ELECTROPHYSIOLOGICAL SIGNAL PROCESSING FOR INTRAOPERATIVE LOCALIZATION OF SUBTHALAMIC NUCLEUS DURING DEEP BRAIN STIMULATION SURGERY

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ABSTRACT

In this paper, a novel technique is proposed for localization of Subthalamic Nucleus (STN) during deep brain stimulation (DBS) Surgery. DBS surgery is performed on individuals living with Parkinson's disease (PD) to permanently implant stimulation electrodes for managing some motor symptoms of PD. The most challenging part of this surgery is to accurately place the electrodes inside the STN. Commonly, microelectrode recordings (MERs) are interpreted by the surgical team intraoperatively to estimate the location of electrodes and detect the borders of the STN. In this work, we aim to automate the process of localizing the STN using a machine learning technique (trained based on the electrophysiological signals that we have collected during 20 surgeries). The proposed approach is capable of detecting the dorsal borders of the STN during the procedure with high accuracy (85%), and outperforms the current state-of-the-art approach for this application.

Index Terms— Electrophysiological Signal Processing, supervised machine learning, STN localization, DBS surgery, Parkinson's disease.

1. INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder [1]. PD is caused by deficiency of dopamine in substantia nigra pars compacta of the basal ganglia (BG). Motor symptomatology includes: tremor, rigidity, bradykinesia, and postured instability [2]. Deep brain stimulation (DBS) has been used in severe cases to alleviate these symptoms. The most common surgical target is the Subthalamic Nucleus (STN) of the BG. DBS surgery involves permanent implantation of therapeutic electrodes that deliver electrical current to the motor region of the STN [3]. The motor region of the STN is a very small target and the surgical outcome depends highly on the accuracy of the therapeutic electrodes. Sub-optimal positioning of DBS electrodes accounts for 40% of cases of inadequate efficacy of stimulation post operation [4]. Localizing the borders of STN for accurate placement of electrodes is a challenging, time consuming and sensitive surgical task [5]. Preoperative Magnetic Resonance Imaging (MRI) is the most common modality which has been used to plan the insertion trajectory of the electrodes [6]. Generally, five microelectrodes are inserted and lowered into the STN through a burr hole in the skull. The target is planned for the center of the STN using preoperative MRI. The final stage, prior to implantation of the therapeutic electrode, involves selecting which microelectrode is positioned most optimally within the STN. Most centers do not have the technology required to capture intraoperative images and they rely on interpretation of the MERs. Disparate electro-physiological activities exist between different brain structures, which is utilized when interpreting the MER data [6, 7]. Currently, neurosurgeons monitor the raw neural spikes to determine the microelectrodes that entered the STN and at which depth.

This study presents a novel intraoperative learning algorithm to assist the neurosurgeon in determining the optimal placement of electrodes. This has the potential to (a) save time during the surgery, and (b) enhance the accuracy of electrode placement which directly enhances the quality of treatment. Over the past few years, researchers have tried to find the signature of STN using MER signals. The most significant criteria of STN are the increase in spike firing rate and changes in the spike firing patterns [8]. The state-of-the-art techniques have

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been reported in [9, 10, 11]. In this regard, [9] has suggested thirteen MER features to identify the dorsal border of the STN using an unsupervised machine learning algorithm. This work was completed in 2015 with the development of a new feature selection and normalization method that is based on the previously-suggested thirteen features [11]. In [11], ten out of the thirteen features were suggested as the best features to use in the classification problem. In addition, in the literature, four classifiers are evaluated in [11]; among them the Logistic Regression (LR) algorithm is reported as the most accurate scheme. In addition to the above, in [10], four features are selected from [9], and a Support Vector Machine (SVM) technique is used as the classifier. Although in [11] and [10], high accuracy is reported for classifying the STN based on a specific data set, the technique was not designed to be used in an intraoperative manner. In this regard, it should be mentioned that for calculation of the features designed in [11], information about the whole insertion trajectory is required. Thus, the algorithm in [11] and [10] can be used as a postoperative validation method. However, it cannot guide the neurosurgeon during the DBS surgical procedure. In order to address the above-mentioned issue, in this paper we present a new method of feature selection using a Fourier transform that can be extracted from the MER signals in an intraoperative manner. The Fourier transform has been widely used in the literature to extract features from brain signals. To evaluate the performance of the proposed technique, in comparison to the most recent accurate existing methods in the literature (published in [11]) we have conducted a retrospective clinical study. In the study, we extracted MER signals from 20 patients with PD who had previously undergone the DBS procedure. The data was collected during DBS surgeries performed in University Hospital, London, ON, Canada. To conduct the comparison, the ten best features (which need to be calculated in a postoperative manner) proposed in [11] have been calculated and used to implement the method proposed in [11] based on the LR algorithm. The performance of the method proposed in this paper is also evaluated based on the collected clinical data. The results of the comparative study, support the effectiveness of the designed technique in comparison to the existing methods in the literature. It has been shown that the method proposed in this paper significantly improved the accuracy of STN localization while using MER features that can be collected during surgery intraoperatively. As a result, the proposed technique has the potential to be used in the operating room for assisting neurosurgeons, while reducing the operating time.

2. METHODS AND MATERIALS

2.1. Demographic Data and Data Acquisition

In this study, we used MER signals from 20 PD patients who had previously undergone DBS implantation. The average age was 59 ± 8 (13 male and 7 female). Most of the patients have 5 implanted microelectrodes bilaterally. The patient data was collected at University Hospital in London, ON, Canada. The study was approved by the Human Subject Research Ethics Board (HSREB) office at the University of Western Ontario. A preoperative MRI was obtained to determine the coordinates of the Anterior Commissure (AC), Posterior Commissure (PC) and the STN using an axial T2-weighted image (Signa, 1.5T, General Electric, Milwaukee, Wis). The center of the STN was used as the surgical zero-point. Following stereotactic placement of the surgical Leksell frame on the patients' head (Elekta instruments, Sweden), a stereotactic CT was obtained and fused with the preoperative MRIs (StealthStation, Medtronic Corp, MN). In the operating room, a burr hole was drilled just anterior to the coronal suture. The dura mater was opened and the pial surface was coagulated. The Leksell arc was attached to the head frame and set to the planned coordinates. The StarDrive (FHC Inc., Bowdoinham, ME) was mounted at 30.0 mm above the surgical target and 5 cannulas with stylets were lowered to 10.0 mm above the target. The stylets were then removed and five 60 μm diameter tungsten microelectrodes were inserted with an impedance of 0.5-1.0 $m\Omega$ at 1kHz (FHC Inc., Bowdoinham, ME). Fig.1 is the MRI image of post-operation which shows electrodes and their trajectories inside the brain. Signals were recorded from 10.0 mm above the preoperatively determined target to well below the ventral border of the STN, generally looking for activity indicative of the substantia nigra (4.0 - 5.0 mm below the zero-point). The advancement of the microelectrode unit was performed with a computer-controlled motor drive (FHC Inc., Bowdoinham, ME). The microelectrodes were advanced in 1.0 mm increments from 10.0 mm to 5.0 mm above the target. From 5.0 mm to the end of the trajectory the microelectrodes were advanced in 0.5 mm increments. At each depth, advancement was paused to allow any drive or neural artifact to be resolved. Once a clean recording was visualized a 10 second recording was collected prior to advancing the microelectrodes further. The signals were sampled (24kHz, 8-bit), amplified (gain: 10000) and digitally filtered (bandpass: 500-5000 Hz, notch: 60 Hz) with the Leadpoint recording station (Leadpoint 5, Medtronic). A sample MER signal from a right-side anterior trajectory is shown in Fig.2 . This figure demonstrates the difference in electrophysiological signal inside and outside of the STN.

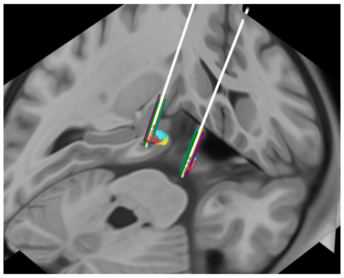

Fig. 1. DBS electrode reconstruction and microelectrode trajectory inside brain (T2-weighted preoperative MRI was co-registered to postoperative T1-weighted MRI).

2.2. Feature Extraction: State-of-the-art Technique

To compare the performance of the technique proposed in this paper with that of previous studies, we have extracted the most effective ten state-of-the-art features reported in [9], [11], and [10]. A list of the these features for one 10-second interval is given below (the definitions are taken from [11, 10]):

1) Number of spikes per the 10-second interval;
2) Standard deviation of time differences between the spikes of the 10-second interval;
3) Pause index: the ratio between the number of spikes greater than 50 ms to the number of spikes less than 50 ms;
4) Pause ratio: the ratio between the total time of inter spike intervals greater than 50ms to the total time of those less than 50ms;
5) Root Mean Square (RMS) value of the signal amplitude in the 10-second interval;
6) Spiking rate: number of spikes per unit time.
7) Teager Energy, which can be calculated as follows:

$$E = \sum_{i=2}^{N-1} x_i^2 - x_{i-1}x_{i+1}; \tag{1}$$

where, $x_i \in X = \{x_1, x_2 .....x_n\}$ and N is the number of samples in each signal;

8) Zero crossing: the number of zero crossings in each interval;
9) Curve length: the sum of consecutive distances between points in the 10-second interval

$$L = \sum_{i=1}^{N-1} |x_{i+1} - x_i| \tag{2}$$

10) Threshold (γ):

$$\gamma = \frac{3}{N-1}\sqrt{\sum_{i=1}^{N}(x_i - \bar{X})} \tag{3}$$

where $\bar{X}$ is the average of the 10(s) time interval.

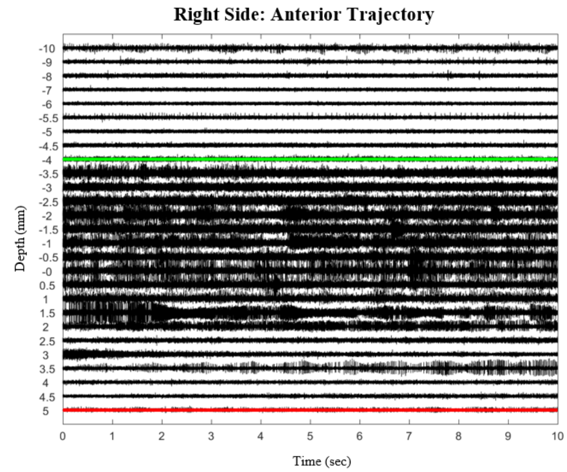

Fig. 2. MER trace from an anterior microelectrode trajectory from a STN-DBS case at University Hospital. The microelectrodes advance from 10.0 mm to 5.0 mm in 1.0 mm intervals. From 5.0 mm to the end of the trajectory the unit is advanced in 0.5 mm increments. The green line indicates the dorsal border of the STN and the red line indicates the ventral border of the STN, as decided by the neurosurgeon.

It is important to note that the technique proposed in [9] and the improved version of it reported in [11], require a specifically-designed normalization and standardization process before classification. This is due to the possibility of instability in feature calculation and significant errors in classification. However, it is not possible to conduct the needed normalization steps, used in [9] and [11] during the surgery. This makes the techniques proposed in [9] and [11] as approaches which can be used for postoperative assessment. As suggested in [11], the above-mentioned features are subtracted by the mean and divided by standard deviation of features in one trajectory. Thus, this method requires the MER data from one trajectory prior to implementation, which is not feasible intraoperatively.

2.3. Feature Extraction: Fast Fourier Transformation

The discrete Fourier Transformation (DFT) has been widely used to extract features from biomedical signals. Moreover, the fast Fourier Transform (FFT) is an efficient way to calculate the DFT. When the microelectrode is within the STN, there is a shift in frequency domain of the MER signal. Thus, the FFT coefficients can provide information about when the microelectrode enters the STN. Importantly, there is no need to normalize FFT coefficients so these features can be extracted in an intraoperative manner from the MER signals during the operation. Also, there is no concern of stability. It is worth mentioning that using the conventional features

Table 1. Accuracy of Classifiers for Localizing STN

Features\classifiers	LR	SVM(Linear Kernel)	SVM(Quadratic Kernel)	SVM(Cubic Kernel)
The 10 extracted features used in [11]	71%	70%	72%	76%
FFT coefficients	81%	80%	82%	85%

(shown in *section II-B*) there is a concern of stability in feature calculation due to the existence of ratio-based calculations. This has been discussed in [9].

3. CLASSIFIERS

After extracting features from MER signals, two classifiers, Logistic Regression and Support Vector Machines were applied to the signals. Each of these signals was labeled as zero or one. Label zero indicates that the electrode was outside of the STN and label one means that electrode was inside the STN. These labels were determined by the neurosurgeon and (with experience of more that 200 DBS surgeries) during the surgical procedure.

3.1. Logistic Regression

Logistic Regression (LR) has been widely used in statistical analysis and this classifier is especially useful for problems with continuous features and discrete target outputs. The LR model calculates the class membership probability in the data set [12] as shown below.

$$P(1|x,\theta) = \frac{1}{1+e^{-\theta x}}, P(0|x,\theta) = 1 - P(1|x,\theta) \qquad (4)$$

In (4) , P is the probability of the class, x is the sample signal and θ is determined based on the dataset, usually by maximum-likelihood estimation.

3.2. Support Vector Machine

The Support Vector Machine (SVM) separated boundaries of data sets by solving an optimization problem. Depending on the kernel function of SVM, this separation can be linear or nonlinear with different degrees of nonlinearity and flexibility [13]. In this paper, we have tried different kernels including Linear, Quadratic and Cubic polynomials to separate our two classes [14].

Let $x_i \in R, i = 0,1,...,N$ (N is size of the training set) be the input vector and $y_i \in 0,1$ be the corresponding labels. Label zero indicates the signals were outside the STN and label one corresponds to signals inside.

$$y(x) = sign(\sum_{i=1}^{N} \alpha_i y_i \phi(x,x_i) + b) \qquad (5)$$

where α_i are positive real constants and b is a real constant. $\phi(x,x_i)$ indicates the kernel of the classifier which can be linear: $\phi(x,x_i) = x_i^T x$ or polynomial: $\phi(x,x_i) = (x_i^T + 1)^d$ in which d indicates the degree of the polynomial. In Quadratic and Cubic kernels, d is equal to two and three respectively.

4. RESULTS

As mentioned in section 2.1 each signal was a 10 second recording from a specific depth. On average we had signals for 25 depths for each electrode. Furthermore, an average of ten microelectrodes were used for each patient. This study used MER data from 20 patients who had undergone DBS surgery previously. Most of the patients had bilateral DBS, while only a few had unilateral. Thus, the total number of samples was 3986. We extracted the ten features explained in Section 2.2 in addition to the FFT coefficients from the electrophysiological signals. Table (1) contains the results of ten-fold cross validation. As can be seen, the highest accuracy has been achieved using FFT features and the SVM classifier with a Cubic kernel. Thus, we proposed this combination for detection of STN during DBS surgeries. Based on the achieved results, we can conclude that FFT features may be more informative than conventional features used in the literature. This might be due to the capability of FFT features in highlighting the differences in spike activities in the frequency domain. Also, unlike conventional techniques, using FFT there is no concern of instability in feature calculation, and there is no need for post-normalization of the features; thus the features can be calculated during the surgery and this makes it possible to help the neurosurgeon during the DBS procedure.

5. CONCLUSION

This study presented a new technique that can be used to assist a neurosurgeon during the DBS procedure by providing an objective assessment of the location of the subthalamic nucleus (STN). Based on the conducted study, a combination of FFT-based features and a Cubic kernel SVM algorithm was proposed as a high-performance approach that can localize STN during surgery. A study was conducted to compare the accuracy of the method with that of the current state-of-the-art technique. The results showed that the proposed approach (a) is capable of localizing the STN with an accuracy of 85%; (b) has superior performance over current clinical techniques; and (c) can be used as a cueing tool in the operating room to assist neurosurgeons with surgical targeting of STN.

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