brain tissue damage by stimulation parameter settings of high amplitudes and wide pulse widths.

It prolongs battery longevity of the impulse generator; etc.

VII. ADDITIONAL COMMENTS / REMARKS

7.1 Regarding neurosurgeons implanting activity, the CLnS impulse generator (pacemaker) must be implanted away from bony structures and muscle tissue to minimize pain at the pacemaker site. This also helps to minimize the possibility of skeletal muscle stimulation. For connections, the surgeon has to wipe off any body fluids on the extension or lead contacts or connector before connecting. Contamination of connections can cause intermittent stimulation or shorts in the neurostimulation circuit (Medtronic, Soletra, 2003).

7.2 High frequency test stimulation is a standard procedure for target localization in deep brain stimulation treatments of patients with tremor. However, this method does not work in cases where the tremor disappears under global anesthesia as well as it is used during insertion of an electrode. To avoid this problem a new stimulation technique has been developed that evokes tremor in a well-defined manner even when the patient is under anesthesia. This technique uses patterned low-frequency stimulation in the form of brief high-frequency pulse trains applied at pulse rates similar to typical neuronal burst frequencies. This makes it possible to attain higher charge densities in the target area without violating safety criteria. Numerical simulations of a network of interacting neurons have shown that patterned low-frequency stimulation can synchronize the cells in a mode that is phase-locked to the stimulation pulse. When subsequently applying this approach to patients with pronounced tremor, the results were found to be in accordance with the mathematical calculations, and the target selection was confirmed by excellent postoperative tremor suppression (BioSim Group at the Jülich Research Centre, Aug. 2009).
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REFERENCES


