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Unsupervised Clustering of Micro-Electrophysiological Signals for localization of Subthalamic Nucleus during DBS Surgery*

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Abstract— **In this paper, an unsupervised machine learning technique is proposed to localize the Subthalamic Nucleus (STN) during deep brain stimulation (DBS) Surgery. DBS is one of most common treatments for advanced Parkinson's disease (PD). The purpose of this surgery is to permanently implant stimulation electrodes inside the STN to deliver electrical currents. It is clinically shown that DBS surgery can significantly reduce motor symptoms of PD (such as tremor). However, the outcome of this surgery is highly dependent on the location of the stimulating electrode. Since STN is a very small region inside the basal ganglia, accurate placement of the electrode is a challenging task for the surgical team. During DBS surgery, the team uses Micro-Electrode Recording (MER) of electrophysiological neural activities to intraoperatively track the location of electrodes and estimate the borders of the STN. In this work, we propose a composite unsupervised machine learning clustering approach that is capable of detecting the dorsal borders of the STN during DBS operation. For this, MER signals from 50 PD patients were recorded and used to validate the performance of the proposed method. Results show that the approach is capable of detecting the dorsal border of the STN in an online manner with an accuracy of 80% without using any supervised training.**

I. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases that is caused by loss of dopaminergic neurons in the substantia nigra pars compacta [1]. Movement disorders associated with PD are characterized by tremor, rigidity, postural instability, bradykinesia, and gait issues [2]. Deep Brain Stimulation (DBS) surgery is an effective treatment for advanced PD patients. During DBS surgery, continuous high-frequency electrical current is delivered to the subthalamic nucleus (STN) of the basal ganglia in order to manage some motor symptoms [3]. The surgical outcomes highly depend on the accuracy of the placement of the electrode inside the STN. Since the STN is a very small region (5-7 mm) of the basal ganglia, accurate placement of the stimulating electrode is a challenging task for the surgical team [4]. The sub-optimal positioning of DBS electrodes accounts for 40% of cases in which inadequate postoperative efficacy of stimulation is reported [4].

A common technique to target the STN is through the use of preoperative Magnetic Resonance Imaging (MRI) [5]. However, the exact location of the STN cannot always be identified accurately using MRI. As a result, intraoperative Micro-Electrode Recording (MER) has been used for localizing the STN. In general, up to five microelectrodes are inserted through a burr hole in the skull on each side of the brain. The microelectrodes record the electrophysiological activities of the neurons along the insertion trajectory. Typically, MER signals are observed visually by the surgical team during the operation. Electrophysiological activities vary along the insertion trajectory when the electrode passes through different structures of the brain. This variation is interpreted by the experienced surgical team to localize the STN. The neurosurgeon then determines the border of the STN and selects one of the five electrodes for permanent implantation of the stimulating electrode [5], [6]. Several important criteria are considered by the surgical team in order to localize STN, such as an increase in the background noise level, spike firing count, and changes in the spike firing patterns. Based on these criteria, neurosurgeons determine the choice of microelectrodes for permanent stimulation [7].

The purpose of this paper is to design an autonomous algorithm (trained based on a clinical dataset) that can assist neurosurgeons in localizing the STN during DBS surgery. An autonomous STN localization that can provide feedback to a neurosurgeon during the procedure can help to reduce the time during the DBS procedure and can have several clinical benefits. The technique can also be beneficial for enhancing the quality of outcomes by reducing possible placement errors. In this particular study, we show that even without using the labels (that mark the STN) provided by a neurosurgeon, the proposed technique is capable of localizing the STN with an accuracy of 80%. For this, we designed a composite unsupervised machine learning algorithm to localize the STN and assist the

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neurosurgeon in determining the optimal placement of electrodes.

The topic of STN localization has been studied in the literature and several advanced techniques have been implemented (e.g., [8], [9], [10]). Most of the existing techniques use supervised classifiers. In this regard, a state-of-the-art approach was recently reported in [10]. Although high performance has been reported in the literature, most of the existing techniques cannot be implemented in the operating room *during* surgery. The reason is that the extracted features used in conventional techniques require some offline post-operative processing steps (such as spike sorting and a specific normalization algorithm that requires information from the whole insertion trajectory) [8] [10]. This makes the existing approaches essentially post-operative validation techniques which can help to evaluate the quality of the conducted procedure. However, it does not allow for STN localization during the operation.

In this study, instead of using the conventional feature space, we evaluate the performance of Fast Fourier Transformation (FFT) as the tool to populate the feature space for our clustering approach. The FFT-based feature space can be obtained during surgery and does not need any pre- or post- processing information.

In the second step, we initially evaluate the performance of two unsupervised learning methods: K-means clustering and Self Organized Map (SOM) Neural Network, on the dataset that we collected during DBS surgeries from 50 PD patients. We compared the output clusters generated by the above-mentioned two clustering algorithms with the labels provided by an experienced neurosurgeon who has done more that 200 DBS surgeries. The results show that using the FFT-based features, the unsupervised algorithms are capable of detecting the signature of STN and localize it with an accuracy about 75%.

In the third step, a composite approach is evaluated that includes both K-means and SOM clustering as two sequential layers of processing. The first layer is a K means clustering technique which is used to reduce the size of the feature space through locating the sub-centers of the input data (FFT-based feature space). The second layer is an SOM neural network that is used to separate the two main clusters (STN versus outside of STN). We have shown that the proposed composite technique is capable of localizing the STN with an accuracy of 80%. It also reduces the training complexity, and therefore the clustering time.

II. Methods and Materials

A. Demographic Data

For this study, we collected and used MER signals from 50 individuals with PD who had previously undergone DBS implantation. The average age was 60 $\pm$ 6 years (34 male and 16 female). On average, each patient had 10 microelectrodes inserted into their brain. Details of the data acquisition procedure are provided in the next subsection.

B. Surgical Procedure and Data Acquisition

All patients discontinued short-acting Parkinson medications 12-hours prior to surgery. Preoperative MRI was obtained to done the coordinates of the anterior commissure (AC), posterior commissure (PC) and the STN. An axial T2-weighted image and postgadolinium (Gd) volumetric axial T1-weighted sequence was used for the coordinate localization (Signa, 1.5T, General Electric, Milwaukee, Wis). STN target planning was carried out using the mid-point between the AC and PC points and the standard stereotactic coordinates: 12.0 mm lateral, 2.0 mm posterior and 4.0 mm ventral. The center of the STN was used as the surgical zero-point. Trajectory planning for the microelectrodes was done using the post-Gd volumetric T1-weighted sequence, ensuring avoidance of the ventricles and blood vessels. All surgical planning was done using the StealthStation (StealthStation, Medtronic Corp, MN). A burr-hole was drilled in the skull. The StarDrive (FHC Inc., Bowdoinham, ME) was mounted to the arc at 30.0 mm above the surgical target and five cannulas with stylets were lowered to 10.0 mm above the target. The stylets were then removed from the cannulas and five 60 μm diameter tungsten microelectrodes were inserted into the cannulas with an impedance of 0.5-1.0 mΩ at 1kHz (FHC Inc., Bowdoinham, ME). Signals were recorded from 10.0 mm above the preoperatively determined target zero point to well below the ventral (bottom) border of the STN, generally looking for activity indicative of the substantia nigra (4.0 - 5.0 mm below the zero-point). The drive was advanced in 1.0 mm increments and 0.5 mm increments within the target nucleus. At each depth, advancement was paused to allow any artifact to be resolved. Once a clean recording was observed a 10-second recording was collected prior to advancing the electrodes further. The signals were sampled (24kHz, 8 bit), amplified (gain: 10,000) and digitally filtered (bandpass: 500-5000 Hz, notch: 60Hz) using the Leadpoint recording station (Leadpoint 5, Medtronic). A sample MER signal from a right-side anterior trajectory is given in Figure 1. As shown in Fig. 1, some differences in electrophysiological activities can be seen when comparing signals from the inside and outside of the STN.

C. Feature Extraction: Fast Fourier Transformation

In this study, we calculated the FFT of the electrophysiological signals and use the FFT coefficients as the feature space for the clustering approach. As can be seen in Figure 2, an increase in the magnitude of the FFT coefficients can be visually observed when the electrode is inside the STN. An FFT-based feature space can provide valuable information about the location of the microelectrodes since they encode the frequency

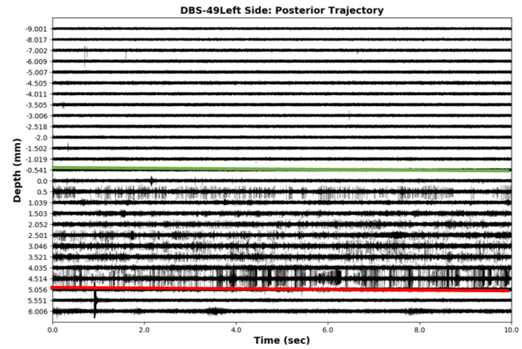

Fig. 1. MER from an anterior electrode trajectory collected during an STN-DBS case. Negative depth values indicate above the nucleus and positive values indicate below. The green line indicates the dorsal border of STN and the red line indicates the ventral border of STN, as decided by the neurosurgical team.

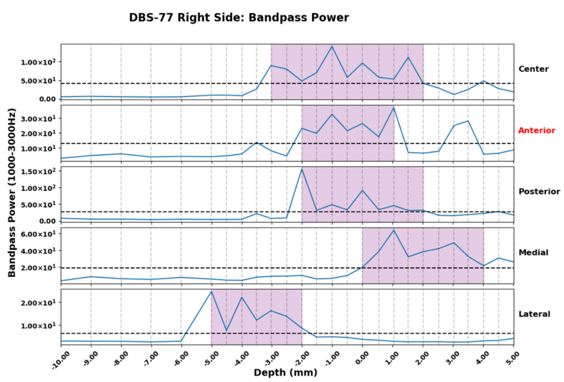

Fig. 2. The figure shows power from the Discrete Fourier transform (DFT) in the frequency of 1000-3000Hz indicating single-unit activity. The purple shaded area indicates where the nucleus was determined to be located based on the recordings. Red highlighted depth indicates which channel the surgeon decided to use. Each dotted line represents a recording depth. Negative depth values are above the nucleus and positive values are below.

context of neural activities and the corresponding variation along the insertion path. The FFT-based feature space can be populated during the surgery when the neurosurgeon guides the electrodes toward the target (i.e., the STN). This means that the feature space can be calculated during the operation and no post-operative processing (e.g., spike sorting, normalization along the path) is needed. This is an advantage of the FFT-based feature space in comparison to the ones used in the literature (such as [8], [10]).

D. Feature Extraction: Conventional Offline Features

As mentioned earlier, the techniques reported in the literature mainly rely on a specific offline feature space designed for the supervised classification of the STN. In this paper, in order to evaluate the performance of the proposed online unsupervised technique in comparison with those in the existing literature, the same feature space is also implemented in addition to the proposed FFT-base feature space. For this purpose, to populate the offline feature space based on the most effective ten state-of-the-art features reported in [8], [10], and [9] are calculated. The offline features are given in the following: *(a)* the number of spikes per the 10-second interval; (b) the standard deviation of time differences between the spikes; (c) the pause index; (d) the pause ratio; (e) the Root Mean Square (RMS) value of the signal amplitude; (f) the spiking rate (g) the teager energy (h) the number of zero crossings; (i) the curve length; (j) the threshold. The list given above is for a 10-second time window; detailed definitions can be found in [8], [10].

It should be noted that the offline feature space reported in [8], [10], [9] requires a specifically-designed normalization and standardization process which can only be done post-operatively. As explained in [10] the offline features should be normalized considering the standard deviation of the calculated features in the entire insertion trajectory. Thus, this requires the MER data from the entire trajectory, which is not feasible during online processing of the neural activities. The above-mentioned process is required due to the possibility of instability in feature calculations [8]. This makes the existing approaches post-operative validation techniques which can help to evaluate the quality of the conducted operation. However, it does not allow for STN localization during the operation.

III. Classifiers

A. K-means

K-means clustering is used to partition signals into k clusters. First, it initializes cluster centers randomly or according to the user's specifications and then iteratively refining the new cluster centers. If the given data set is $X = x_1, ... x_N, x_n \in R^d$. K-means separates k clusters such that a clustering criterion is optimized.

$$E(m_1, m_2, ..., m_M) = \sum_{i=1}^{N} \sum_{k=1}^{M} I(x_i \in C_k)|x_i - m_k|^2 \qquad (1)$$

In (1) , $m_1, m_2, ..., m_M$ are cluster centers and $I(X) = 1$ if X is true and 0 otherwise.

B. Self Organized Map

The SOM is an unsupervised learning neural network method which gives a similarity graph of input data [11]. The SOM usually has two layers; an input layer and an output layer which are directly connected together [12]. The SOM consists of neurons on a low dimensional grid; usually two dimensional (2-D). The input of the first layer consists of feature vectors $x_i = [x_i1, x_i2, ..., x_id] \in R^d$. Each neuron has a dimensional weight vector $w_u = [w_u1, w_u2, ..., w_ud] \in R^d$. At the beginning of training, w_u is initialized randomly from the input vector domain. The Euclidean distances from x_i and all w_u are computed. The winning neuron or best match unit (BMU) is the one that has the w_u closest to x_i [13]. The SOM has been widely used in dimension

TABLE I
ACCURACY OF UNSUPERVISED CLUSTERING ALGORITHMS

Features \ Clustering method	SOM Neural Network	K-means	Composite K-mean-SOM Clustering
10 extracted features	58.4%	61.8%	64%
FFT coefficients	74%	76.7%	80%

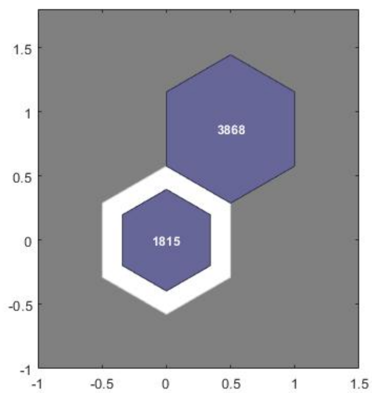

Fig. 3. Hit Map units of the Self Organized Map with two neurons for FFT features. It shows the two clusters from the data. 3868 signals were labeled as zero and 1815 was labeled as class one.

reduction classification problems. Fig. 3 shows the Hit Map of the FFT features with two neurons.

C. Composite K-means-SOM

Combinations of K-means and SOM have been commonly used to achieve a better performance than using the individual methods [14]. So in this work, we used a composite of K-means and SOM as two layers of processing to increase the clustering accuracy. In the first step, K-means clustering is applied on the signals to reduce the dimension of the feature space. Then, in the second step, the SOM Neural Network is used on the reduced-order feature space to combine and fuse the sub-centers, detect the connections, and form the two main clusters (inside and outside of STN). By using this combination, we achieved a higher accuracy and reduced the training complexity and time.

IV. RESULT

In our dataset, we had a ten-second recording from up to 25 depths. On average, each patient had 10 microelectrodes inserted into their brain. The number of signals that we used from 50 patients was 5683. In this study, we have two sets of features (the FFT-based space and the off-line based spaces) and three unsupervised clustering algorithms (K-means, SOM Neural Network, Composite K-means-SOM), and two clusters.

To calculate and evaluate the performance of the proposed composite technique in comparison to the other mentioned approaches [8], [10], we used the labels provided by the neurosurgeon during the operation. The results of this comprehensive comparative study are given in Table 1. As can be seen in the table, using the FFT-based feature space, the K-mean clustering technique was able to localize the STN with an accuracy of 76.7%. However, using the offline feature space results in a significant drop in the accuracy to a range of 58.4%-61.8%. It should be noted that the proposed composite technique, using the FFT-based feature space, represented the highest accuracy (80%) in comparison to the other approaches. Thus, from the results shown in Table I, the FFT feature space extracted from the MER signals provides rich features for the clustering algorithms and the composite K-means-SOM is a strong unsupervised tool for clustering the STN.

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