Partitioning Methods used in DBS Treatments Analysis Results

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Abstract— **Parkinson's disease is a neurodegenerative disorder and is associated with motor symptoms, including tremor. The DBS (Deep Brain Stimulation) involves electrode implantation into subcortical structures for long-term stimulation at frequencies greater than 100Hz. The mechanism by which chronic, electrical Deep Brain Stimulation with high frequency, suppresses tremor in Parkinson's disease is unknown, but might involve a gradual change in network properties controlling the generation of tremor.**

First, we performed linear and nonlinear analysis of the tremor signals to determine a set of parameters and rules for recognizing the behavior of the investigated patient and to characterize the typical responses for several forms of DBS.

Second, we found patterns for homogeneous group for data reduction. We used Data Mining and Knowledge discovery techniques to reduce the number of data. Then, we found "clusters" the most well-known used and commonly partitioning methods used: K-means and K-medoids. To support such predictions, we develop a model of the tremor, to perform tests determining the DBS reducing the tremor or inducing tolerance and lesion if the stimulation is chronic.

I. Introduction

PARKINSON's disease is a serious neurological disorder with a large spectrum of symptoms. One of the disabling symptoms is the tremor that has a large amplitude and low frequency (4-6Hz).

The disease manifests itself very differently from one individual to another, sometimes years to go to observe a significant limitation of daily activities. Symptoms become increasingly evident as the disease evolves [1].

Deep Brain Stimulation (DBS) is an electric therapy approved by FDA for the treatment of Parkinson's disease (PD) in 2002 and used now to treat the motor symptoms like essential tremor. It consists of a regular high frequency stimulation of specific subcortical sites involved in the movement-related neural patterns [2].

Neural stimulator generated constant-width current pulses at a frequency between 130 and 185 Hz and delivered through subcutaneous wires and microelectrodes to one among the subthalamic nucleus (STN), the internal part of the globus pallidus (GPi) or the nucleus ventralis intermediate of thalamus (Vim) [1]. The choice of the target depends on the type of disease to be treated, with the Vim usually preferred in the case of essential or Parkinsonian tremor and the motor part of STN or GPi in case of dystonia or PD [2].

Commercially available implanted pulse generators are able to vary the amplitude, pulse width and frequency of the pulsatile current applied to the large nucleus. Due to limitations in the current systems, electrical stimulus is applied in a controlled-voltage manner.

The exact neurobiological mechanism by which DBS exerts modulator effects on brain tissue are not yet full understood. It is unknown which part of the neuronal structure (cell body, axon) is primarily modulated by DBS.

Stimulation parameters (amplitude, pulse width, duration, amplitude) also clearly have an impact on the effect: a nonlinear relationship between stimulus duration and amplitude (voltage/current) has been observed [2]. Neurophysiologic recordings during stimulation in patient with Parkinson's disease have demonstrated, that the oscillatory activity occurring between cortex and midbrain in modulated by DBS. In summary, effects of DBS crucially depend on the target and the stimulation parameters [2].

The current study was motivated by the wish to develop a batter understanding of potential; mechanisms of the effects of Deep Brain Stimulation on Parkinsonian tremor by studying the tremor dynamics that occur during the on/off of high frequency DBS in subjects with Parkinson's disease.

First, we made a linear and nonlinear analysis [3], [4] of the tremor signals (available on the internet at [5]) to determine a set of parameters and rules for recognizing the behavior of the investigated patient and to characterize the typical responses for several forms of DBS.

Second, we found representatives for homogeneous groups in order to *data reduction*. Then we found "clusters" and describe their unknown properties. We used K-means and k-medoids Clustering Algorithms because these algorithms solved the well known clustering problem. The procedure follows a simple and easy way to classify a given data set through a certain number of clusters (assume k clusters) fixed a priori.

Therefore, it is desirable to predict, before we pursuit with this type of operation, if the DBS will give good results in a specific case. To make such predictions, we need a model of the tremor, on which to perform tests to determine if the DBS procedure will reduce the tremor.

A general mathematical structure capable of incorporating this kind of dynamical behavior is necessary to develop an accurate functional model of the behavior of biological systems.

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An accurate, general model of a system can allow the investigation of a wide variety of inputs and behaviors in sillico, without the time or resources required to perform the same investigations in vivo.

II. Clinical Databases Structure

Parkinsonian tremor time series are available on internet.

These data were recorded using a low-intensity velocity laser in subjects with Parkinson's disease receiving chronic, high frequency DBS at a sampling rate of 100 Hz.

Tremor signals were recorded to the subject's index finger in a resting position continuously throughout switching the DBS on and off. Tremor in the finger is detected and coverted to a calibrated voltage output that is proportional to finger velocity.

Databases were collected using the MacLab data acquisition system (V 3.5.6/S, AD Instruments Pty Ltd., Castle Hill Australia) and exported to Matlab for plotting. The data were converted from volts to meters/second and a three-point median filter was applied to interpolate across artifact in the data created by the rotation of the laser wheel [5].

The amplitude and the pulse duration of DBS were constant in a particular subject, but varied between subjects, since the parameters are determined clinically to optimized tremor suppression and to minimize undesirable effects for each individual [5].

Tremor was recorded under five conditions:

--no DBS and no medication

--DBS on and no medication

--no DBS and no medication

--DBS on and medication on

--no DBS and no medication (but subjects initially received DBS and data were recorded 15, 30, 45, 60 minutes after the end of the DBS).

We analyzed tremor signals from 16 subjects with Parkinson disease, ages between 37 and 71 years, 11 men and 5 women, which resulted in a number of over 101 recordings, as in the database.

For the "medication off" condition, the subject did not take any medication for at least 12 hours. For the "medication on" condition, the subject took 150% of his or her morning dose of Modopar and testing began after the neurologist determined the medication had taken effect (approximately 40 minutes) [5].

The 16 subjects can be divided into two groups:

--Subjects 1-8 with high amplitude tremor (HAT) who are receiving DBS to relieve tremor (Group 1),

--Subjects 9-16 with low amplitude tremor (LAT) who are receiving DBS to relieve other symptoms such as rigidity or dyskinesia (Group 2). [5]

The recordings of this database are of rest tremor velocity in the index finger of 16 subjects with Parkinson's disease (PD) who receive chronic high frequency electrical Deep Brain Stimulation (DBS) either uni- or bi-laterally within one of three targets:

--Vim = the ventro-intermediate nucleus of the thalamus (3 subjects),

--GPi = the internal Globus pallidus (7 subjects),

--STN = the subthalamic nucleus (6 subjects).

III. Methods

We demonstrate that the nonlinear dynamics parameters of a Parkinsonian tremor have certain peculiarities and can be used on knowledge discovery.

For the linear and nonlinear analysis of tremor signals, using linear and nonlinear dynamic parameters, we used several software packages, like CDA (Chaos Data Analyzer Programs), NLyzer (Nonlinear Analysis in Real Time) [6], TISEAN (Nonlinear Time Series Analysis), WFDB Software, Matlab Software, Physio Toolkit Software.

The CDA software allows us to study the phase diagram, the probability distribution, power spectrum, Lyapunov exponent, correlation dimension, capacity dimension, self-correlation function, Poincare sections.

The NLyzer is a software package used for both linear and nonlinear analysis of signals. TISEAN package does contain a number of tools for *linear* time series analysis (spectrum, autocorrelation function, histograms, etc.), these are only suitable for a quick inspection of the data.

The methods used in our research were:

--statistical analysis – the skewness, data distribution and Shannon entropy (using SPSS and SAS toolkit Software);

--linear analysis – self-correlation function of the time series, Fourier analysis, power spectrum;

--nonlinear analysis – auto mutual information (multi dimensional embedding), fractal dimension, spectral density of the time series, time delay embedding, Lyapunov exponent.

For Data Mining and Cluster Analysis using Partitioning Methods (centroid-based technique – the K-means methods and representative object-based technique – the k-medoids methods) we used STATISTICA Software version 9.

IV. Data Analysis

A. Conventional methods used to analyze tremor

Conventional methods used to analyze tremor include amplitude and frequency analysis. Amplitude are often given in Root Mean Square, amplitude distributions, peak to peak amplitude, average absolute amplitude.

Frequencies are often presented in half power frequency, total power in consecutive band, semi-inter quartile range, number of movement reversals [2].

Ganter et al. in 1992 were the first to consider nonlinear dynamics approaches to tremor time series analysis. They measured acceleration of the stretched hand and applied three methods to the tremor time series: the correlation dimension, a test for linearity in the form of an autoregressive moving average ARMA model, and the fitting the data to linear state space model.

There is a growing agreement among tremor researchers that Parkinson tremor is associated with cluster of neurons, located in subcortical structures such as thalamus and/or basal ganglia.

B. Linear and nonlinear time series analysis of Parkinsonian tremor

Linear analysis of the signal is mainly using Fourier analysis and reporting made comparison of the amplitude frequency bands. Based on the Fourier spectrum in the range of 0-25 Hz and amplitude-time representation, a number of parameters are used to characterize the tremor signal [3].

Linear analysis of the signals is mainly performed using Fourier analysis and do a comparative report on different amplitude bands. For each time series (2131 samples) of analysis we chose the following parameters: the autocorrelation function - ACF (Correlation length = 604), spectrum of power - FFT (60 dB resolution), deviation, fast mutual information, conditional entropy.

Filtering a time series may be thought of as removing some components of its Fourier transform and then taking the inverse Fourier transform to get a new time series that is a filtered version of the original. Aside from amplitude, the most often used measure of tremor is frequency [4]. Many reports suggest that Parkinsonian tremor is typically in the range of 4-6 Hz, and the essential tremor is in the range of 4-12 Hz.

There is evidence that physiological tremor is a linear stochastic process and it has been suggested that pathological tremor are more nonlinear and possibly more deterministic [7], [8].

For each of the four cases pursued (DBS on / medication on, DBS on / medication off, DBS off / medication on, DBS off / medication off), for both Parkinsonian tremor signals of high amplitude tremor HAT and for the low amplitude tremor LAT we made linear and nonlinear analysis.

Subsequently, we are interested for starters only in two classes:

--Class 2 - High Amplitude Tremor DBS on / medication off;

--Class 4 - High Amplitude Tremor DBS off / medication off (Simple Parkinson Tremor – highlighted in Table 1).

As it can be seen in Figure 1 and Figure 2, the studied parameters have different evolutions for every type of Parkinsonian tremor, moreover significant differences appear between the signals recorded after 15, 30, 45 and, respectively, 60 minutes after ceasing the DBS action.

The three nonlinear dynamic parameters are represented in detail in Figure 1, Figure 2 and Figure 3.

The values of the correlation dimension will be used in the knowledge-discovery process for the Parkinsonian tremor.

Analyzing the data, we observed that the fractal dimension allows us to recognize with good accuracy the high-amplitude tremor classes.

Using the other parameters/rules, the classification becomes more accurate.

TABLE I
PARKINSONIAN TREMOR CLASSES

Class	Description
Class 1	High or Low DBS on/medication on
Class 2	**High or Low DBS on/medication off**
Class 3	High or Low DBS off/medication on
Class 4	**High or Low DBS off/medication off**
Class 5	High or Low DBS off/medication off – 15 min
Class 6	High or Low DBS off/medication off – 30 min
Class 7	High or Low DBS off/medication off – 45 min
Class 8	High or Low DBS off/medication off – 60 min

Based on the information in Figure 1, Figure 2 and Figure 3 we may conclude:

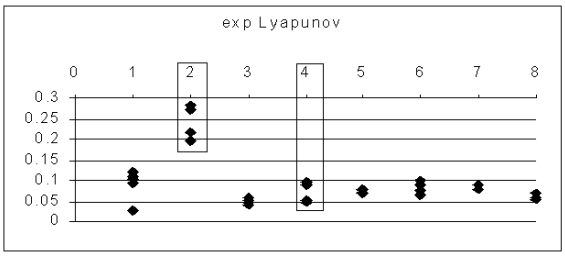

Fig. 1. The values of Lyapunov exponent. For Class 2 (**DSB on and medication off**) using the values of Lyapunov exponent we may distinguish Class 2 from all the other classes

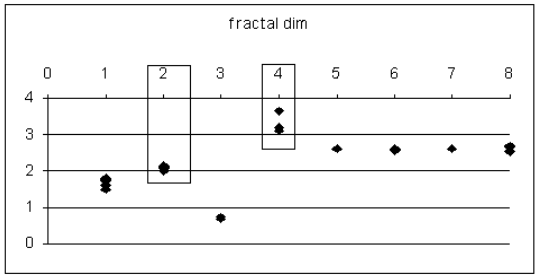

Fig. 2. Graphical values representation for fractal dimension. We observe that in case of Class 4 (**DBS off/medication off** – simple Parkinsonian tremor) there are important differences relative to other classes

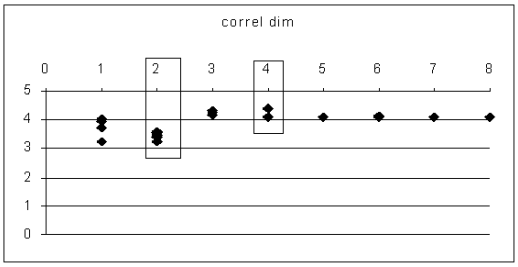

Fig. 3. Graphical values representation for correlation dimension. Only for Class 4 (**DBS off/medication off**) the correlation dimension can reach a value of 4.5 (this value does not exist for any other class)

--using the values of the Lyapunov exponent, we may distinguish class 2 (DBS on/medication off) from all the other classes; in this case the values of Lyapunov exponent are between 0.2 and 0.28;

--using the values of the fractal dimension, we observe that in case of Class 4 (DBS off/medication off – simple Parkinsonian tremor) there are important differences relative to other classes (for Class 4, values between 3.2 and 3.8);

--using the correlation dimension, we notice that for class

2 (DBS on/medication off), its values are between 3.3 and 3.7, and for Class 4 (DBS off/medication off) the correlation dimension can reach a value of 4.5 (this value does not exist for any other class);

--to establish a set of rules for the analyzed classes (2 and 4), we cannot use the correlation dimension; its values are not specific.

In conclusion, for the patients with Parkinson's disease, using the correlation dimension and calculation of Lyapunov exponents, we found evidence that the dynamics are generated by a nonlinear deterministic and chaotic process.

We argue that nonlinear dynamic parameters of Parkinsonian tremor have certain peculiarities and can be used in knowledge-discovery. This data and new knowledge will be integrated in a Knowledge-based System aimed to identify each class of tremor, to worn on atypical responses at DBS and to recommend the stimulation targets (thalamus nucleus).

C. Partitioning Methods

Cluster analysis tools based on k-means, k-medoids, and several other methods have also been buit into many statistical analysis software systems, such as SAS, SPSS and STATISTICA. Given a data set of n objects, and K = the number of clusters to form, a partitioning algorithm organizes the objects into k partitions, where each partition represents a cluster. We adopt two of a few popular heuristic methods, such as:

--the k-means algorithm, where each cluster is represented by the mean value of the objectsin the cluster

--the k-medoids algorithm, where each cluster is represented by one of the objects located near the center of the cluster.

As noted, only the usual parameters (statistics) or just the unusual (nonlinear) taken separately can not identify known dataset/Classes tremble known.

We have 8 preset classes - kinds of tremor (detailed in Table 1), with 10 elements in each class - 10 subjects in each class and one computer for every 10 statistical features of time series.

Because it is easier to illustrate, but also because, classes 2 and 4 are the most significant (Class 2 - signals acquired from patients tremor with DBS without medication, Class 4 - patients without medication and without DBS), we will continue this K-means algorithm and k-medoids algorithm only for these classes.

An important component of a clustering algorithm is the distance measure between data points. If the components of the data instance vectors are all in the same physical units then it is possible that the simple Euclidean distance metric is sufficient to successfully group similar data instances. However, even in this case the Euclidean distance can sometimes be misleading.

The main idea is to define k centroids, one for each cluster. This algorithm aims at minimizing an objective function, in this case a squared error function.

The K-means algorithm is composed of the following steps [9]:

1. place K points into the space represented by the objects that are being clustered; these points represent initial group centroids;

2. assign each object to the group that has the closest centroid;

3. when all objects have been assigned, recalculate the positions of the K centroids;

4. repeat Steps 2 and 3 until the centroids no longer move; this produces a separation of the objects into groups from which the metric to be minimized can be calculated.

Although it can be proved that the procedure will always terminate, the k-means algorithm does not necessarily find the most optimal configuration, corresponding to the global objective function minimum. The algorithm is also significantly sensitive to the initial randomly selected cluster centers. The k-means algorithm can be run multiple times to reduce this effect.

After statistical analysis of data, we obtained a description of prototypes for each class.

Using STATISTICA software version 9 for classes 2 and 4 we obtained the following results:

The K-medoids algorithm is a cluster algorithm related the K-means algorithm and the medoidshift algorithm.

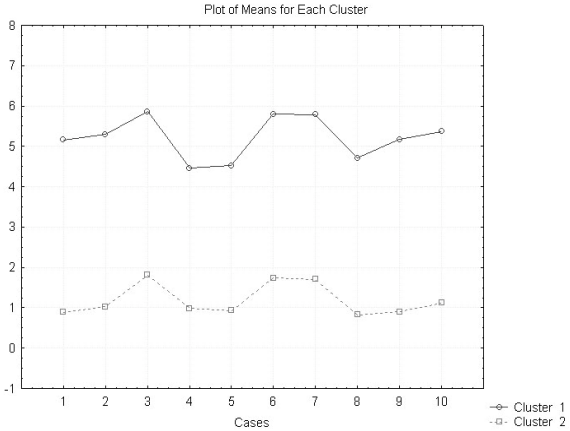

Fig. 4. K-Means Clustering Algorithm for Class 2 and 4 (cluster 1 is Class 2 - High or Low DBS on/medication off and cluster 2 is Class 4 – High or Low DBS off and medication off)

Both the K-means and K-medoids algorithms are partitioned (breaking the dataset up into groups) and both attempt to minimize squared error, the distance between points labeled to be in a cluster and a point designated as the center of that cluster. In contrast to the K-means algorithm, K-medoids chooses datapoints as center.

The most common realization of k-medoid clustering is the Partitioning Around Medoids (PAM) algorithm and is as follows [10]:

1. Initialize: randomly select k of the n data points as the medoids;

2. Associate each data point to the closest medoid. ("closest" here is defined using any valid distance metric, most commonly Euclidian distance or Minkowski distance);

3. For each medoid m

For each non-medoid data point o and swap m and o and compute the total cost of the configuration;

4. Select the configuration with the lowest cost;

5. repeat steps 2 to 5 until there is no change in the

medoid.

We have shown that applied K-means clustering algorithm and K-medoids clustering algorithm solve the well known clustering problem and DBS treatments results identify.

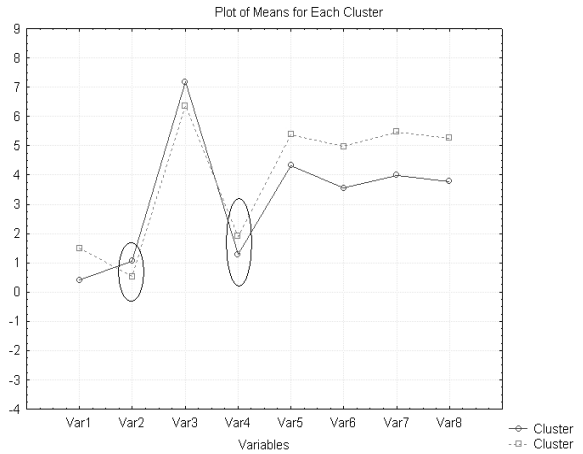

Fig. 5. K-medoids Clustering Algorithm for 2 and 4 classes (var1..var8 represent the 8 classes described in Table 1)

Being an invasive method it is important to predict patient's response to DBS and therefore the next step is to model the Parkinsonian tremor.

D. A model of the Parkinsonian tremor

Modeling of biological systems is difficult due to nonlinearities, time dependence and internal interactions common in physiological and neural systems. To get a true understanding of the behavioral of complex biological systems techniques of nonlinear dynamical systems modeling can be used.

Modeling complex biological systems is very difficult, but the simplest method for predicting output from input is the linear regression. Complexity is added by attempting to model nonlinear relations between input and output.

In [11], [12], we proposed the usage of a nonlinear iterated function in modeling simple biological processes. Controlling the parameters of the nonlinear function, we control the dynamic of the generated process.

To model the nonlinear process of Parkinsonian tremor, we used a mathematical model – van der Pol equation, proposed by Austin and Tsai in 1962.

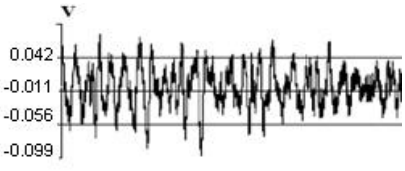

Fig. 6. Time series for a preliminary model obtained by adapting the parameters

Mathematical models of the effect of DBS electrodes on neighboring neural tissue suggest a complex combination of excitation and/or inhibition of neighboring cells, future DBS design may be able to capitalize on this knowledge to tailor DBS electrode geometries and stimulus parameters to selectively isolate intended neural substrate and minimize side effects from stimulation-induced effects on neighboring structures.

E. Model vs. Parkinson tremor Analysis

The statistical analysis for model and original signal (Parkinsonian tremor) is presented in Figure 7, Figure 8 and Figure 9.

As we can see there are visible similarities from statistical point of view, between the original Parkinson tremor and the model.

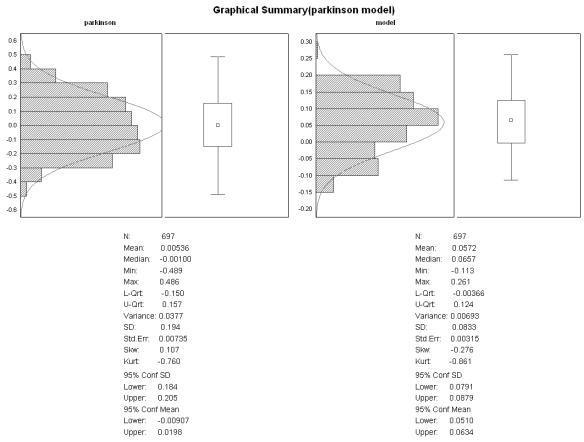

Fig. 7. Model vs. parkinsonian tremor – statistical analysis (I). Can be observed close values of statistical parameters for signal and its model. The number of points in time series is identical, N=697

We notice that between the original Parkinson tremor and the model there are visible similarities up to the time scale.

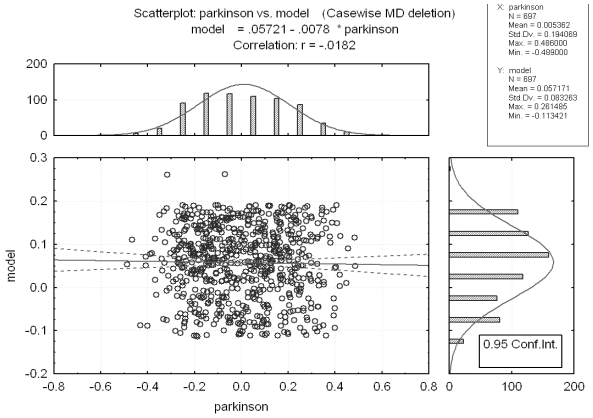

Fig. 8. Model vs. Parkinsonian tremor – statistical analysis (II). Can be observed Confident Interval 0.95, and close values for Mean, Standard Deviation, Max, Min between model and Parkinsonian tremor

The model based on adaptive systems searching the matching Lyapunov exponent, is a preliminary model, which can be further improved.

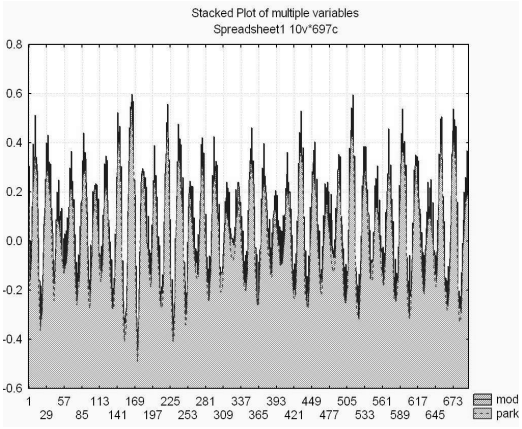

Fig. 9. Model vs. Parkinsonian tremor – time series (III)

The obvious improvement is to use a more elaborated matching criterion, requiring matching several fractal dimensions of the model to the modeled process.

Such an improvement is desirable to avoid time series with similar Lyapunov exponent but differing in other characteristics, including the general appearance [13], [14].

Developing an accurate nonlinear dynamical model of a patient's PD symptoms as a function of DBS could both increase the effectiveness of DBS and reduce the clinical time needed to program the implanted stimulator.

If the model were able to accurately predict the level of symptoms as a result of past stimulation, the model could be used to test all possible parameter settings very quickly in simulation to identify the globally optimal stimulus parameters [8].

V. Conclusions

As it has been demonstrated, classes 2 and 4 are easy to identify, which reinforces the following conclusions:

--only ordinary statistical parameters are not enough for identifying the tremor classes;

--the nonlinear dynamic parameters are not sufficient in distinguishing between different tremor classes;

--a more careful analysis of elements from point 1 and 2 helps to a more easy class identification;

--refinement of current indication for DBS procedure is possible, regarding the risks and benefits of STN versus GPi DBS for PD.

--there is no medical treatment of PD, although medication is available offering significant alleviation of symptoms, especially at the early stage of the disease (the analysis made by us have shown that using only the medication, the symptoms do not disappear - Class 3 (DBS off/ medication on).

--the effect persists for DBS, tremor symptom does not reappear (see Class 4,...,8 DBS off/medication off - tremor signal was recorded after 15, 30, 45, 60 minutes after ceasing the DBS action) .

--to determine if the DBS procedure will reduce the tremor, we need a model of the tremor, on which to perform tests.

We demonstrated that nonlinear dynamic parameters of a Parkinsonian tremor have certain peculiarities and can be used in knowledge-discovery. K-means and K-medoids cluster algorithms are simple algorithms that have been adapted to many problem domains, like identifying DBS classes.

For further research we will use also other unsupervised classification algorithms like: Fuzzy C-means, Hierarchical clustering, Mixture of Gaussians to determine the intrinsic grouping in a set of unlabeled data. Moreover, we compared our results with the result that was obtained by kernel Support Vector Machines using Weka tools [14].

The results obtained are encouraging and we will continue the research on this issue, by modeling other known nonlinear processes. We also demonstrated that, by iterating a linear function, we could model a Parkinsonian tremor, and we developed an adaptive system to build this model [11] - [13].

These data and new knowledge will be integrated in a knowledge-based system aimed to identify each class of tremor, to warn on atypical responses at DBS and to recommend the stimulation targets (thalamic nucleus).

Even if the moment the DBS results seem to be well known, meaning the GPi and STN talamus nucleus stimulation produces Parkinson control (Vim electrical stimulation produces tremor reduction) the mechanism of such effects apparition are not completely unknown.

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