International Research Journal of Engineering and Technology (IRJET) e-ISSN: 2395-0056
Volume: 07 Issue: 01 | Jan 2020 www.irjet.net p-ISSN: 2395-0072

Differentiation of Brain Sub-Cortical-Structures with Effective Micro Neuro Sensors Recording Based Support Vector Machines through Deep Brain Stimulator in Parkinson`s Disease

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Abstract - *In this study, we investigated an efficient novel methodology for the classification of Microelectroneurosensor Signals recording (or Microelectrode Recording (MER) of subthalamic-nuclei (STN) neurons obtained though deep brain stimulator in Parkinson's disease (PD) by employing Support Vector Machines concept. We report some preliminary results. Two models are employed in this study, namely, a model that elicitates and extrapolates certain features through electro-neuro-physiological MER signals and by using support vector machines that mainly classify through supervised machine learning. The two model techniques are made as a method and applied to the problem of the detection of sub-cortical structures of PD brain, such as STN, substantia-nigra (SN) pars compacta (SNpc)/ pars reticulata (SNpc), thalamus-nucleus (TN), and zona-incerta (Zi). The results showed excellent classification circa ~ 99%. The investigation in this study certainly avoids human intervention through subjectivity in pinpointing or confining the subcortical structures particularly STN. We used microelectrodes as micro-neuro sensors vis-□-vis and vice-versa. Deep Brain Stimulator (DBS) is a device-based well-developed and well-established innovative/frontier neurosurgical-therapeutic-method that reduces the symptoms of Parkinson`s disease(PD) and restores/increases motor-functioning. DBS gives a unique-opportunity to study the electrical-oscillatory neural-activity of various sub-cortical-structures in PD-subjects.*

Key Words**:** *Deep Brain Stimulation (DBS), Microelectrode Recording (MER), Parkinson`s Disease (PD), Subthalamic-Nuclei (STN).*

1. INTRODUCTION

One of the most commonest neurologic disorders that elders experience, Parkinson's disease (PD) is a devastating diagnosis affecting approximately 2 of every 1,000 older adults. Although there is currently no cure and current PD treatments help alleviate only the symptoms rather than the disease's progression, fresh hope such as deep brain stimulation (DBS) lies in new research focused on neuroscience especially computational neuroscience and cognitive system for neuroprotection using the novel engineering developments which are major breakthroughs in engineering and medical sciences such as magnetic resonance imaging (MRI), DatScan, Positron Emitted Tomography (PET), Microelectrode Recording (MER) and Deep Brain Stimulator (DBS)[1]-[15]. Parkinson`s disease (PD) is though caused by a depletion of dopamine in the Basal Ganglia region of the brain, it is usually treated by medical prescriptions such as levodopa (L-dopa) medication through hospital administration and management that restores the dopamine levels. However, through L-dopa there are many side-effects such as dyskinesias (cognitive dysfunction, cognitive dementia, depression, hallucinations, and axial symptoms like body speech problems and many more). Microelectrode guided neurosurgery can also be used for treating PD in severe cases or when medication through medical management does not function. These surgical procedures include a pallidotomy or a Deep Brain Stimulation (DBS). During a pallidotomy a lesion is made in the basal ganglia, while in a DBS a microelectrode is implanted to stimulate the neuronal cells in the Basal Ganglia [1].

However, the exact causes of PD are unknown, and it is a chronic, progressive brain disorder that belongs to a larger class of disorders called movement disorders. In PD, one particular population of brain cells—those that produce a chemical messenger called dopamine—become impaired and are lost over time. "The loss of these brain cells causes circuits in the brain to function abnormally, and those abnormal circuits result in movement problems," [1]-[15]. Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the convolution of four classes of cardinal motor symptoms or feature manifestations, namely, frequency of tremor, Bradykinesia, rigidity, and postural instability. Because, there is currently no definitive test for

PD, the diagnosis is based on the presence of clinical-symptoms and the response to antiparkinsonian-medications [1]. One of the most established scale for assessing disability and impairment in PD is the Unified Parkinson's Disease Rating Scale (UPDRS) part III score of Hoehn & Yahr stage (H&Y) [2], which is based on subjective clinical evaluation of symptoms. A need therefore exists to objectively quantify PD characteristics in order to improve the diagnosis, define disease subtypes, monitor disease progression and demonstrate treatment efficacy [3], [4]. Surgical approaches to the treatment of Parkinson's disease (PD) have been developed primarily in response to the failure of medical therapies to provide long-term relief from the disabling motor symptoms of the disease. Refined microelectrode recording (MER) techniques allow more detailed physiologic mapping of the subthalamic-nuclei structures in the brain operating room, providing more detailed knowledge of micro-neuro-sensors (the microelectrodes) location prior to neuro-ablation or embedding the stimulating microelectrodes to be implanted in the surgical theaters. The introduction of long-term deep brain stimulation (DBS) as an alternative to irreversible neuroablative procedures may amplify, embellish, enhance, improve and exaggerate the safety of these procedures while maintaining therapeutic efficacy.

The signal analysis methods of electrical and electronics biomedical engineering and microelectrode recordings (MER) is largely an art developed by engineering community and practiced by the skilled neurosurgeons in multispecialty multinational superspecilized hospitals and research and development laboratories who view and listen to the extracellular electrical-activity of neurons along a linear-trajectory towards the nominal target-area or target-region. Presently the interpretation of MER signals examination is primarily performed by the stereotactic functional neurosurgeon based on the properties of the MER signals determined by examining the time domain behavior of the signal simultaneously (parallelly) or concurrently on computer monitors and on oscilloscopes and listening to the signal through multimedia tool-kits such as conventional and cutting edge technological loud-speakers. As the neural activity varies from one structure to another within the brain, hence, the possibility of targeting errors to DBS necessitates the use of some form of intraoperative neurophysiologic monitoring to confirm the correct targeting during surgery [2]-[3].

The purpose of the development of artificial intelligence based machine learning techniques for MER processing is to assist the surgical team in determining the optimal location of the lesion or DBS lead [4]-[6]. Support Vector Machines (SVM) are powerful automatic learning structures, based on the statistical theory of learning, capable of resolving classification, regression and estimation problems. The techniques have been the aim of much research in recent years. The method is given in [7] in the late seventies for solving pattern recognition problems. In the 1990s, use of the method became widespread [8] and it is currently the object of great interest. Support Vector Machines offer improvements over traditional learning methods: the size of the network is not established from the outset and the maximum generalization level is guaranteed mathematically. The work in this study reports supervised machine learning to integrate certain features. Specifically, we use 6 mathematical features [6], each measuring different characteristics of the signals from the microelectrode recordings, in order to quantify changes in neural activity from subcortical structures, and that could be used in DBS. We analyzed the changes of Unified Parkinson's Disease Rating Scale (UPDRS) part III score of Hoehn & Yahr stage (H&Y), the decrease in anti-Parkinsonian medication (L-dopa prescribed by the medical management or administration), and adverse effects. Furthermore, in this study, the possible correlation between the microelectrode location and prognostic clinical outcome was addressed. This issue has recently gained more attention in DBS and related follow--up studies.

2. OBJECIVES

The aim of the study is to develop the mathematical frameworks and techniques for microelectroneurosensor signals recording (MER) of subthalamic-nucleus (STN) processing and is to aid the stereotactic functional neurosurgical team for determining the optimal location of the lesion or DBS microelectroneurosensor (the microelectrode). Each of these mathematical features measures different characteristics of the signals from MER, in order to compute the changes in neural-activity from sub-cortical structures like STN, SN which is highly useful for the deep brain stimulus. For optimal therapeutic efficacy of DBS, it is imperative to have accurate microelectrode placement.

3. METHODS AND TECHNIQUES

A retrospective study was carried out at a tertiary care hospital with a dedicated movement disorder unit from South India. 46 patients with diagnosis of PD as per United Kingdom Parkinson disease society brain bank criteria were included. All the patients were willing to undergo the procedure and fulfilled the following criteria to be eligible for STN-DBS i.e., they had disease duration of 6 years or more, good response to levodopa, able to walk independently in drug "on" state and had normal cognition. All PD patients who were wheelchair or bed bound, had dementia or severe psychiatric disturbances were excluded. Surgery was performed in all by a qualified neurosurgeon. Stereotactic targets were acquired using a specialized system with a stereotactic frame (CRW) which has a luminant MR localiser. The targeting was performed according to Lozano's technique – 2mm sections are taken parallel to the plane of anterior comissure-posterior commissure line and at the level with maximum volume of red nucleus, STN is targeted at 3 mm lateral to the anterolateral border of red nucleus.

The co-ordinates are entered into a stereocalc software which gives the co-ordinates of the STN. Another neuro

navigation software –framelink is also used to plot the course of the electrodes and to avoid vessels. The surgery is performed with two burr holes on the two sides based on the co-ordinates. Five channels with are introduced with the central channel representing the MRI target while medial and lateral are placed in the x axis while anterior and posterior are placed in the y axis to cover an area of 5 mm diameter. Intra-operative recording was performed in all 5 channels. All five microelectrodes are slowly passed through the STN and recording is performed from 10mm above to 10mm below the STN calculated on the MRI. STN IS identified by a high noise with a large baseline and an irregular discharge with multiple frequencies. Fig 2 shows the microelectrode recording which is obtained from the STN. The channel with maximum recording and the earliest recording were recorded on both sides. Intraoperative test stimulation was performed in all channels from the level at the onset of MER recording. Stimulation was done at 1mv, 3mv to assess the improvement in Bradykinesia, rigidity and tremor. Appearance of dyskinesias was considered to be associated with accurate targeting. Side effects were assessed at 5mv and 7mv to ensure that the final channel chosen had maximum improvement with least side effects. Correlation was assessed between the aspects of MER and the final channel chosen in 46 patients (92 sides).

3.1. The Database

Intra-operative microelectrode signal recordings and analysis were performed on six PD patients who were locally anesthetized and underwent for the implantation of the microelectrodes through DBS surgery. Four patient's recordings performed. Visualization of neural data started 10 mm above the target data. Every 1 mm one new site was created if the distance between the microelectrode and the target point was larger than 3 mm. At distances less than 3 mm, sites were created every 0.5 mm. MER signals were labeled by the movement disorders specialists in neurosurgery and neurology and also neurophysiology. At each site the acquisition lasted two seconds with a sampling frequency of 25 kilo-Hertz and 16-bit of resolution of analogue to digital converter. In total, there are 52 neural recordings divided in four classes: 13 signals from STN, 13 signals from SNpc, 13 signals from TN, and 13 from Zi. These procedures were performed at a tertiary care hospital in south India. The following Figures shows MER signal recordings of STN, SNpc, Thalamus, and Zona-Incerta.

The first Figure depicts the subthalamic-nucleus recording, second substantia nigra, third zona-incerta, and fourth Thalamus Nucleus.

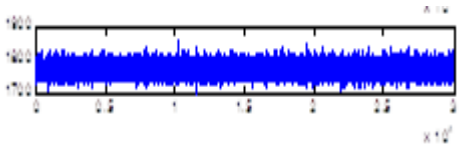

Fig 1. Microelectrode recording of STN signal

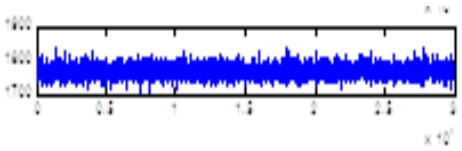

Fig 2. Microelectrode recording of SNpc signal

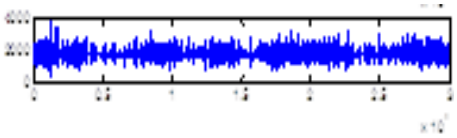

Fig 3. Microelectrode recording of Zona-Incerta signal

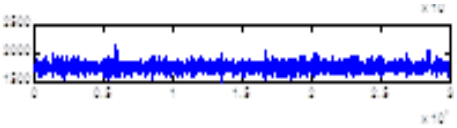

Fig 4. Microelectrode recording of Thalamus

3.2 Computational Features

The features are briefly discussed in below. A brief description of each of the feature vector and the corresponding formula for its computation is explained here. Where, *X* is the data epoch vector of length *N*.

3.2.1. The Length-of-Curve

It is used to obtain the stability of the values of a signal, i.e., the STN neuron stability. If the value of this feature is low in an interval, provided by the user, the signal is stable, else, it is unstable. The following expression (1) defines the computation of this calculation:

$$L = \sum_{i=1}^{N} |(x_{i+1} - x_i)| \qquad (1)$$

Here, x_i is the sample size of the data-set X

Which is equal to (x_1, x_2, x_3, …, x_N), i.e.,

$$X = (x_1, x_2, x_3, \ldots, x_N).$$

Upon computing the curve-length (L), the threshold value is calculated in the following

3.2.2. The Threshold

The determination of the threshold is based on the computation of the deviation of the data to confine how the data in a window of size *N* are scattered. This feature can be computed by the following expression (2)

$$\gamma = \frac{3}{N-1}\sqrt{\sum_{i=1}^{N}(x_i - \overline{X})^2} \qquad (2)$$

where, Ẋ is the average of the data-set.

3.2.3. Peak to peak signal strength

The peak to peak (maximum positive peak (+Ve) to maximum negative (-Ve) peak, i.e., number of peaks whose value is positive (+Ve) is verified by the following expression

$$K = \frac{1}{2}\sum_{i=1}^{N} max\{0, |sgn[x_{i+1} - x_i] - sgn[x_{i+2} - x_{i+1}]|\} \quad (3)$$

where

$$\max(a, b) = \begin{cases} a & if\ a > b \\ b & if\ a < b \\ a\ o\ b & if\ a = b \end{cases}$$

$$\text{sgn}(x) = \begin{cases} 1\ if\ x > 0 \\ 0\ if\ =< 0 \\ -1\ if\ x < 0 \end{cases}$$

3.2.4. Root Mean Square (RMS)

The RMS is defined as the square root of the average of the sum of the squares of the signal. It is mainly to represent the amplitude (strength of the STN neural signal) of the tremor. The root mean square value is computed by the following expression

$$\delta = \sqrt{\frac{1}{N}(\sum_{i=1}^{N} x_i^2} \quad (4)$$

3.2.5. The Normalization of Non-Liner Energy

The process of converting given signal into different phase values/different amplitudes and with different phase frequencies is normally defined as nonlinear processing. The phase of the signal or waveform represents the shape of the signal/waveform. This feature gives the stability of the STN neurons and its average is evaluated by the following expression

$$\Psi = (\frac{1}{N-2})\ \sum_{i=2}^{N-1} x_i^2 - x_{i-1}x_{i+1} \quad (5)$$

3.2.6. Turns Amplitudes (TA)

The turns amplitudes or zero-crossings or turns amplitude analysis (TAS) are all synonymously used in medical diagnostics especially in electro-neuro-medical diagnostics which is also called Willison`s (1962) method. This feature represents the strength of the signal and is computed by the following expression.

$$K = (\frac{1}{2})\sum_{i=1}^{N-1} |sgn(x_{i+1}) - sgn(x_i) \quad (6)$$

3.2.6. Support Vector Machines

This approach is a new model and module for efficient data classification and also regression [7]. It is coupled with statistical learning theory and hypothesis very efficiently [8] Which is an estimation algorithm that separates the data in to two classes, however, as all classification problems are capable of be restricted to reflection of the two class taxonomy problem without loss of generality or simplification, and this technique is capable of classification of tough tasks especially as an application in medical diagnostics for categorization. This uses instances of information inside the decision borders referred to as *support vectors* and, by means of quadratic programming, which attempt to induce linear or hyper plane separators which exploit and maximize the minimum distance between the classes. In order to process non linear ratios, it uses kernel-functions to project the information in spaces of greater dimensionality and then transform them into linearly separable classes (see Fig. 5).

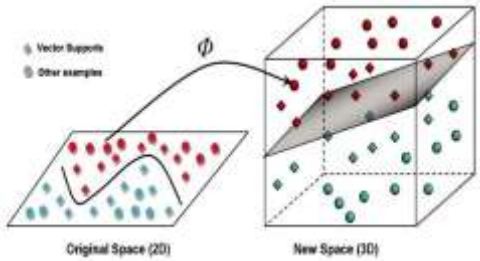

Fig. 5 Paradigm shift from original two-dimensional-space to three-dimensional-space to separate the classes linearly (of instances projection from 2D to 3D).

Note that here in this SVM the kernel is not fixed unlike in some signal transforms such as Discrete Fourier Transform. The SVM is a learning machine, and therefore it is based on imparting training, testing and performance evaluation, and validating that are common steps in every learning-procedure. Imparting training involves optimization of a convex-cost-function where there is no local minima to obscure the learning process. The testing is based on the model evaluation using the support vectors to classify a test dataset. Performance is based on error rate determination as test-set data-size tends to perpetuity (in continuous loop infinitely).

4. IMPLEMENTATION AND PERFORMANCE

A two seconds data was recorded with a sampling frequency at the rate of twenty four thousand cycles per second (i.e., 24000 Hz) leading to 48,000 samples for each recording. Considering a trajectory of 13 records for each of the subcortical structures, the final trajectory is made up of 52 recordings and has a total of 2,496,000 samples. Then the final trajectory is divided into consecutive windows of 4,992 samples and for each of these windows we determined the six computational features obtaining a total of 500 instances

(the signatures or patterns) per feature which is given in the following expression

$$X = \begin{array}{c} \\ X_1 \\ X_2 \\ \vdots \\ \vdots \\ X_n \end{array} \begin{array}{c} \begin{array}{cccccc} V_1 & V_2 & \cdots & \cdots & V_p \end{array} \\ \begin{bmatrix} x_{11} & x_{12} & \cdots & \cdots & x_{1p} \\ x_{21} & x_{22} & \cdots & \cdots & x_{2p} \\ \vdots & \vdots & \ddots & \cdots & \vdots \\ \vdots & \vdots & \cdots & \ddots & \vdots \\ x_{n1} & x_{n2} & \cdots & \cdots & x_{np} \end{bmatrix} \end{array}$$

Fig. 6. Vector Data Matrix

where n = 500 instances y p = 6 variables i.e., computational features.

The vector data-matrix is amassed so that the first 125-instances correspond to the STN, second 125 instances correspond to the SNpc, third 125 correspond to the TN, and the last 125-instances correspond to the Zi. The computational features (or Statistical indexes) of this study performed using Mat-Lab.

5. RESULTS

The Gaussian and polynomial-kernels, with different parameter-values, were used to obtain the best-support-vector-machine-model. The best-model was the one which reached the highest-value of Kappa *K-Statistic* using *n*-fold cross-validation. The *n*-fold cross validation methodology allows us to obtain realistic errors using the complete database. Cross-validation consists of dividing the initial database into *n-subsets* and selecting *n-1 subsets* to generate the model. The *subset* not used in the process is used to compute the error. This procedure is repeated n-times, each time using a different-test-subset. Lastly, the error was computed by the arithmetic-mean of the *n-partial-samples of errors*. In our study, *n*=10. The Kappa *K*-statistic is one of the most widely-used parameters. This coefficient determines the degree of agreement between categorical variables. It is an efficient-parameter than the % of correctly classified examples (*Precision*) since *K* also takes into account those cases in which agreement occurs by chance. Thus, a *K*-value of 1.0 represents a statistically perfect-model while *K*=0 is the value expected for a model obtained by chance. According to some authors [10], *K* can be considered excellent for values greater than 0.75, good between 0.40 and 0.75 and poor for values below the 0.40. Other parameters were used to evaluate the models prediction capacity. *Precision* is one of these parameters, defined as the proportion of examples correctly classified divided by all the elements that were classified for this class. *Evoke (or recall)* is defined as the proportion of examples correctly classified divided by all elements of this class. *F-Measure* is the harmonic mean of *accuracy* (or precision) and *Recall*. Values of these parameters close to one indicate good exactness in the predictions for each-class. To obtain a best model, different values of the complexity parameter *C* were tested with $C = 10^k$ where *k*-values were from –3 to 3 with a step of 0.2 (31 values). Also, different values of the exponent (*e*) for the *polynomial kernel* and gamma (*g*) for the *Gaussian kernel* were used. In particular, *e* values were 1, 2 and 3, and *g* values were 0.005, 0.01, 0.02, 0.03, 0.05 and 0.1. Therefore, the number of models trained with *polynomial kernel* was ninety three 93 (C x e= 31x3 =) and with *Gaussian kernel it* was 186. The results of the best model obtained with *polynomial kernel*, *C* = 10.0 and *e* = 1 are shown in Figure 6.

```
Time taken to build model: 0.75 seconds

=== Stratified cross-validation ===
=== Summary ===

Correctly Classified Instances         497               99.4    %
Incorrectly Classified Instances         3                0.6    %
Kappa statistic                          0.992
Mean absolute error                      0.2507
Root mean squared error                  0.3126
Relative absolute error                 66.8405 %
Root relative squared error             72.1988 %
Coverage of cases (0.95 level)         100      %
Mean rel. region size (0.95 level)      75.25   %
Total Number of Instances              500

=== Detailed Accuracy By Class ===

               TP Rate   FP Rate   Precision   Recall  F-Measure   ROC Area  Class
                 1         0          1         1         1          1        Thalamus
                 0.992     0.003      0.992     0.992     0.992      0.996    Zona Incerta
                 0.992     0.003      0.992     0.992     0.992      0.997    Subthalamic Nucleus
                 0.992     0.003      0.992     0.992     0.992      0.995    Substantia Nigra
Weighted Avg.    0.994     0.002      0.994     0.994     0.994      0.997

=== Confusion Matrix ===

   a   b   c   d   <-- classified as
 125   0   0   0 |   a = Thalamus
   0 124   0   1 |   b = Zona Incerta
   0   1 124   0 |   c = Subthalamic Nucleus
   0   0   1 124 |   d = Substantia Nigra
=== Confusion Matrix ===

   a   b   c   d   <-- classified as
 125   0   0   0 |   a = Thalamus
   0 124   0   1 |   b = Zona Incerta
   0   1 124   0 |   c = Subthalamic Nucleus
   0   0   1 124 |   d = Substantia Nigra
```

Fig. 6. 10-folds cross-validation results obtained with the best SVM model

In the above Figure 6, it is possible to observe that the SVM model was able to classify correctly 497 (99%) from a total of 500 instances. Parameters like *accuracy* or *evoke*, with values over 0.99 for the four classes (STN, SNpc, TN, and Zi), would be considered exceptional. Also, the ROC-Areas values were very high. Finally, in the confusion matrix we can observe that only three cases were not classified correctly and according to *K,* the best model obtained was first-rate (*K* = 0.992) and is exceptional.

6. CONCLUSION

This work presented the results of our basis study and groundwork study making use of two methodologies for the characterization of subcorticals structures from Parkinson's disease patients. The results obtained show how the computational features applied in this work a MER from Parkinson's patients are able to extract, quantify and differentiate the information contained of the neural activity between the subcortical structures. After obtaining the computational-features for each sub-cortical-structures, and using them on the SVM algorithm for classification, the results showed that SVM was be able to classify acceptably 497 (99%) from the 500 instances. Lastly, various

parameters to evaluate the prediction capacity of the model were obtained, indicating good accuracy in the predictions for each sub-cortical-structure (the class). Since the neural activity varies from one structure to another within the brain, the possibility of targeting errors to DBS necessitates the use of some form of intraoperative electro-neuro-physiologic monitoring to confirm the exact-targeting during-surgery, so that the use of methodologies from data mining like the one presented in this work could be used in the process of localization of the subcortical structures and mainly the subthalamic nucleus (STN) for neurostimulation.

ACKNOWLEDGEMENT

The authors wish to thank the Dept of Science & Technology (DST) for the Cognitive Science Research Initiative CSRI Project Grant [# SR/CSRI/201/2016] funded by the DST, Ministry of Science & Technology (MST), Govt of India (GoI), New Delhi.

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