LOCALIZATION OF SUBTHALAMIC NUCLEUS FROM MICROELECTRODE RECORDINGS WITH K-MEANS CLUSTERING

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and approved by

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ABSTRACT OF THE THESIS

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**Background:** Microelectrode recordings (MERs) of the neural activities are a useful tool for subthalamic nucleus localization (STN) in the process of deep brain stimulation (DBS) surgery for neurological and neuropsychiatric disorders, like Parkinson’s disease. Currently, the localization of STN relies on manual demarcation performed by a neurophysiologist. It is also difficult to give an exact detection of the STN borders, especially the one between the STN and the substantia nigra pars reticulata (SNr). As a result, investigators are looking for a multi-feature machine learning method for accurate automated STN localization. We used K-means clustering and a novel set of features that are based on a combination of spike-based and spike independent metrics to address these shortcomings.

**Methods:** We extracted 18 computational features from 31 bandpass filtered (0.5 kHz - 8 kHz) MERs of 20 patients who underwent DBS implantation surgery. 12 of these 18 features were spike-based and the other 6 were spike independent. Square root transformation was performed on those positively skewed features. All features were standardized and normalized to scale [0, 1]. We additionally integrated a depth vector into the original feature matrix. The newly formed feature matrix was fed into the k-means clustering algorithm. K was chosen to be 4 because the trajectories, under
most circumstances, went through four consecutive structures in the brain. The STN
demarcations were predicted by a combination of k-means clustering and feature activ-
ity maps. The results were later compared to the decisions of a human expert.

**Results:** Two of the four newly designed features, i.e. mean inter-spike interval and
bursting rate, showed good discriminatory power between STN-SNr region and all the
other regions. The modified k-means clustering with \( k = 4 \) identified the STN entry
and STN exit with an error of \( 0.0443 \pm 0.2190 \) and \( 0.2555 \pm 0.4005 \), respectively (mean
\( \pm \) standard deviation), and achieved detection sensitivity (error < 0.5 mm) of 93.5%
and 80.6%, respectively.

**Conclusion:** The combination of k-means clustering and a novel feature activity map
provided a simple and robust method for STN localization. Further integration of the
depth information into the original feature matrix has substantial effect in reducing
the noise existed in the clustering results given by k-means clustering alone. Since our
unsupervised learning approach does not require manual demarcation on its output,
the degree of automation has improved. This is expected to lead into a decreased time
spent inside the operation room and hopefully improve the clinical outcomes.
Acknowledgements

The author would like to thank the neurosurgeons team in Rutgers-RWJ University Hospital, Dr. Shabbar F. Danish, MD; Prof. Stephen Wong, MD and Dr. Eric Hargreaves for providing the microelectrode recordings and technical supports from a clinical perspective.
Dedication

This thesis is dedicated to my parents with love.
Table of Contents

Abstract ................................................................. ii
Acknowledgements ..................................................... iv
Dedication ............................................................... v

List of Tables ........................................................... viii
List of Figures .......................................................... ix

1. Introduction .......................................................... 1

2. Methods .............................................................. 4
   2.1. Subject Enrollment ........................................ 4
   2.2. Clinical Procedure ......................................... 4
   2.3. Data Collection and Preprocessing ....................... 5
   2.4. Feature Extraction .......................................... 6
   2.5. Feature Transformations .................................... 6
       2.5.1. Square Root Transformation ......................... 6
       2.5.2. Standardization ....................................... 9
       2.5.3. Outlier Detection .................................... 9
       2.5.4. Normalization ....................................... 12
   2.6. Feature Activity Maps ...................................... 13
   2.7. K-means Clustering .......................................... 13

3. Results .............................................................. 15
   3.1. Feature Activity Maps ...................................... 15
   3.2. K-means Clustering .......................................... 17
List of Tables

2.1. Spike Dependent Features (1/2) ................................. 8
2.2. Spike Dependent Features (2/2) ................................. 9
2.3. Spike Independent Features ................................. 10
3.1. Prediction on STN Boundaries ................................. 21
## List of Figures

1.1. Functional Targeting of Subthalamic Nucleus with Microelectrode Recordings. .................................................. 3

2.1. Finite Impulse Response (FIR) Filter with Band-pass between 500 Hz and 8000 Hz. .................................................. 5

2.2. Pairwise Scatter Plots and Histograms of Features Before Transformations. .................................................. 7

2.3. John Tukey’s 1.5IQR Rule for Outlier Detection and Removal. .................................................. 11

2.4. Pairwise Scatter Plots and Histograms of Features After Transformations. .................................................. 12

2.5. K-means Clustering from Curve Length and Spike Count Perspective .................................................. 14

3.1. Conversion of Band-pass Filtered Raw Signal to Activity Maps of Normalized Features .................................................. 16

3.2. Grouping of Data Points Over Time by K-means Clustering .................................................. 17

3.3. K-means Clustering Result with Different Depth Scales .................................................. 18

3.4. K-means Clustering Result Expressed in Curve Length .................................................. 19

3.5. A Special Case .................................................. 20

3.6. Sensitivity Analysis for 0.5 mm Accuracy .................................................. 22
Chapter 1
Introduction

Deep brain stimulation (DBS) is a neurosurgical procedure used to treat a variety of disabling neurological symptoms – most commonly the debilitating symptoms of Parkinson’s disease (PD), such as tremor, slowed movement, rigidity, stiffness, and walking problems. It involves the implantation of a medical device called a neurostimulator, sometimes referred to as a "brain pacemaker". Similar to how a cardiac pacemaker works, this device sends high-frequency electrical pulses to the subthalamic nucleus (STN) region to suppress the symptoms related to Parkinson’s disease. Acute and long-term applications of DBS show a stable and dramatic improvement of a patient’s clinical conditions [2, 3, 5, 15]. Magnetic resonance imaging and stereotactic methods are employed to conduct preoperative localization of the STN. Later high-precision implantation of the DBS electrodes relies on functional localization via microelectrode recordings (MERs) [23, 33]. In addition, intraoperative neurophysiologic confirmation using MER reduces targeting errors resulted from inherent resolution limitations of neuroimaging and anatomic shifts during surgery [9, 13, 20, 29].

As one or more microelectrodes travels along the putative implantation path, the information is recorded in terms of MERs. The resulting pattern of neural activities (i.e. MERs) is transformed to audio signals. In practice, functional localization of STN via MERs relies on trained clinical neurophysiologists to recognize the entry and exit boundaries of STN region based on a variety of acoustic patterns displayed in Figure 1.1. Over the past decade, researchers have made different attempts to localize STN section in the microelectrode recordings using spike-related features. Attempts to standardize and automate this procedure include spike sorting which extracts firing features from single neuron activities [11, 21, 24, 25]. This procedure is labor intensive because it
requires the electrode to stay stationary in order to collect single neuron activities, followed by spike sorting algorithms to separate action potentials from different individual neurons prior to the classification or clustering algorithms for STN localization. The limitation for this method is that spiking characteristics between STN and neighboring subcortical structures can overlap to a significant degree [14, 17, 11].

Several research groups have also investigated neuronal population-based characteristics attempting to find more stable and reliable quantitative properties [11, 22, 21]. However, any single measurement of neural activity can be negatively affected by variation in neurophysiologic patterns and technical artifacts introduced during recording. One approach to counter this is to integrate multiple measures to gain potentially reliable information. This strategy ensures a relatively robust machine learning model of the neural activity.

Other efforts to automate MER interpretation have been put on introducing the concept of spike-independent features [8]. A library of features can be extracted from MER data that might be of value to localization of STN. These features may be combined to establish a multi-dimensional feature space from which supervised [26, 30] and unsupervised [31] machine learning models can be built to demarcate the entry and exit of STN on the MER signal.

The strategy we employ here involves extraction of both the spike-dependent features and spike-independent features and K-means clustering, a very commonly used unsupervised learning method. We use 18 features, each representing a distinct signal characteristic of the microelectrode trajectory and combine them into a feature matrix. We later feed this feature matrix into the clustering algorithm. Unlike a previous study of conducted by Wong’s group [31] in which the output color-coded activity map required manual demarcation to give the STN boundaries, our modified K-means clustering can directly output the STN entry and exit. What’s more, the novel idea of introducing depth vector into the feature matrix greatly reduced the noise in the original clustering result and make automatic demarcation possible.
Figure 1.1: Functional Targeting of Subthalamic Nucleus with Microelectrode Recordings.

(A) A schematic sagittal view of the typical trajectory of microelectrode displaying midbrain structures: around 12 mm lateral to the midline, beginning around 2 cm above the presumptive target. The subcortical structures along the trajectory include the thalamus, zona incerta, subthalamic nucleus, and substantia nigra. (B) Spiking and spike background patterns corresponding to different brain regions as the electrode proceeds. In this picture, the fast firing rate within SN is consistent with a typical pars reticulata (SNr) neuron.
Chapter 2

Methods

2.1 Subject Enrollment

All subjects were consented and enrolled for microelectrode recording collection in accordance with an internal review board-approved protocol. 53 microelectrode recordings were collected from 24 consecutive patients during DBS surgery over a 1.25 year period at Robert Wood Johnson University Hospital. Four microelectrode recordings were used to tune the spike detector, feature calculations, and activity map generation process. The MER data has 48-kHz sampling frequency and was filtered between 0.1 - 10,000 Hz.

2.2 Clinical Procedure

FA Leksell stereotactic frame was used for preoperative MRI targeting on the morning surgery. It involves three methods: (1) direct localization according to the output of MRI; (2) indirect localization according to a stereotaxic atlas [28] i.e. anatomical knowledge of human brain; and (3) surgical planning by the Medtronic StimPilot Surgical Navigation system. Burrholes were put approximately 4 cm lateral to the midline. Starting from the frontal pre-motor cortex, the microelectrode trajectory terminated in the substantia nigra (SN), going through a path lateral to the lateral ventricles. This was designed to avoid such regions like sulci, major veins, ventricles, and the internal capsule. The trajectory, under most circumstances, went through the following consecutive structures: thalamus, zona incerta, H2 Field of Forel, subthalamic nucleus, and substantia nigra (Figure 1.1). A guiding cannula was penetrated into the brain through the estimated trajectory until it reached 15 mm above the pre-calculated target. This
typically led to the fact that the microelectrode tip started its recording from within the thalamus. During the surgery, a clinical neurophysiologist demarcated the STN boundaries by identifying an irregular firing pattern, an increase in the neuronal firing rates and background noise, and a positive sensorimotor response characterized by an increase in firing rate upon tactile stimulation and passive movement of the patients’ extremities [4, 27].

2.3 Data Collection and Preprocessing

![Finite Impulse Response (FIR) Filter with Band-pass between 500 Hz and 8000 Hz.](image)

Figure 2.1: Finite Impulse Response (FIR) Filter with Band-pass between 500 Hz and 8000 Hz.

The detailed recording setup is described by another paper [19]. A 60 μm diameter tungsten tip microelectrode (FHC inc., Bowdoinham, ME) with an impedance of 0.5-1.0MΩ was employed for recording the brain signal. Being passed into a modified FHC HiZx8 pre-amplifier probe, the signal was then transformed to a low-impedance signal and sent to a FHC HiZx8 amplifier. The raw microelectrode recording was then hardware band-pass filtered between 0.1 Hz and 10kHz, 60Hz notch filtered, amplified 1000 times and later fed into a CED Power1401 analogue-to-digital converter. Digitized at a 16-bit vertical resolution at 24 kHz, the signal was then recorded by a Spike2
software (CED). The signal later further digitally filtered between 0.5 kHz and 8 kHz with a finite impulse response (FIR) filter (Figure 2.1) using Matlab. The subsequent analysis were all performed in Matlab.

2.4 Feature Extraction

The entire microelectrode recording was divided into 4-second data epochs with 50% overlap. We extracted 18 features from each data epoch that were either described in the literature previously [8, 14, 12, 18] or designed by ourselves. The length of the epoch (4 seconds) was determined empirically in hope of obtaining a minimum number of neuronal spikes using our spike detection techniques. The overlapping between adjacent epochs can smooth the appearance of the feature activity maps over time.

Among the 18 features, 12 of them were spike independent, i.e. they required spike detection before feature calculation. To detect the potential spikes, we first identified peaks by setting up an adaptive threshold at 1.5 times the 98th percentile amplitude within each epoch. Adaptive threshold has the advantage over fixed threshold that it can remove the bias caused by higher amplitude background activity in subcortical structures.

The following tables (Table 2.1, 2.2, 2.3) briefly describe each feature and gives a formula if an explicit expression exists. The variable $X$ is the input data epoch vector of length $N$.

2.5 Feature Transformations

We took several transformations consecutively on the 18 features. Each transformation served its own purposes.

2.5.1 Square Root Transformation

Firstly, we took into consideration the skewness in each feature. Since we would later use the squared Euclidean distance as a metric for K-means clustering, either an extreme left skewness or an extreme right one in the feature distribution would drive all the
data points to a corner of the multidimensional feature space, increasing the difficulty of getting an accurate and stable clustering result. While the histograms on the diagonal of the plot matrix (Figure 2.2) tells us the skewness of the data distribution in each feature, the scatter plots located off-diagonal indicate the pairwise relationships of the features. By observation, 14 out of 18 features have right skewness (a long tail on the right end of the distribution). We applied the typical square root transformation to counter this skewness.

Figure 2.2: Pairwise Scatter Plots and Histograms of Features Before Transformations.

This matrix of plots has histograms on its diagonal and pairwise scatter plots off-diagonal. For illustration purposes, we only showed the first 5 features (MISI, SISI, CVISI, PS, and BR) instead of the whole 18 x 18 matrix. It’s easy to identify that all of the 5 features in this figure are skewed to the right.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
</table>
| (1) MISI     | The inter-spike interval sequences \((ISI_n)\) are defined as the history of time intervals between consecutive spikes in the spike sequence. Let \(t_n\) be the occurrence time of the \(n\)th spike in a set of \(N\) spikes. \[ISI_n = t_{n+1} - t_n\quad n = 1, 2, ..., N - 1\]
|              | **Mean of Inter-Spike Interval (MISI)** is the arithmetic mean of inter-spike intervals. \[MISI = \frac{1}{N-1} \sum_{n=1}^{N-1} ISI_n\] |
| (2) SISI     | **Standard Deviation of Inter-Spike Interval (SISI)** is the standard deviation of inter-spike intervals \(ISI_n\). |
| (3) CVISI    | **Coefficient of Variation of Inter-Spike Interval (CVISI)** is the coefficient of variation of the inter-spike intervals \(ISI_n\). |
| (4) PS       | **Percentage of Spikes in the Spike Signal (PS)** is the percentage of the length of the spikes accounted for that of the whole signal in the data epoch. |
| (5) BR       | Bursts are electrical spikes firing with a high frequency, which are the most important property in synaptic plasticity and information processing in the central nervous system. The algorithm to detect burst consists of the following steps [7]:
|              | · Determine MISI. |
|              | · Construct a new ISI sequence, \(L(n)\), which can be extracted from the original \(ISI_n\) sequence. If the \(ISI_n < MISI\), then put it into the sequence \(L(n)\). |
|              | · Calculate the mean of \(L(n)\) and term this value \(ML\). |
|              | · Define bursts as two or more successive ISIs in the original \(ISI_n\) sequence with a mean value smaller than \(ML\). \[\frac{1}{k} \sum_{i=k}^{i+k} ISI_n \leq ML, \quad k = 2, 3, ...\] |
|              | **Bursting Rate (BR)** is the number of bursts per second. |
| (6) PB       | **Percentage of Bursts (PB)** is the percentage of time bursts take in each data epoch. |
| (7) FR       | **Firing Rate (FR)** is the number of spikes per second. |

**Table 2.1:** Spike Dependent Features (1/2)
### Spike Dependent Features

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>(8) MBI</td>
<td><em>Modified Burst Index (MBI)</em> is the ratio of the number of ISIs less than 10 ms to the number of ISIs greater than 10 ms.</td>
</tr>
<tr>
<td>(9) PI</td>
<td><em>Pause Index (PI)</em> is the ratio of the number of ISIs greater than 50 ms to the number of ISIs less than 50 ms.</td>
</tr>
<tr>
<td>(10) PR</td>
<td><em>Pause Ratio (PR)</em> is the ratio of cumulative time of ISIs greater than 50 ms to the cumulative time of ISIs less than 50 ms.</td>
</tr>
<tr>
<td>(11) SC</td>
<td><em>Spike Count (SC)</em> is the number of spikes detected in each data epoch.</td>
</tr>
<tr>
<td>(12) MSAD</td>
<td><em>Mean Spike Amplitude Differential (MSAD)</em> is the 80% trimmed mean of the difference between consecutive spike amplitudes.</td>
</tr>
</tbody>
</table>

**Table 2.2: Spike Dependent Features (2/2)**

#### 2.5.2 Standardization

Standardization impose adjustments on the distributions with different mean and spread.

\[
\text{standardized value} = \frac{\text{value} - \text{mean}}{\text{spread}} \]

\[
z_i = \frac{x_i - \overline{X}}{\sqrt{\frac{1}{N-1} \sum_{i=1}^{N} (x_i - \overline{X})^2}}
\]  

(2.1)

Standardized values have mean 0 and standard deviation 1 and have no units. Therefore standardization is useful for comparing features expressed in different units. It also does not change the shape of a distribution.

#### 2.5.3 Outlier Detection

We combined sliding window method and John Tukey’s 1.5IQR rule to detect outliers. For each of the feature activity map, a sliding window included three parts: the current data point under consideration, 10 data points before the current point, and 10 data points that follow. We employed John Tukey’s 1.5IQR rule for outlier detection and assign the outlier with a relatively less extreme value. The algorithm is described as follows:
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
</table>
| (13) CL     | Curve Length (CL)  
\[ CL = \sum_{i=1}^{N-1} |x_{i+1} - x_i| \]  
where \( x_i \in X \), \( X = \{x_1, x_2, ..., x_N\} \) = input data vector. |
| (14) TH     | Threshold (TH)  
\[ TH = \frac{3}{N-1} \sqrt{\frac{1}{N} \sum_{i=1}^{N} (x_i - \bar{X})^2} \]  
where \( \bar{X} \) is the mean of the data vector \( X \). |
| (15) PK     | Peaks (PK)  
\[ PK = \frac{1}{2} \sum_{i=1}^{N-2} \max \left(0, \text{sgn}(x_{i+1} - x_i) - \text{sgn}(x_{i+2} - x_{i+1})\right) \] |
| (16) RMSA   | Root Mean Square Amplitude (RMSA)  
\[ RMSA = \sqrt{\frac{1}{N} \sum_{i=1}^{N} x_i^2} \] |
| (17) ANE    | Average Non-linear Energy (ANE)  
\[ ANE = \frac{1}{N-2} \sum_{i=2}^{N-1} \left(x_i^2 - x_{i-1}x_{i+1}\right) \] |
| (18) ZC     | Zero Crossings (ZC)  
\[ ZS = \frac{1}{2} \sum_{i=1}^{N-1} |\text{sgn}(x_{i+1}) - \text{sgn}(x_i)| \] |

Table 2.3: Spike Independent Features
1. Arrange the 21 data points of the sliding window in order.

2. Calculate the 1st quartile ($Q_1$), 3rd quartile ($Q_3$), and the interquartile range ($IQR = Q_3 - Q_1$).

3. Assign $Q_1 - 1.5IQR$ as lower bound and $Q_3 + 1.5IQR$ as upper bound. Anything outside this range is an outlier.

4. Assign an outlier that exceeded the lower bound with the value of the lower bound. Assign an outlier that exceeded the upper bound with the value of the upper bound.

Figure 2.3: John Tukey’s 1.5IQR Rule for Outlier Detection and Removal. Only the activity map of feature bursting rate (BR) is shown here as a demonstration of the effect of outlier removal. (A) Before outlier removal, the red box included an outlier which distorted the scale of the whole activity map. (B) After the outlier was removed, we can clearly identify a high level of bursting rate at the STN region (shaded area).

Figure 2.3 gives an example to show the effect of outlier removal. Removing the
outlier shown in the red box made the high level of bursting rate in the STN region (shaded area) become more obvious.

2.5.4 Normalization

The range of the resulting data was used to scale the original features to the $[0, 1]$ range so that features with different scales would have the same influence on clustering. Comparing with the figure 2.2, histograms of the features after transformation in figure 2.4 have distributions closer to normal distribution and their scale also been converted to the range of $[0, 1]$.

![Figure 2.4: Pairwise Scatter Plots and Histograms of Features After Transformations.](image)

Like figure 2.2, plots on the diagonal are histograms for each feature and those off-diagonal are pairwise scatter plots. For illustration purposes, we only showed the first 5 features ($MISI$, $SISI$, $CVISI$, $PS$, and $BR$) instead of the whole $18 \times 18$ matrix. The square root transformation on the original features reduced their skewness. They now have a distribution closer to normal distributions. Normalization has brought features with different scales to the same range $[0, 1]$. 
2.6 Feature Activity Maps

Next we entered the modeling phase. After the necessary transformations, all the features were in unit scale and became comparable to one another. We then plotted the activity map for each feature to observe the their changes over time. This is not only a straightforward way to discover the inherent relationship between the features and anatomical regions but also a good method to explore the relationship between the features over time, a good addition to the scatter plot method.

2.7 K-means Clustering

We chose K-means clustering [16] as our algorithm to separate the STN region from its surrounding regions and employed the default squared Euclidean distance as the metric. Before using any algorithm, we need to be aware of its assumptions. K-means assumes (1) the prior probability for all k clusters are the same, i.e. each cluster has roughly equal number of data points; (2) the distribution of each feature within each cluster is spherical; (3) all features have the same variance. The transformations taken previously helped adapt the data points better to these assumptions. In addition, the trajectory, under most circumstances, went through the four consecutive structures depicted in figure 1.1. As a result, the number of clusters \( k \) we want to set is just 4. Besides the set cluster number, lower computation complexity \( O(n) \) also makes K-means clustering a superior choice over other distance based clustering algorithms such as the hierarchical clustering, which generally has a worst-case time complexity of \( O(n^2) \) or higher. With respect to the density based clustering algorithms, such as DBSCAN [10] and OPTICS [1], they tend to perform poorly (related results are not shown here) in the cases where different clusters in the data have different densities. They also require a careful selection of hyper-parameters: DBSCAN has two, OPTICS (an improved version of DBSCAN) has one. These limitations make them bad choices in dealing with the medical data because of its complex nature. As shown in the 2-dimensional plot\(^1\) in figure 2.5, under real medical settings data points hardly share

\(^1\)The selection of features may not limit to curve length and spike count.
a uniform density among all clusters. But K-means could still perform well given the violation of this assumption.

Figure 2.5: K-means Clustering from Curve Length and Spike Count Perspective

We did k-means clustering on the data with $k = 4$. For illustration purposes, we picked two features, curve length (CL) and spike count, to show the clustering result in a 2-dimensional space. Data points in the four clusters were marked with different colors: red, blue, cyan and green. The bold crossings represent the cluster centroids.
Chapter 3

Results

3.1 Feature Activity Maps

The feature activities over time is shown in figure 3.1. Activity map interpretation requires the connection between feature space and real anatomical space (figure 1.1). By observing the feature activity maps, it is not hard to find that our feature measurements generally had a good discriminatory power between STN/SN region and ZI region. Many of the features displayed a dramatic change in their activity levels in the STN and SN region. On the one hand, spike dependent features, like firing rate (FR), spike count (SC), and bursting rate (BR), achieved a high activity level in STN/SN region but kept insignificant in the ZI region. Mean inter-spike interval (MISI) and standard deviation of inter-spike interval (SISI) showed the opposite property: low level in STN/SN region and high level on other regions. On the other hand, activity maps for some of the spike independent features, like curve length (CL), root mean square amplitude (RMSA), and average non-linear energy (ANE) demonstrate good ability in distinguishing the STN/SN boundary because of their drastic change from STN to SN. In general, it is impossible to identify a single feature that can be regarded as a golden standard to demarcate both the entry and exit of STN region. We have to take advantage of all the feature information to learn a model which might give us a more accurate localization result.
Figure 3.1: Conversion of Band-pass Filtered Raw Signal to Activity Maps of Normalized Features

(A) shows how the bandpass filtered (0.5 kHz - 8 kHz) raw signal looks like. (B) and (C) are activity maps for the spike dependent features and spike independent features respectively. Activity from STN, demarcated by the clinical neurophysiologist, is highlighted in gray in all plots. The data used in this figure belong to the same patient as that in figure 2.5.
3.2 K-means Clustering

By feeding all 18 features into k-means clustering algorithm, we got 4 clusters and plot them over time as shown in figure 3.2. From this result, we could roughly identify that there exists a group of points correspond to the shaded STN region. This grouping result was jeopardized by heavy noise all across the time line. To achieve the automatic identification of STN boundaries, we need to answers the following two questions:

1. How to reduce the noise in the clustering result?
2. How can you identify the cluster corresponding to the STN region?

![Figure 3.2: Grouping of Data Points Over Time by K-means Clustering](image)

This figure depicts the grouping result over time. The x axis is time. The y axis is the group number. The shaded area represents the STN region. It was demarcated by clinical neurophysiologist and served as the ground truth. To be consistent, the data we used here is the same as that used in figure 2.5 and figure 3.1.

3.2.1 Noise Reduction

To solve the first problem, we introduced the depth information into the model. Every data point in the 18-dimensional space had a corresponding depth. The traditional
k-means clustering do not use this information. As you can see in figure 3.2, the noise in clustering result can be defined as a data point which happened earlier in time but was grouped into the cluster that corresponded to a later region down the path of the trajectory. Introducing the depth vector as the 19th feature to the original feature space, we gave k-means clustering algorithm the ability to reduce the noise in its clustering result. As shown in figure 3.3, the larger scale we put on the depth vector the less chance of clustering distant data points into the same group. That was because enlarging depth scale led to dramatic increase in the Euclidean distance between two distant points on the trajectory but had less effect on those points in close anatomical proximity. With the noise reduced, we could potentially give the STN boundaries without conducting manual demarcations. We now can proceed to solve the second problem, i.e. identifying the cluster that corresponds to the STN region.

![Figure 3.3: K-means Clustering Result with Different Depth Scales](image)

This group of plots shows the effect of integration of depth vector with different scales to clustering result. Plot (A) is the original clustering result with no depth vector integrated into the feature matrix. Plot (B) has a normalized depth vector added to its feature space. And thus depth scale equals 1. To observe the effect of increasing scale in depth vector, we rescaled the depth vector to have range [0, 2] in plot (C), [0, 3] in (D), and so on. The data we used was the same as that we used in figure 2.5, 3.1 and 3.2 for comparison purposes.
3.2.2 Identification of the STN Region in Clustering Result

We have already reduced the noise in the clustering result by introducing the depth vector to the input feature space. To tell which cluster corresponds to the STN region, we should take advantage of the information in feature activity maps. Since STN region typically has a high level of curve length (CL) as shown in figure 3.1. Therefore, we could use the curve length level on y-axis of clustering result instead of using the group numbers. We calculated the average level of curve length for each group and plotted the clustering result again in figure 3.4. We can see that the cluster with the highest level of curve length overlapped quite well with the shaded part, i.e. the ground truth of STN region.

![Figure 3.4: K-means Clustering Result Expressed in Curve Length](image)

Similar to figure 3.3, this figure has plots for k-means clustering results with different depth scales. The x-axis is still time (in seconds). The difference is that these plots used normalized curve length as their y-axis and thus had range [0, 1]. The data we used in this figure was the same as that we used in figure 3.3 for comparison purposes.

What’s more, not all the trajectories have the same route as we depicted in figure 1.1. Sometimes the microelectrode recording may neither start from the thalamus nor end in the substantia nigra. Under such circumstances, the number of clusters we should have set might be less than 4 if less regions were penetrated by the probe or more than that otherwise. But we can still make use of the information in the activity
maps to simplify these cases. Figure 3.5 has shown such a special case where the initial clustering result in curve length seems to have two levels instead of four. In such a case, we would combine the clusters with similar curve length level into a new cluster.

![Figure 3.5: A Special Case](image)

3.3 Model Evaluation

We applied the modeling method described above to all the 28 trajectories that were successfully demarcated by a clinical neurophysiologist. The prediction result by our model together with the ground truth values were listed in table 3.1. To tell whether our model have the ability to predict the correct STN boundaries, we employed paired t-test to justify if the prediction and the ground truth sequences have equal means. A paired t-test can be more powerful than a 2-sample t-test because the latter includes additional variation occurring from the independence of the observations. A paired t-test is not subject to this variation because the paired observations are dependent. In addition, a paired t-test does not require both samples to have equal variance. The null and alternative hypotheses we want to test are shown as follows.
Table 3.1: Prediction on STN Boundaries

<table>
<thead>
<tr>
<th>Trajectory</th>
<th>Prediction</th>
<th>Truth</th>
<th>Difference</th>
<th>Prediction</th>
<th>Truth</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>0.71</td>
<td>0.65</td>
<td>0.06</td>
<td>-3.81</td>
<td>-3.82</td>
<td>0.01</td>
</tr>
<tr>
<td>(2)</td>
<td>6.00</td>
<td>5.51</td>
<td>0.49</td>
<td>1.50</td>
<td>0.80</td>
<td>0.7</td>
</tr>
<tr>
<td>(3)</td>
<td>4.09</td>
<td>4.20</td>
<td>-0.11</td>
<td>-0.09</td>
<td>-0.40</td>
<td>0.31</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>(29)</td>
<td>5.81</td>
<td>5.90</td>
<td>-0.09</td>
<td>0.06</td>
<td>-0.11</td>
<td>0.17</td>
</tr>
<tr>
<td>(30)</td>
<td>5.22</td>
<td>5.30</td>
<td>-0.08</td>
<td>-0.06</td>
<td>-0.05</td>
<td>-0.01</td>
</tr>
<tr>
<td>(31)</td>
<td>3.06</td>
<td>3.10</td>
<td>-0.04</td>
<td>-1.42</td>
<td>-0.18</td>
<td>0.38</td>
</tr>
</tbody>
</table>

\[ H_0 : \bar{d} = 0 \quad \text{vs.} \quad H_1 : \bar{d} \neq 0 \]

where

\[ d_i = \text{pred}_i - \text{true}_i \text{ for all } i = 1, 2, ..., n \]  \hspace{1cm} (3.1)

\[ \bar{d} = \frac{1}{n} \sum_{i=1}^{n} d_i \]

The mean STN entry depth (\( \bar{d}_{\text{entry}} \)) predicted by our method was 0.0443 mm above the dorsal STN edge determined by the neurophysiologist. The standard deviation for this mean (\( \text{std}(\bar{d}_{\text{entry}}) \)) was 0.2190 mm. The mean STN exit depth (\( \bar{d}_{\text{exit}} \)) predicted was 0.2555 mm above the ventral STN edge determined by the expert. Its standard deviation (\( \text{std}(\bar{d}_{\text{exit}}) \)) was 0.4005 mm.

It would be useful to calculate a confidence interval for the mean difference to tell us within what limits the true difference is likely to lie. We calculated the 95\% confidence intervals for the two predicted STN boundaries using the following formula.

\[ \bar{d} \pm t_{n-1} \cdot \frac{\text{std}(\bar{d})}{\sqrt{n}} \]  \hspace{1cm} (3.2)

where \( t_{n-1} \) is the 2.5\% point of the t-distribution on \( n - 1 \) degrees of freedom. In our case, since we have 31 trajectories, \( n = 31 \). The T-Score \( t_{n-1} = t_{30} = 2.0423 \). We then calculated the 95\% confidence intervals for the activity map STN entry and exit.
Figure 3.6: Sensitivity Analysis for 0.5 mm Accuracy

Subplot (A) shows the difference between predicted STN entry and the ground truth STN entry demarcated by the neurophysiologist. Subplot (B) shows the STN exit counterpart. While value 0 in the y-axis in both graphs means the model prediction matches that given by the human expert, a positive/negative value indicates how far the prediction value lies dorsal/ventral to the ground truth.

The intervals were 0.1246 mm above to 0.0361 mm below the neurophysiologist’s STN entry depth, and 0.1086 mm to 0.4024 mm above the neurophysiologist’s STN
exit depth. Note that the 95% CI for STN entry prediction covers the value of 0 mm difference relative to the clinical neurophysiologist (null hypothesis $H_0 : \bar{d} = 0$). Although the 95% CI for STN exit prediction does not cover the value of 0 mm, it does not deviate from the true value too much considering its relative small value in comparison to the 4.4758 mm mean length of STN region. Both intervals have a small range demonstrating a good stability in the model performance. As shown in figure 3.6, the map STN entry depth was within 0.5 mm of the clinical neurophysiologist in 29 out of 31 cases, for a sensitivity of 93.5%. The map STN exit depth was within 0.5 mm of the clinical neurophysiologist in 25 out of 31 cases, for a sensitivity of 80.7%. The sensitivities for 1 mm accuracy in entry and exit rose to 100% and 93.5%, respectively.
Chapter 4

Discussion

We described an unsupervised machine learning procedure, i.e. K-means clustering, with 4 new spike dependent features, namely, the mean inter-spike interval (MISI), the coefficient of variation of inter-spike interval (CVISI), the Bursting Rate (BR), and the percentage of bursts (PB). Detailed definition of these features are described in table 2.1. The feature activity maps (figure 3.1) have verified that MISI and BR have the power for discriminating STN region from the other parts of the trajectory. By feeding 18 normalized features into the K-means clustering model, we would be able to find out a vague clustering result with a lot of noise. Then, we integrated the depth information into the original feature matrix as a new normalized vector. By gradually increasing the depth scale, we reduced the noise in each cluster and made automatic STN detection possible. To identify the cluster that corresponds to STN territory we replaced the group labels with the average curve length level within each cluster. Because curve length is a feature that possesses good discriminatory value between STN and SNr. Therefore the cluster with the highest curve length level corresponds to the STN territory where its left boundary represents the STN entry and its right boundary predicts the STN exit.

Nowadays it is common to use the MERs along preplanned trajectories to localize the STN territory during DBS surgery for patients with Parkinson’s disease. Current studies in automatic detection and visualization of STN with MERs have led to the discovery of numerous features that appear to have discriminatory power in STN identification [8, 11, 14, 21, 22, 31, 30]. It is desirable to have an enhanced localization ability by combining these features. Some study [26] further attempts to optimized the set of computational features from MERs to reduce computational complexity.
Several studies have proposed methods for automation of STN detection and visualization using quantitative MER features. On the one hand, some research groups developed rule-based STN detection methods [21, 6]. But they are not capable of giving the direct STN-SNr boundary. For example, the algorithm developed by Cagnan et al [6] required a white matter gap in the trajectory between the STN and the SNr to demarcate the STN exit. In addition, these rule-based detection algorithms are too complex and may not generalize well to DBS surgeries conducted in other medical centers. On the other hand, machine learning techniques were employed to automate the decision boundary detection process in other studies [18, 32, 31, 30]. These machine learning algorithms either belong to supervised learning where labeled signals are required for training or unsupervised learning where the algorithm works on unlabeled data. The supervised learning algorithm used by Zaidel et al [32] was HMM. They used the normalized root mean square (NRMS) and power spectral density (PSD) of $\beta$-oscillations to identify STN boundaries. The weakness of this and many other supervised learning methods under medical settings is that medical data usually have a small sample size and present high variability and complexity. This might limit the generalization of the model to new data. Unsupervised learning deduce patterns only from the input feature space extracted from individual MER and can avoid the patient-wise variability. Wong et al [31] combined the fuzzy c-means algorithm and the feature activity maps for a better demarcation of STN boundaries. But the major drawback of this method is that it requires a human observer to label the STN boundaries. This limits the automation of this algorithms. Instead of using fuzzy c-means, we employed the traditional k-means clustering algorithm.

There are several advantages in our approach.

(1) Clean result for automatic localization
Integration of the depth vector into the original feature space increased the distance between two anatomically distant points in the feature space, making them less likely to be grouped into the same cluster. The following equation is the squared Euclidean distance function for the new feature space. The first term on the RHS of the equation is the sum of all the squared distance for each feature. The second term is the squared
anatomical depth difference multiplied by a scale factor. This part is our modification.

\[ \text{dist}(\mathbf{x}_1, \mathbf{x}_2) = \left[ \sum_{i=1}^{d} (x_{2,i} - x_{1,i})^2 \right] + \left[ \text{scale} \cdot (x_{2,\text{depth}} - x_{1,\text{depth}}) \right]^2 \] (4.1)

While the distance between data points in close proximity anatomically were not affected by the integration of the depth vector, those distant points tend to have a dramatic increase in their spacial distance because of a large value in the second term. With augmented scale factor, the originally intertwined clustering result becomes more and more clear as is shown in figure 3.3 and 3.4. This makes the automation of STN demarcation possible. We have to mention that unlimited increase of the depth scale factor would eventually jeopardize the clustering result. An optimal scale varies slightly among patients.

(2) Easy interpretation
Since the trajectories basically go through the four structures depicted in figure 1.1, we choose \( k = 4 \) as the only hyper-parameter for our algorithm. Feature activity maps illustrate that the STN region has a high level of curve length. These two restrictions help locate the STN region. It’s very simple algorithm comparing with fuzzy c-means and hidden Markov model used in other studies.

(3) Lower computational complexity
K-means tends to be less computationally expensive than fuzzy-c means. For each point, fuzzy c-means needs to conduct a full inverse-distance weighting with each cluster. This leads to more operations involved in each step.

(4) Generalization
Medical data is highly variable. Patient-wise and trajectory-wise differences in MERs may lead to different lengths and relative STN locations in the trajectories. It becomes advantage for a simple unsupervised learning algorithm like k-means clustering to have the ability to learn from the input itself and draw conclusions for each particular case.

Besides the advantages of our algorithm, there are also some common concerns.

(1) Number of clusters chosen
As we illustrated before, we chose \( k = 4 \) because the trajectory commonly passes through four regions in the brain. Indeed, a slight change in the cluster number would
not lead to a dramatic change in STN demarcation (data not shown).

(2) Unstable clustering results

For some data, the clustering result may differ over different trials. This is an inherent problem for k-means clustering. Because k-means clustering chooses an arbitrary k centroids to start with each time. The result may sometimes be trapped in a local minimum of its cost function. By setting a relatively large number of repetitions, we can get a clustering result with the lowest within-cluster sums of point-to-centroid distances.

Although our approach has good prediction accuracy on STN entries, its performance in STN exit demarcation remains to be improved. As more and more research groups chose to use power spectrum density in 5-300Hz as an important feature, we would consider to include it in our future models. Furthermore, it would be ideal to establish a library of MERs from DBS surgeries conducted in multiple medical centers all over the world. A large sample size helps verify the applicability of each algorithm and makes possible the comparison of the STN detection results using different algorithms.
Chapter 5

Conclusion

In conclusion, this study gives a detailed description of the traditional k-means clustering algorithm and its application on STN localization. We introduced a novel set of features into the model. 12 of these features were spike-based and the other 6 features were spike independent. The feature activity maps of the newly designed features, mean inter-spike interval (MISI) and bursting rate (BR), demonstrated that they have good discriminatory power in STN identification. Data preprocessing may be simple but not trivial. Unlike many other similar studies where researchers did standardization and normalization only, we also considered the skewness in each feature. An additional square root transformation was conducted on those features with a strong positive skewness. The reduction of skewness in the feature space proved to be helpful in getting a good clustering result when our k-means clustering algorithm employed squared euclidean distance as its distance metric. Furthermore, modification of the original k-means clustering by integrating the depth information enables the algorithm to generate clustering result with much less noise. A clean clustering result makes the automated identification of STN boundaries possible, removing the necessity of manual demarcation. The simpleness of this unsupervised learning algorithm provides our methodology with many advantages such as easy interpretation, low computational complexity, and good generalization. We are optimistic that the further development of simple and effective machine learning algorithms on microelectrode recordings will eventually provide online solutions to all kinds of localization problems in the brain. From a clinical perspective, this is expected to lead into a decreased time spent inside the operation room and hopefully improve the clinical outcomes.
References


