

Resting tremor classification and detection in Parkinson's disease patients

Carmen Camara^{a,b,*}, Pedro Isasi^b, Kevin Warwick^c, Virginie Ruiz^c,
Tipu Aziz^d, John Stein^e, Eduard Bakštein^f

^a Center for Biomedical Technology, Technical University of Madrid, Spain

^b Dept. of Computer Science, Carlos III University of Madrid, Spain

^c Dept. of Cybernetics, University of Reading, UK

^d Dept. of Surgery, John Radcliffe Hospital, Oxford, UK

^e University Laboratory of Physiology, University of Oxford, UK

^f Dept. of Cybernetics FEE, Czech Technical University, Czech Republic

ARTICLE INFO

Article history:

Received 4 March 2014

Received in revised form 1 September 2014

Accepted 22 September 2014

Available online 8 November 2014

Keywords:

Parkinson's disease (PD)

Tremor

Local field potential (LFP)

Deep brain stimulation (DBS)

Discrete wavelet transform (DWT)

Artificial neural network (ANN)

ABSTRACT

Parkinson is a neurodegenerative disease, in which tremor is the main symptom. This paper investigates the use of different classification methods to identify tremors experienced by Parkinsonian patients. Some previous research has focussed tremor analysis on external body signals (e.g., electromyography, accelerometer signals, etc.). Our advantage is that we have access to sub-cortical data, which facilitates the applicability of the obtained results into real medical devices since we are dealing with brain signals directly.

Local field potentials (LFP) were recorded in the subthalamic nucleus of 7 Parkinsonian patients through the implanted electrodes of a deep brain stimulation (DBS) device prior to its internalization. Measured LFP signals were preprocessed by means of splinting, down sampling, filtering, normalization and rectification. Then, feature extraction was conducted through a multi-level decomposition via a wavelet transform. Finally, artificial intelligence techniques were applied to feature selection, clustering of tremor types, and tremor detection.

The key contribution of this paper is to present initial results which indicate, to a high degree of certainty, that there appear to be two distinct subgroups of patients within the group-1 of patients according to the Consensus Statement of the Movement Disorder Society on Tremor. Such results may well lead to different resultant treatments for the patients involved, depending on how their tremor has been classified.

Moreover, we propose a new approach for demand driven stimulation, in which tremor detection is also based on the subtype of tremor the patient has. Applying this knowledge to the tremor detection problem, it can be concluded that the results improve when patient clustering is applied prior to detection.

© 2014 Elsevier Ltd. All rights reserved.

1. Introduction

1.1. Background

Different parts of the brain perform distinct tasks. There are areas devoted to control vision, memory, movement, and so on. The synchronization process between neurons is crucial. A

* Corresponding author at: Center for Biomedical Technology, Technical University of Madrid (UPM), Montegancedo Campus, 28223 Pozuelo de Alarcón, Madrid, Spain.

E-mail address: carmen.camara@ctb.upm.es (C. Camara).

well-coordinated synchrony between neuronal populations results in a decisive mechanism for neural signaling and information processing [1–3]. Some degree of de-synchronization however is the key-point to the proper functioning of neurons [4]. If neurons that do not work properly are in the circuits of the motor functions, this implies a dysfunction of the motor system, which results in conditions such as Parkinson's Disease (PD) [5,6]. In PD the neurons start firing themselves collectively in a periodic manner due to the loss of dopamine secretion [7], and this is the cause of the resting tremor (RT), being characteristic of PD in 70% of patients [8–10].

In this study we have dealt with signals captured through surgical intervention from the Subthalamic Nucleus (STN), the affected

region in all of the analysed patients. In the following sections we refer to this area of the brain when we mention the collected signal. Moreover, the subthalamic nucleus is the preferred target for deep brain stimulation in patients with advanced PD [11].

Parkinson is a neurodegenerative disease, in which patients suffer different symptoms: resting tremor, akinesia and rigidity [12–14]. Some existing patients may have a very severe disabling tremor, while others may not have any tremor at all. In this way, different studies refer to patient classification between tremor-dominant and non-tremor-dominant [15–18]. PD affects approximately 1% of the population over 55 years of age, although it can occur in younger subjects [19], it being the second most common neurodegenerative disease after Alzheimer's disease [20].

There is no recognized cure for PD, although there is treatment for the symptoms [21]. The main drug is L-dopa (L-3,4-dihydroxyphenylalanine – levodopa), the principal metabolic precursor of dopamine. However, the continued use of levodopa, in advanced stages of the disease, entails the so-called ON-OFF effect in patients. The patient goes through OFF periods, in which, despite receiving medication, a worsening of the symptoms appears involving increased rigidity, resting tremor and bradykinesia, in a severe, abrupt and unpredictable way. Moreover, OFF periods alter with ON periods, in which the effect of medication leads to dyskinesia episodes (levodopa-induced dyskinesia (LID)) into patients [22,23].

Several previous works have studied diverse methods to detect and quantify PD tremors [24–26]. Most of them focus the analysis on external body signals such as accelerometry, electromyography (EMG) and/or electroencephalography (EEG) – not exploring what exactly is happening in the areas of interest inside the brain but conversely dealing with the question as a black-box problem. Fortunately, the advantage of our experimentation is that we have access to sub-cortical data, which facilitates the applicability of the obtained results into real medical devices since we are directly dealing with brain signals.

1.1.1. Deep brain stimulation

Applying real-time medical imaging techniques, neurologists can recognize the optimal stimulatory target based on diagnosis for each patient. Electrical stimulation using electrodes implanted into this area then allows significant suppression of PD symptoms. This procedure is called deep brain stimulation (DBS) and is employed in patients who no longer respond properly to their medication [27–29].

The positioning and fine tuning of deep brain stimulation has become very accurate. Nowadays, surgeons can place electrodes in numerous areas of the brain, to turn-on or turn-off, stimulate or inhibit neuronal populations, in order to correct the malfunction of the regions in which the electrodes are implanted [28,30–32]. This technique is not only used in PD, but also in various neurological conditions such as dystonia, epilepsy, depression, or obsessive compulsive disorder.

This therapy is carried out with the use of an implanted medical device called a neurostimulator. Neurostimulators transmit continually high frequency electrical signals (typically 150–180Hz) through one or more electrodes to various parts of the brain, stimulating or suppressing abnormal neuronal activity. Regarding PD, this treatment restores the natural frequencies of neurons, giving back their asynchronous functioning [27,28,33].

Numerous studies conclude that DBS is as effective as ablative therapies [28,30,32]. Furthermore, it has the noticeable advantage of being a reversible therapy and the treatment can be adjusted for each patient – modulating the stimulation supplied by the device.

Implantable medical devices are equipped with an integrated battery. The battery energizes the implant for treatment, monitoring and wireless communication tasks. Once implanted, it can last for up to 8 years, in the case of neurostimulators [34],

to 10 in the case of other implants such as pacemakers [35]. Battery consumption has a direct impact on the device lifetime. Once empty, it has to be replaced, which requires further surgery and may entail some risks [36]. Alternatively a battery can be recharged externally by using magnetic fields, but this option is not available in most stimulators.

Demand driven stimulation (DDS) has already been proposed in previous works [37,38]. The main goal of DDS is to achieve a more intelligent way of stimulation, such that it is only administered when it is necessary. Under this approach, it allows for the brain structures, in which the electrodes are implanted, to perform normally during non-tremor activity instead of being stimulated all the time. This would be beneficial, not only in the case of Parkinson Disease, but also for other movement disorders such as Essential Tremor, in which the patients have a lower degree of tremor. Moreover, the battery would be used in a more efficient way, independently of the way of charging it or the use of more advanced batteries.

Making the neurostimulator into a smart device is also interesting for other approaches. For instance, the processing and analysis of electrophysiological activity by the demand driven stimulation (DDS) device could provide clinically relevant information, such as duration of ON/OFF episodes, tremor frequency, etc.

In this paper we propose a new approach for DDS, in which the detection of tremor is also based on the tremor subtype the patient suffers.

1.2. Tremor

Tremor is a rhythmic and involuntary movement that appears in one or more parts of the body [39]. There are different kinds of tremor, depending on: (1) the circumstances in which it appears: at rest, during maintenance of certain positions or while performing voluntary actions; (2) the affected body area: hands, arms and other body parts; and (3) the frequency at which the tremor manifests itself: low (<4 Hz), medium (4–7 Hz) or high (>7 Hz) frequency bands. According to these three factors, tremor can be classified within a movement disorder pathology.

The Consensus Statement of the Movement Disorder Society on Tremor [40] categorizes subtypes of tremor for this condition into 3 distinctly separate groups:

1. Resting tremor (RT), which is the most characteristic of PD tremors, occurs at a frequency band between 4 and 6 Hz [41] and disappears when a voluntary movement is performed. Its presence is a good criterion for the diagnosis of PD, since this sort of tremor is usually not associated with other pathologies. On the other hand, for the vast majority of PD patients, the resting tremor emerges along with postural and/or kinetic tremors at the same frequency. Therefore many studies simply assume that it is a continuation of the resting tremor under postural, kinetic conditions or vice versa [42–48].
2. Postural tremor takes place when the patient suffers a tremor episode maintaining a position against gravity, for instance keeping the arms 90° horizontally relative to the trunk. Meanwhile kinetic tremor occurs when the subject performs any voluntary movement.
3. The second group is made up of PD patients who have episodes of RT together with postural/kinetic tremor episodes at higher frequencies than the resting tremor, referred to as Essential Tremor (ET). Many research studies justify this since ET episodes can co-exist together with RT episodes in PD [33].
4. The last group includes patients who do not have resting tremor episodes. This subgroup of patients is only affected by kinetic and postural tremor episodes [49].

In this work, using clustering techniques, we show the existence of two patient subgroups within the group-1 of patients mentioned above according to the Consensus Statement of the Movement Disorder Society on Tremor. That is, patients with resting tremor in the band 4–6 Hz. We show that these group-1 patients can be clearly grouped into two further different subgroups. Unfortunately we do not present any particular physiological reasoning behind this result/conclusion, merely it is an observation from the available signals. Nevertheless we hope that this result can be used to conduct research on the existence of these sub-groups of patients and, above all, can be used to improve the treatment of PD.

Apart from this, we also propose, based on this classification, a tremor detection system that distinguishes between the aforementioned subgroups, obtaining better results (higher accuracy) than if clustering is not done (i.e., a detection system that does not segregate into subgroups) as shown in Section 3.2. This approach thus could potentially be used as an effective tool for categorizing the DDS required.

2. Materials and methods

2.1. Patient dataset

Electrophysiology is concerned with the study of electrical activity in the body [50]. If we need to monitor the activity of a small population of neurons, extracellular physiology is currently the best technique.

Using electrodes we can measure the activity of few cells (spiking activity – SA) or instead sense the activity of a larger group of cells (local field potentials – LFP) [51]. In this study we have worked with LFP from the STN. The LFP is a massed neuronal signal obtained using a two step procedure. First we measure the extracellular electrical potential with one of several intracranial microelectrodes. Then the signal is filtered and the resulting signal represents the LFP. In this procedure, the positioning of electrodes has to be very accurate in order to prevent a particular cell dominating the electrophysiological signal. Note that LFP is a signal composed of the activity of a population of cells, which range in number from a few hundred to thousands.

2.1.1. Dataset description and data preprocessing

The dataset used in this study is composed of files from seven patients, who were diagnosed with tremor-dominant PD, and who all underwent surgery for the implantation of a neurostimulator (DBS treatment) at the John Radcliffe Hospital in Oxford, UK. The local research ethics committee of the Oxfordshire Health Authority approved the recordings and informed consent was obtained from each patient.

For gathering the data, patients took part in an observation period of approximately two weeks immediately following implantation, in which recording of data from the electrodes was possible during different sessions effectively at this time the electrodes were semi-implanted. The purpose of this period was to find the most suitable stimulation parameters for tremor suppression. Once the observation period was concluded, the electrodes were connected to the implantable pulse generator (IPG), internalized and the implantation procedure was complete.

To the best of our knowledge, nowadays, this observation period is often suppressed in the majority of hospitals in order to prevent infections and other possible complications. The patient leaves the operating theater with the device – DBS electrodes and IPG – fully implanted. As consequence of this is that a dataset of the same nature (tremor and non-tremor episodes) to the one used in this paper [52] could not be collected. Moreover, considering that the neurostimulator – unlike other devices, such as pacemakers or

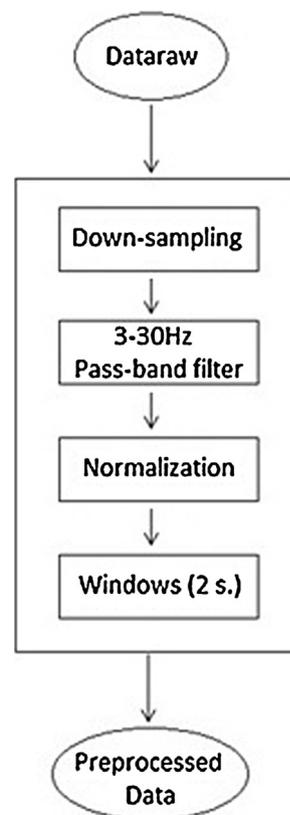


Fig. 1. Preprocessing procedure.

insulin pumps, does not perform a sensing function, it is not viable to obtain the data via telemetry.

On the other hand, during the surgical implantation, in general the patient is continually trembling (medication is suppressed), since the best position for the electrode is chosen by measuring (and actually looking at) the extent of the tremor in real-time. Summarizing, collecting a dataset with both – tremor and no tremor episodes – it is now often a much more difficult task than it used to be. This fact is relevant and was taken into consideration in our experimentation, as explained below.

The DBS device employed was a “Medtronic 3387” with four electrodes spaced 1.5 mm apart and placed in the STN. In each of the patients the electrodes were monitored and a considerable collection of data was obtained for each person. The data was time stamped and labeled by the surgeons involved, distinguishing clearly between tremor and non-tremor episodes.

Before dealing with the data, some signal manipulations were needed. The preprocessing procedure is summarized in Fig. 1 and explained below:

First the signals were down-sampled to the lowest sampling frequency used (250 Hz), since not all the files were originally sampled at 250 Hz.

Secondly a 3–30 Hz Chebyshev Type II passband filter was used on the LFP signals. LFP signals contain movement artefacts at 1–2 Hz and this set to 3 Hz the low cut-off frequency. Frequencies above the beta-band (>30 Hz) are considered to have little tremor-related information [53]. By fixing the upper cut-off frequency at 30 Hz we excluded the 50 Hz line noise as well. We chose the Chebyshev type II filter because it does not produce any ripple in the pass band and thus does not alter the frequency of the signal.

Third, an amplitude normalization is performed in order to reduce amplitude variations across patients, prior comparison between them.

Finally we split the data into 2 s windows with 0% overlapping. We opted to use 2 s windows due to the number of samples available to us and the desired resolution. The window size is based on achieving a trade-off between the temporal resolution and the number of available samples. That is, the greater is the windows size the higher temporal resolution we have at the expense of having fewer windows which is counter-productive for the machine learning algorithms. The use of 2 s windows provides an adequate temporal resolution, since we can study what happens every 1/2 Hz, while we count with a significant number of windows – an average of 42 per patient. Since the sampling frequency is set to 250 Hz, each window consists of 500 samples.

2.2. Feature extraction

Once signals had been preprocessed, each window was characterized in terms of a set of features. To extract these features, signals could be analyzed in either the time or frequency domain. The fast Fourier transform (FFT) is the most used tool for frequency domain analysis; however temporal information is lost once the transformation is performed.

If the signal is non-stationary, such as LFP signals, both the temporal and frequency components contain relevant information about the signal. The short-time Fourier transform (STFT) divides the signal into windows and applies the FFT to each of them. Although we have a time-frequency representation of the signal, it has the restriction that the window size is fixed and resolution is thus limited by the selected window.

A wavelet transform (WT) is a multi-resolution transformation that uses a variable window size at each level. This allows us to get more information about the signal in the time-frequency (time-scale) domain. Motivated by this fact WT was used in our experimentation.

In particular, we used the discrete wavelet transform (DWT). The resolution was set to 6 levels, which is the maximum possible decomposition that can be performed considering a sampling frequency at 250 Hz (number of levels $\leq \log_2(250/2) - 1$). Therefore each 2 s window is represented by 6 vectors $\{X_i\}_{i=1}^6$, which symbolize the wavelet coefficients at each of the levels. In fact, we dealt with the square value of the coefficients, which represents its power. For each of these vectors (levels), we calculated 5 features, which have proven to be valid in previous studies [38]:

- Energy: power sum of the coefficients at the i -th level. For a vector X_i of length n , the energy is defined as:

$$e_i = \sum_{k=1}^n X_i(k) \quad (1)$$

- Average value: represents the mean value of the coefficients power at the i -th level. For a vector X_i of length n , the average energy is defined as:

$$\mu_i = \frac{1}{n} \sum_{k=1}^n X_i(k) \quad (2)$$

- Variance: represents a dispersion measure from the mean energy at each level. For a vector X_i of length n , the variance of the energy is defined as:

$$\sigma_i = \frac{1}{n} \sum_{k=1}^n (X_i(k) - \mu_i)^2 \quad (3)$$

- First derivate: average value of the first derivate of the energy at each level. For a vector X_i of length n , the average value of the first derivate is defined as:

$$\delta_i = \frac{1}{n-1} \sum_{k=2}^n (X_i(k) - X_i(k-1)) \quad (4)$$

- Entropy: represents the uncertainty value of the energy at each level. Let $\mathcal{X} = \{X, p\}$ a discrete space of probability. That is, $X = \{X_i, X_n\}$ is a finite set in which each element has probability $p(X_i)$. Then, the Shannon entropy s_i is defined as:

$$s_i = - \sum_{k=1}^n p[X_i(k)] \cdot \log_2 p[X_i(k)] \quad (5)$$

Summarizing; each window of 2 s (500 samples) is characterized by 30 values (6 levels \times 5 features), which represents a 94% reduction of the input space. Mathematically, each sample can be represented by a vector as shown below:

$$[e_1 \mu_1 \sigma_1 \delta_1 s_1, \dots, e_6 \mu_6 \sigma_6 \delta_6 s_6] \quad (6)$$

3. Proposed system and results

3.1. Clustering

As previously discussed in Section 2.1, our studies were based on data collected from seven patients; in five cases we had available data representing both tremor and no tremor episodes, whilst in the remaining two cases only tremor episodes were evident.

Clustering was only performed with tremor episodes. This can be justified based on two main reasons:

1. We understand that the samples from which we attempt to differentiate patients are tremor episodes. We have studied non-tremor episodes and these are much more homogeneous and similar among patients. From this we postulate that during non-tremor episodes there is no significant difference in the sub-thalamus activity between healthy and Parkinsonian patients.
2. As consequence of suppressing the observation period after the surgical procedure, only tremor episodes are currently available. This data can be gathered during the electrode implantation, as mentioned in Section 2.1.1. It prevents the possibility of training a neural network for a new patient. Only tremor samples would be available for this new patient and the system would not be able to learn what non-tremor means in this case, impeding the automation of the tremor detection.

The goal at this point is to find out whether it is possible to cluster into groups the tremor instances for the set of patients. If so, this would indicate the existence of different types of patient, or different classes of resting tremor to be more precise.

The dataset employed was composed of seven patients; and 30, 84, 96, 82, 53, 36 and 114 tremor instances were available for each of them respectively.

3.1.1. Clustering results

We opted for using the K-means technique since this is one of the most used clustering methods in practice. In short, this is an unsupervised system. The main goal of clustering algorithms is to sort the different instances into groups, so that the degree of association between instances is maximized for the same group. That is, the goal is to group instances by proximity. This is performed by measuring distances between instances. In particular, the squared Euclidean distance is used as metric.

Table 1
Clustering results: training and testing patients.

	Training patients					Testing patients	
	BE	MA	DC	RB	SW	GC	EP
Cluster 1	1	2	20	0	1	0	0
Cluster 2	24	40	45	1	1	23	73
Cluster 3	1	0	0	1	38	2	4
Cluster 4	3	0	5	1	0	0	0
Cluster 5	0	7	18	79	12	3	10
Cluster 6	1	35	8	0	1	8	27
Total instances	26	77	73	1	3	31	100
Type A	(96.3%)	(91.7%)	(80.2%)	(1.2%)	(5.7%)	(86.1%)	(87.7%)
Total instances	1	7	18	80	50	5	14
Type B	(3.7%)	(8.3%)	(19.8%)	(98.8%)	(94.3%)	(13.9%)	(12.3%)

In our experimentation, the clustering system was trained in order to group instances of five patients into six different clusters. The number of clusters were determined following the algorithm proposed by Jain and Dubes [54]:

1. Select an initial partition with K clusters; repeat steps 2 and 3 until cluster membership stabilizes.
2. Generate a new partition by assigning each pattern to its closest cluster center.
3. Compute new cluster centers.

The clustering results are conclusive since the groups obtained clearly facilitate the distinguishing of instances into two different types of tremor:

1. Tremor type A, which corresponds to clusters 1, 2 and 6.
2. Tremor type B, which corresponds to clusters 3 and 5.

Table 2
Statistical analysis of extracted features.

Features	Wavelets levels	Mean		Standard deviation	
		Tremor type		Tremor type	
		A	B	A	B
Energy	Level 1	2.8794	3.5678	0.9643	1.9809
	Level 2	2.7769	1.5300	0.9284	1.0444
	Level 3	1.6990	0.4289	0.8238	0.4406
	Level 4	0.7595	0.1874	0.5471	0.1594
	Level 5	0.1270	0.0411	0.1201	0.0449
	Level 6	0.0023	7.4885×10^{-4}	0.0024	8.0716×10^{-4}
Average	Level 1	5.8866	6.5612	1.0281	2.0794
	Level 2	5.7777	4.2117	0.9925	1.3368
	Level 3	5.0119	2.7299	1.0504	0.9913
	Level 4	4.0653	2.3625	1.1451	0.9953
	Level 5	2.4918	1.5018	1.0263	0.9079
	Level 6	0.4059	0.1612	0.3393	0.1524
Variance	Level 1	5.9025	7.3970	2.1965	4.1806
	Level 2	5.8478	3.1928	1.8891	2.5782
	Level 3	3.6547	0.7607	1.9497	1.3641
	Level 4	1.4299	0.2845	1.2834	0.6132
	Level 5	0.1045	0.0360	0.1944	0.1922
	Level 6	3.8229×10^{-5}	1.3967×10^{-5}	8.5761×10^{-5}	7.7135×10^{-5}
First derivative	Level 1	8.9264	10.4965	2.0333	4.1639
	Level 2	9.2509	6.1841	1.9076	2.7438
	Level 3	7.6489	3.1558	2.0878	2.1637
	Level 4	5.1144	2.4593	2.1153	1.7638
	Level 5	1.6085	0.5211	1.4206	0.9605
	Level 6	0.0153	0.0048	0.0305	0.0250
Entropy	Level 1	0.1120	0.1097	0.0112	0.0112
	Level 2	0.1076	0.1017	0.0117	0.0158
	Level 3	0.0758	0.0738	0.0065	0.0093
	Level 4	0.0493	0.0453	0.0037	0.0081
	Level 5	0.0299	0.0282	0.0025	0.0050
	Level 6	0.0181	0.0171	0.0013	0.0026

The tremor exhibited by each of the training patients (BE to SW) in our study belongs unequivocally to one and only one of these tremor types. Table 1 shows the results. Note that cluster 4 is not taken into consideration due to the tiny number of instances within it.

Once trained using data from 5 patients only, the system was tested with data from the two patients (GC and EP) which was not used during training. The results, displayed on the right side of Table 1, continue to show a clear tendency to cluster each of the patients into one of the groups previously found. In particular, in this case both subjects belong to the group or type of tremor A.

From the results obtained in the clustering task, we can conclude that each patient presents one particular type of tremor only. But it is interesting to point out that for all the patients, regardless of the fact that they are presumed to belong to a particular group, there are a very small number of tremor instances that are classified into the other existing group. This misclassification could be caused by physical or neurological causes but the particular reason

Table 3
Training of networks 1 and 2 (with cross-validation).

	Network 1	Network 2
Used instances	520	278
% Total accuracy	87	81.5
% Tremor accuracy	97	82.5
% Non-tremor accuracy	94	82

is unknown. Therefore, neuronal activity during tremor episodes can be to some extent different for the same patient whilst the physical symptom is the same. It may well be however that by further studying the exact nature of the tremor in each case this will reveal that there are also physical differences between types A and B.

In Table 2 we summarize the average and standard deviation for the calculated multi-level features for each group of patients. By analyzing these results, we can conclude that the energy, average, variance, and first derivative are the features where the differences between patients are more significant. We have confirmed this by running an algorithm for feature selection. In detail, the Best-First and Correlation Feature Selection have been the algorithms used as attribute evaluator and search method, respectively.

Once executed, the selected features are: Energy (levels 1–4), Average (levels 3 and 4), Variance (level 3), First Derivative (levels 2–4). Therefore energy, average, variance and first derivative seem to be good distinguishers of subthalamic cell activity. Although, these ten values are the most representative, in our experimentation we finally used the whole set of features since the dimension of vectors (i.e., 1×30) is manageable and slightly improved results are obtained.

3.2. Detection (proposed system)

Previous works have studied the possibility of demand driven stimulation in DBS, as opposed to continual stimulation which is the present norm. In this article, due to the knowledge we have acquired about tremor types, we find it logical to integrate these results with the tremor detection task. Therefore, the proposed system combines the tasks of clustering and detection. For this, we have designed a detection algorithm in which two different neural networks are trained (using tremor and non-tremor instances): one per each patient type, A and B, as shown in Table 1. The number of instances that are evaluated on each network is shown in Table 3 in Section 3.2.1, which arguably gives the clearest indication of the existence of different tremor types. In the validation phase, each patient (tremor instances) is evaluated by the clustering module and depending of this result, each sample is assessed in the corresponding network. Although mostly each patient belongs to one type, all of them have tremor instances in both groups, as shown in Table 4 in Section 3.2.2. In Table 5 we computed the degree of accuracy in tremor detection for both networks. The weighted average value is used since each patient did not have the same number of instances in each network.

Table 4
Number of instances in networks 1 and 2.

Patient ID	Number of instances	
	Network 1 type A	Network 2 type B
Patient BE	26	1
Patient MA	77	7
Patient GC	31	5
Patient RB	1	80
Patient SW	3	50
Patient EP	100	14
Patient DC	73	18

Table 5
Testing of Networks 1 and 2 – proposed system.

Patient ID	Accuracy		
	Network 1 type A	Network 2 type B	% Patient weighted average
Patient BE	100	100	100
Patient MA	100	85.7	98.8
Patient GC	93.6	80	91.7
Patient RB	100	76.6	76.9
Patient SW	100	90	90.6
Patient EP	99	64.3	94.7
Patient DC	70	88.9	73.8
Overall performance	92.0	81.4	89.5

The overall system operation scheme (tremor classification type and tremor detection), applied for each patient, is shown in Fig. 2.

3.2.1. Neuronal network design

We opted to use a neural network given its history of successful application in pattern recognition problems. In our case a Back Propagation Multi-Layer Perceptron with one hidden layer with 16 neurons was chosen. The mathematical statement of the MLP is determined by the following equation, from which the corresponding outputs to the inputs provided to the network are calculated:

$$\gamma = \varphi\left(\sum_{i=1}^n \omega_i x_i + b\right) = \varphi(\omega^T x + b) \quad (7)$$

where x is the input vector, ω is the vector of weights, b is the bias parameter and φ is the network's activation function. In our case we chosen for φ one of the two most frequently functions used, the sigmoid function $1/(1 + e^{-x})$.

MLP networks are normally used to solve supervised learning problems. That is, when the set of inputs and corresponding outputs are completely known – in our case, using 30 features per window as input, and the presence or absence of tremor as output – the system learnt the relationship between inputs and outputs.

Therefore the feature extraction procedure plays a key role. It is only as a result of this that the network can be adequately trained to identify the tremor and non-tremor windows. If the features are poor, the system would fail in its attempt.

As shown in Fig. 2, we used two neuronal networks. The input to both of the networks, in the training phase, consisted of the whole signal (tremor and non-tremor episodes) for each of the five training patients. More precisely, network 1 is trained with data from patients of type A: patients BE, MA and GC, with a total of 520 instances for all of them. For its part, network 2 is trained with patients of type B: patients RB and SW, with a total of 278 instances.

For the training parameters of both networks we opted for training with 80%, and testing with the remaining 20% of samples. We chose these percentages because the goal at this phase was only to train the networks with the validation process at a later stage. Note that we did not use 100% of the samples for training in order to avoid over-learning.

The obtained results are summarized in Tables 3 and 4.

3.2.2. Network validation

Once the two networks were trained, we validated them. At this stage, only tremor episodes were used. This has a twofold justification. On one hand, tremor detection is the main goal of our system. On the other hand, and due to the abolition of the semi-implanted period in much present-day neurostimulator implantation, if the system is employed with a new patient, only tremor episodes would be available.

The whole set of patients was tested in the two networks and validation was carried out using cross-validation with ten folds.

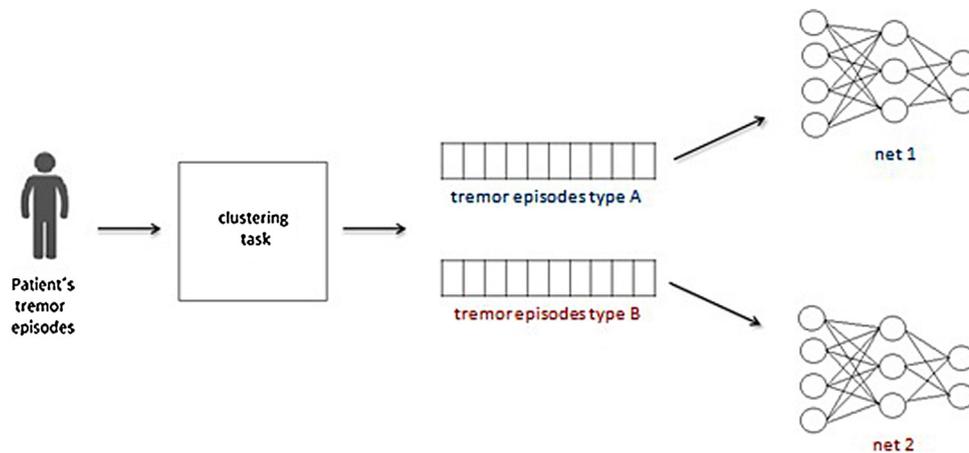


Fig. 2. System operation scheme.

Table 5 shows the accuracy obtained per patient, dividing their tremor episodes between the networks, which is based on the clustering results. The degree of overall success is the weighted average. All patients exceeded 73% accuracy, achieving 100% accuracy in the group of patients used in training (20% of their instances were not employed in the training), and 94.7% in the case of the patients not utilized during the training. From the obtained results, it seems that the system works very well with a high overall accuracy (89.5% of overall performance).

4. Discussion (performance evaluation)

In order to validate our proposal, we compared the obtained results with those obtained when patient data was classified with a neural network without tremor distinction. Therefore, no classification was made distinguishing between types of tremor and the clustering of the patients was omitted.

In this case, the same type of neuronal network was trained using the 30 features as previously described: a Multi-Layer Perceptron with 80% of samples for training and 20% for testing, and with 1 hidden layer composed of 16 neurons. The network was trained with data from the first five patients (*BE* to *SW*), which have tremor and non-tremor episodes. In this group of patients, there were two different types of tremor episodes, as was shown before, but this fact was omitted in order to perform a comparison with our proposed system. That is, we trained only a network with all members of this group of 5 patients, instead of training 2 different networks (each per type of patient/tremor).

After training, the network was tested with the tremor episodes of each of the 7 patients.

Comparing the results obtained using this approach (see Table 6) with those obtained in the previous section (see Table 5), it can be concluded that the performance improves when clustering is applied prior to detection. Generally there is an increment in the

Table 6
Detection without tremor type clustering.

Patient ID	Accuracy
Patient BE	100
Patient MA	100
Patient GC	83.3
Patient RB	73.17
Patient SW	92.45
Patient EP	92.98
Patient DC	55.20
Overall performance	83.2

average accuracy of detection and a greater stability is achieved for all the patients.

5. Conclusions

In this paper we have studied resting tremor through the LPF signals collected from the subthalamus in patients diagnosed with tremor dominant idiopathic PD. All the patients present the same symptomatology RT in the frequency band between 4 and 6 Hz. We aimed to look for the existence of sub-group(s) of patients (tremor sub-group). From our experimentation and as a result we showed the existence of two subgroups of patients within the group-1 of patients according to the Consensus Statement of the Movement Disorder Society on Tremor [40].

It is acknowledged here that the total number of patients involved in this study is relatively small. That said, there were no cases which disproved the hypothesis and the results obtained are, we feel, strongly supportive. However the next step is to extend the study considerably in order to see if all PD cases fall into one or other of the two subgroups as categorized or if there appear to be any exceptions.

Clearly the physiological causes of this can be a matter for further study and we would not wish to speculate on them here. In particular it would be interesting to study, at the neurological level, what are the particular causes for this distinction in relation to the underlying subthalamic activity. Nevertheless we hope that this result may be used as the basis to advance the research into types of patients and tremors in Parkinson's disease. Moreover, this research advance may help to develop improved and more specialized therapies to treat PD.

Finally, using the obtained results, we propose a novel tremor detection mechanism that distinguishes between sub-groups of patients and obtains a higher performance (accuracy) than a detection system that treats all the patients in the same single group. Therefore, our proposed system seems an effective tool to assist in demand driven deep brain stimulation.

Appendix A. Clustering

In order to ensure that two different types of tremor exist in our patient dataset, we performed several clustering trials. In each experiment, we varied the training set of patients. Our goal here was to ascertain if the two groups (type A and B) observed in the initial configuration remain irrespective of whether a different set of patients is chosen for the training phase.

In this appendix we present some of the tested configurations. Two different types are obtained in all the configurations. More

Table A1
Clustering results: extra trial 1.

	Training patients					Testing patients	
	EP	MA	DC	RB	SW	GC	BE
Cluster 1	38	9	0	0	3	1	22
Cluster 2	23	31	45	1	0	7	2
Cluster 3	3	1	0	1	37	2	1
Cluster 4	42	36	17	0	1	23	2
Cluster 5	8	7	18	79	12	3	0
Cluster 6	0	0	16	1	0	0	3
Total instances	103	76	78	2	4	31	29
Type A	(90.4%)	(90.5%)	(81.3%)	(2.4%)	(7.5%)	(86.1%)	(96.7%)
Total instances	11	8	18	80	49	5	1
Type B	(9.6%)	(9.5%)	(18.7%)	(97.6%)	(92.5%)	(13.9%)	(3.3%)

Tremor type A: clusters 1, 2, 4 and 6; tremor type B: clusters 3 and 5.

Table A2
Clustering results: extra trial 2.

	Training patients					Testing patients	
	BE	EP	DC	RB	SW	GC	MA
Cluster 1	1	3	0	1	38	2	1
Cluster 2	22	40	0	0	1	1	9
Cluster 3	2	17	43	1	0	7	22
Cluster 4	0	8	16	79	12	3	7
Cluster 5	4	0	12	1	2	1	0
Cluster 6	1	46	25	0	0	22	45
Total instances	29	103	80	2	3	31	76
Type A	(96.7%)	(90.4%)	(83.3%)	(2.4%)	(5.7%)	(86.1%)	(90.5%)
Total instances	1	11	16	80	50	5	8
Type B	(3.3%)	(9.6%)	(16.7%)	(97.6%)	(94.3%)	(13.9%)	(9.5%)

Tremor type A: clusters 2, 3, 5 and 6; tremor type B: clusters 1 and 4.

precisely, in all of them patients RB and SW are from a different type than patients BE, EP, MA, DC and GB.

The obtained results are summarized in [Tables A1–A4](#). The following considerations can be extracted when we analyze in depth the data:

- In [Table A1](#) we can observe that patient DC has 16 instances in cluster number 6. In this cluster we do not find any instances of the remaining patients, so determination of type A or B is, in principle, doubtful. We finally classify cluster 6 as type A, because the majority of instances of that patient DC are type A. Furthermore, the other two patients that have instances in that cluster (patients BE and RB), have more instances within type A.
- In [Table A4](#) and only observing the training results, it is questionable whether patient GC belongs to type A or type B, since the

instances of this patient are mostly in cluster 2, which does not have instances from other patients.

From this, we might conclude that a type C also exists. Nevertheless, if we observe the test results, we can clearly determine that cluster 2 belongs to type A – although this decision cannot be determined during the training phase. On the other hand, “this uncertainty” does not appear in the other tables evaluated, where all patients clearly show membership, in training and also in testing, to one of the existing groups (type A or B) – even this patient.

Note that in this configuration we have not considered cluster 3 since the number of samples belonging to this cluster is negligible.

- In all the configurations we can observe that all the patients have instances in both types. But adding the total number of instances

Table A3
Clustering results: extra trial 3.

	Training patients					Testing patients	
	BE	EP	DC	MA	SW	GC	RB
Cluster 1	1	16	43	21	0	16	1
Cluster 2	22	41	9	14	0	2	6
Cluster 3	0	9	17	7	13	3	73
Cluster 4	3	4	1	1	38	2	1
Cluster 5	0	44	7	41	0	12	0
Cluster 6	4	0	19	0	2	1	1
Total instances	27	101	78	76	2	31	8
Type A	(90.0%)	(88.6%)	(81.3%)	(90.5%)	(3.8%)	(86.1%)	(9.8%)
Total instances	3	13	18	8	51	5	74
Type B	(10.0%)	(11.4%)	(18.7%)	(9.5%)	(96.2%)	(13.9%)	(90.2%)

Tremor type A: clusters 1, 2, 5 and 6; tremor type B: clusters 3 and 4.

Table A4
Clustering results: extra trial 4.

	Training patients					Testing patients	
	BE	MA	GC	RB	SW	EP	DC
Cluster 1	1	36	0	0	1	24	15
Cluster 2	0	0	28	0	0	8	16
Cluster 3	3	0	0	1	0	0	2
Cluster 4	2	1	3	1	38	4	5
Cluster 5	24	40	1	1	1	68	38
Cluster 6	0	7	4	79	13	10	20
Total instances	25	76	29	1	2	100	69
Type A	(92.6%)	(90.5%)	(80.5%)	(1.2%)	(3.8%)	(87.7%)	(73.4%)
Total instances	2	8	7	80	51	14	25
Type B	(7.4%)	(9.5%)	(19.5%)	(98.8%)	(96.2%)	(12.3%)	(26.6%)

Tremor type A: clusters 1, 2, and 5; tremor type B: clusters 4 and 6.

it can be seen that every patient clearly belongs to one type. This has been the criterion about membership of a patient to type A or type B.

- We have mentioned that although the patients clearly belong to one type, they have instances from the other type. If we pay more attention to this, it is remarkable that this fact is more noticeable for the patients of type A than for type B. That is, patients of type A have a membership, although clear, which is less strong than patients of type B.

Summarizing, and after conducting in depth experimentation, we conclude that only two types of tremor exist in our patients dataset.

References

[1] M. Steriade, E.G. Jones, R.R. Llinas, *Thalamic Oscillations and Signaling*, John Wiley & Sons, New York, 1990.

[2] W. Singer, C.M. Gray, Visual feature integration and the temporal correlation hypothesis, *Annu. Rev. Neurosci.* 18 (1) (1995) 555–586.

[3] R. Eckhorn, R. Bauer, W. Jordan, M. Brosch, W. Kruse, M. Munk, H. Reitboeck, Coherent oscillations: a mechanism of feature linking in the visual cortex? *Biol. Cybern.* 60 (2) (1988) 121–130, <http://dx.doi.org/10.1007/BF00202899>.

[4] A. Nini, A. Feingold, H. Slovlin, H. Bergman, Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of Parkinsonism, *J. Neurophysiol.* 74 (4) (1995) 1800–1805.

[5] S. Morrison, G. Kerr, K. Newell, P. Silburn, Differential time- and frequency-dependent structure of postural sway and finger tremor in Parkinson's disease, *Neurosci. Lett.* 443 (3) (2008) 123–128.

[6] C. Hammond, H. Bergman, P. Brown, Pathological synchronization in Parkinson's disease: networks, models and treatments, *Trends Neurosci.* 30 (7) (2007) 357–364.

[7] A. Manciooco, F. Chiarotti, A. Vitale, G. Calamandrei, G. Laviola, E. Alleva, The application of russell and burch 3R principle in rodent models of neurodegenerative disease: the case of Parkinson's disease, *Neurosci. Biobehav. Rev.* 33 (1) (2009) 18–32.

[8] W.W. Alberts, E.J. Wright, B. Feinstein, Cortical potenciales and Parkinsonian tremor, *Nature* 221 (1969) 670–672.

[9] F.A. Lenz, H.C. Kwan, R.L. Martin, R.R. Tasker, J.O. Dostrovsky, Y.E. Lenz, Single unit analysis of the human ventral thalamic nuclear group: tremor-related activity in functionally identified cells, *Brain* 117 (3) (1994) 531–543, [doi:10.1093/brain/117.3.531](http://dx.doi.org/10.1093/brain/117.3.531).

[10] D. Par, R. Curro'Dossi, M. Steriade, Neuronal basis of the Parkinsonian resting tremor: a hypothesis and its implications for treatment, *Neuroscience* 35 (2) (1990) 217–226.

[11] W. Hamel, U. Fietzek, A. Morsnowski, B. Schrader, J. Herzog, D. Weinert, G. Pfister, D. Miller, J. Volkmann, G. Deuschl, H.M. Mehdorn, Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: evaluation of active electrode contacts, *J. Neurol. Neurosurg. Psychiatry* 74 (8) (2003) 1036–1046.

[12] A.J. Lees, J. Hardy, T. Revesz, Parkinson's disease, *Lancet* 373 (9680) (2009) 2055–2066.

[13] A.H. Rajput, S. Birdi, Epidemiology of Parkinson disease, *Parkinsonism Relat. Disord.* 3 (4) (1997) 175–186.

[14] J. Parkinson, *An Essay on the Shaking Palsy*, Whittingham and Rowland for Sherwood, Neely & Jones, London, 1817.

[15] W.J. Zetuskay, J. Jankovic, F.J. Pirozzolo, The heterogeneity of Parkinson's disease: clinical and prognostic implications, *Neurology* 35 (4) (1985) 522.

[16] J. Jankovic, M. McDermott, J. Carter, S. Gauthier, C. Goetz, L. Golbe, S. Huber, W. Koller, C. Olanow, I. Shoulson, M. Stern, C. Tanner, W. Weiner, P.S. Group, Variable expression of Parkinson's disease: a baseline analysis of the dat atop cohort, *Neurology* 40 (10) (1990) 1529.

[17] A.H. Rajput, R. Pahwa, P. Pahwa, A. Rajput, Prognostic significance of the onset mode in Parkinsonism, *Neurology* 43 (4) (1993) 829.

[18] S.J.G. Lewis, T. Foltynie, A.D. Blackwell, T.W. Robbins, A.M. Owen, R.A. Barker, Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach, *J. Neurol. Neurosurg. Psychiatry* 76 (3) (2005) 343–348.

[19] G.F. Wooten, L.J. Currie, V.E. Bovbjerg, J.K. Lee, J. Patrie, Are men at greater risk for Parkinson's disease than women? *J. Neurol. Neurosurg. Psychiatry* 75 (4) (2004) 637–639.

[20] M.F. Beal, Experimental models of Parkinson's disease, *Nat. Rev. Neurosci.* 2 (5) (2001) 325–334.

[21] N. Singh, V. Pillay, Y.E. Choonara, Advances in the treatment of Parkinson's disease, *Prog. Neurobiol.* 81 (1) (2007) 29–44.

[22] J.G. Nutt, J. Carter, W.R. Woodward, Long-duration response to levodopa, *Neurology* 45 (8) (1995) 1613–1616.

[23] J.G. Nutt, Levodopa-induced dyskinesia: review, observations, and speculations, *Neurology* 40 (2) (1990) 340–345.

[24] M. Bacher, E. Scholz, H. Diener, 24 hour continuous tremor quantification based on {EMG} recording, *Electroencephalogr. Clin. Neurophysiol.* 72 (2) (1989) 176–183.

[25] S. Spieker, A. Boose, S. Breit, J. Dichgans, Long-term measurement of tremor, *Mov. Disord.* 13 (S3) (1998) 81–84.

[26] K.E. Norman, R.E.A. Beuter, The measurement of tremor using a velocity transducer: comparison to simultaneous recordings using transducers of displacement, acceleration and muscle activity, *J. Neurosci. Methods* 92 (12) (1999) 41–54.

[27] A.L. Benabid, P. Pollak, D. Hoffmann, C. Gervason, M. Hommel, J. Perret, J. de Rougemont, D.M. Gao, Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus, *Lancet* 337 (8738) (1991) 403–406.

[28] A.L. Benabid, A. Benazzouz, P. Pollak, Mechanisms of deep brain stimulation, *Mov. Disord.* 17 (S3) (2002) S73–S74.

[29] A.L. Benabid, A. Benazzouz, D. Hoffmann, P. Limousin, P. Krack, P. Pollak, Long-term electrical inhibition of deep brain targets in movement disorders, *Mov. Disord.* 13 (S3) (1998) 119–125.

[30] L. Garcia, J. Audin, G. D'Alessandro, B. Bioulac, C. Hammond, Dual effect of high-frequency stimulation on subthalamic neuron activity, *J. Neurosci.* 23 (25) (2003) 8743–8751.

[31] M. Filali, W.D. Hutchison, V.N. Palter, A.M. Lozano, J.O. Dostrovsky, Stimulation-induced inhibition of neuronal firing in human subthalamic nucleus, *Exp. Brain Res.* 156 (3) (2004) 274–281.

[32] W. Meissner, A. Leblois, D. Hansel, B. Bioulac, C.E. Gross, A. Benazzouz, T. Boraud, Subthalamic high frequency stimulation resets subthalamic firing and reduces abnormal oscillations, *Brain* 128 (10) (2005) 2372–2382.

[33] A. Hristova, K. Lyons, A. Troster, R. Pahwa, S. Wilkinson, W.C. Koller, Effect and time course of deep brain stimulation of the globus pallidus and subthalamus on motor features of Parkinson's disease, *Clin. Neuropharmacol.* 23 (4) (2000) 208–211.

[34] Medtronic, Parkinson disease, 1; <http://www.medtronic.eu/your-health/parkinsons-disease/device/our-dbs-therapy-products/activaRC/index.htm> (accessed February 2014).

[35] V.S. Mallela, V. Ilankumar, N.S. Rao, Trends in cardiac pacemakers batteries, *Indian Pacing Electrophysiol. J.* 4 (4) (2004) 201–212.

[36] P.A. Gould, A.D. Krahn, Complications associated with implantable cardioverter-defibrillator replacement in response to device advisories, *JAMA* 295 (16) (2006) 1907–1911.

[37] M.N. Gasson, S.Y. Wang, T.Z. Aziz, J.F. Stein, K. Warwick, Towards a demand driven deep-brain stimulator for the treatment of movement disorders, in: Proceedings of the 3rd IEE International Seminar on Medical Applications of Signal Processing, 2005, pp. 83–86.

- [38] E. Bakstein, J. Burgess, K. Warwick, V. Ruiz, T. Aziz, J. Stein, Parkinsonian tremor identification with multiple local field potential feature classification, *J. Neurosci. Methods* 209 (2) (2012) 320–330.
- [39] W.F. Abdo, B.P. van de Warreburg, D.J. Burn, N.P. Quinn, B.R. Bloem, The clinical approach to movement disorders, *Nat. Rev. Neurol.* 6 (1) (2010) 29–37.
- [40] G. Deuschl, P. Bain, M. Brin, Consensus statement of the movement disorder society on tremor, *Mov. Disord.* 13 (S3) (1998) 2–23.
- [41] A.E. Lang, C. Zadikoff, *Handbook of Essential Tremor and other Tremors Disorders*, Taylor and Francis, Boca Raton, FL, 2005.
- [42] J. Jankovic, E. Tolosa, *Parkinsons Disease and Movement Disorders*, Lippincott Williams & Wilkins, 2007.
- [43] J.W. Lance, R.S. Schwab, E.A. Peterson, Action tremors and the cogwheel phenomenon in Parkinson's disease, *Brain* 86 (1) (1963) 95–110.
- [44] E.D. Louis, G. Levy, L.J. Cote, H. Mejia, S. Fahn, K. Marder, Clinical correlates of action tremor in Parkinson disease, *Arch. Neurol.* 58 (10) (2001) 1630–1634.
- [45] W.C. Koller, B. Vter-Overfield, R. Barter, Tremors in early Parkinson disease, *Clin. Neuropharmacol.* 12 (4) (1989) 293–297.
- [46] G. Deuschl, J. Raethjen, R. Baron, M. Lindenmann, H. Wilms, P. Krack, The pathophysiology of Parkinsonian tremor: a review, *J. Neurol.* 247 (5) (2000) V33–V48.
- [47] R. Wenzelburger, J. Raethjen, K. Loffler, H. Stolze, M. Illert, G. Deuschl, Kinetic tremor in a reach-to-grasp movement in Parkinson's disease, *Mov. Disord.* 15 (6) (2000) 1084–1094.
- [48] A. Beuter, E. Barbo, R. Rigal, P.J. Blanchet, Characterization of sub-clinical tremor in Parkinson's disease, *Mov. Disord.* 20 (8) (2005) 945–950.
- [49] J.G. Burgess, K. Warwick, V. Ruiz, M. Gasson, T. Aziz, J.-S. Brittain, J. Stein, Identifying tremor-related characteristics of basal ganglia nuclei during movement in the Parkinsonian patient, *Parkinsonism Relat. Disord.* 16 (10) (2010) 671–675.
- [50] B.J. Harrison, C. Pantelis, *Local Field Potentials*. *Encyclopedia of Psychopharmacology*, Springer, Berlin/Heidelberg, 2010.
- [51] Q. Gaucher, J.M. Edeline, B. Gourevitch, How different are the local field potentials and spiking activities insight from multi-electrodes arrays, *J. Physiol. Paris* 106 (3) (2012) 93–103.
- [52] R.E. Gross, P. Krack, M.C. Rodriguez-Oroz, A.R. Rezai, A.L. Benabid, Electrophysiological mapping for the implantation of deep brain stimulators for Parkinson's disease and tremor, *Mov. Disord.* 21 (14) (2006) S259–S283.
- [53] P. Brown, D. Williams, Basal ganglia local field potential activity: character and functional significance in the human, *Clin. Neurophysiol.* 116 (11) (2005) 1388–2457.
- [54] A.K. Jain, R. Dubes, *Algorithms for Clustering Data*, Prentice Hall, New Jersey, 1988.