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Automatic Identification of Various Nuclei in the Basal Ganglia for Parkinson's Disease Neurosurgery

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***Abstract*— Stereotactic neurosurgery for Parkinsonś disease (PD) is one of the most used treatments for relief symptoms of this degenerative disorder. Current methods include ablation and deep brain stimulation (DBS) that can be applied to the various nuclei in the basal ganglia (BG), for instance to the Subthalamic nucleus (STN) or the Ventral medial nucleus (Vim). Identification of thus regions must be rigorous and within a minimum position error. Usually, skilled specialist identifies the brain area by comparing and listening to the rhythm created by the temporal and spatial aggregation of action potentials presented in microelectrode recordings (MER). We present a novel system for automatic identification of the various nuclei in the BG which addresses the limitations of the subjectivity and the non-stationary nature of MER signals. This system incorporates the time-frequency analysis using the Hilbert-Huang Transform (HHT), which is a recent tool for processing nonlinear and non-stationary data, with a dynamic classifier based on Hidden Markov Models (HMM). Classification accuracy in two different databases is compared to validate the performance of the proposed method. Results show that system can recognize selected nuclei with a mean accuracy of 90%.**

I. INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease [1]; estimated prevalence (per 100,000) for those aged 65-74 years is 598 [2]. PD is a degenerative disorder of the central nervous system that often impairs the persons motor skills and speech, which result in significant decrease in quality of life not only for the patient but the family as well. Parkinsonism has three cardinal motor symptoms: slowness in both the beginning and the execution of a movement (bradykinesia), muscle rigidity, and resting tremor [1], [3]; postural instability (balance impairment) has also been identified in this group of clinical symptoms [4]. Normal movement is initiated by neurons in the cerebral cortex and is modulated by neurons in the basal ganglia (BG) and thalamus. The thalamus form a complex network of pathways between the various nuclei in the BG resulting in inhibition of movement and other pathways resulting in facilitation of the movement. In PD there is an imbalance between inhibition and facilitation, which lead to a hypoactivity of the BG [1]. Normally drug treatment with L-dopa reduces symptoms; however, it has been observed some complications due to the longstanding use of this drug [5]. Stereotactic neurosurgery is used instead when patient does not respond to L-dopa treatment [3], [5], [6]. Commonly two different neurosurgery methods are used: ablation and deep brain stimulation (DBS). Ablation of the various nuclei in the brain was the main treatment form 1950 until 1997. In recent years, ablation has given way to DBS due to the obvious advantage of minimal destruction of brain tissue, also because it can be programmed to the specific needs of the patient, maximizing symptoms relief and minimizing any adverse effects. The success in the DBS procedure is the correct localization of the various nuclei where the stimulation microelectrode will be placed. Despite the used of a stereotactic frame and CT/MR neuroimaging-based techniques for targeting, intraoperative neuronal microelectrode recordings (MER) can be used to improve the accuracy of electrode positioning. In the trajectory to the target, Fig. 1, the microelectrode crosses through different regions with particular electrophysiological characteristics that can be used to discriminate brain zones [8], determine optimal tracks, and to identify the target [7]. Here, we present a novel system for automatic identification of various nuclei (Subthalamic nucleus, thalamus, Substantia Nigra pars reticulata, and Zona incerta) from the time-frequency analysis of MER recordings as a support for adequate placement of the DBS microelectrode in PD neurosurgery (Fig. 2 show typical MER recordings). Comparisons using two different databases of MER recordings are presented to validate the proposed system. The system provides several advantages: (a) for the feature extraction it is not necessary previous

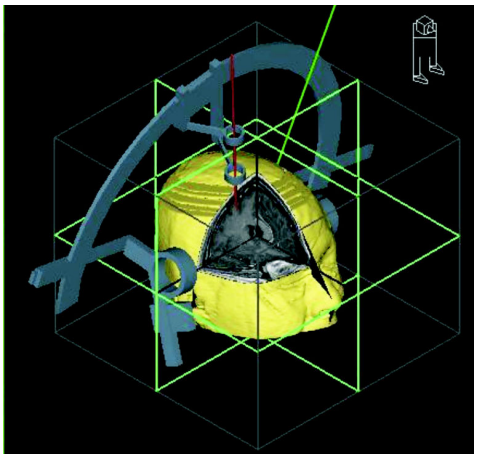

Fig. 1. Bilateral microelectrode trajectory to the target in the basal ganglia for placement of the DBS microlectrode.

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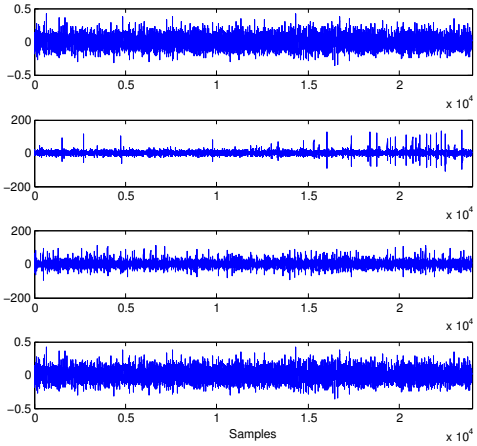

Fig. 2. Tipical MER recordings form various nuclei in the BG. (From top-to-Bottom) Thalamus (TAL), Subthalamic nucleus (STN), Substantia Nigra pars reticulata (SNr), and Zona incerta (ZI)

knowledge about the data and assumptions about linearity or stationary are not necessary, (b) the signal processing used on these MER signals make the system suitable for hardware implementation.

This paper is organized as follows: In Sect. 2, Theoretical methods are reviewed. In Sect. 3 the proposed system is presented. Finally in Sect. 4, results and final discussion is given.

II. Methods

A. Hilbert Spectrum Analysis

MER recordings are non-stationary signals and time-dependent stochastic signal, due to the presence of action potentials [3]. Moreover, it is known that the information contained in biological signals is highly dependent on numerous biological aspects with nonlinear structure, for example, fatigue phenomena that cause nonsymmetrical behavior of spikes, external factor as the cortical pulse generated by respiratory and cardiac activity, systematic amplitude reduction of the potential action when the cell is switching at high frequency, microelectrode movements, background noise, etc [3], [8].

Hilbert-Huang transform is a novel technique for analyzing non-stationary and nonlinear signals development by Huang et al [9], which depends solely on the signal information. The HHT is performed in two main steps: (i) empirical mode decomposition (EMD) and (ii) Hilbert spectral analysis (HSA). The purpose of EMD is to decompose a signal into a finite set of well-behaved Hilbert transform (HT) signals, called intrinsic mode functions (IMF). HSA is designated to calculate the instantaneous frequency and amplitude of IMFs through the HT and to obtain the time-energy-frequency distribution called Hilbert spectrum (HS). In order to define an orthogonal basis and a meaningful instantaneous frequency IMFs must satisfy two conditions: (1) in the whole data set, the number of extreme and the number of zero crossings must either equal or differ at most by one; and (2) at any point, the mean value of the envelope define by the local maxima and the envelope define by the local minimal is zero. The numerical procedure to obtain those IMFs knows as sifting process and is described in detail in [9].

Once IMFs are calculated the analyzed signal can be expressed as follows:

$$x(t) = \sum_{j=1}^{n} c_j(t) + r_n(t) \tag{1}$$

where n is the number of IMFs, $r_n(t)$ is the final residue which can be either the mean trend or a constant, and functions $c_j(t)$ are the IMFs, which are nearly orthogonal to each other, and all have zero means. The second step in the HHT is the Hilbert spectral analysis. After the decomposition step, the IMFs are analyzed using the HT to obtain the instantaneous frequency and the instantaneous amplitude defined as:

$$\omega(t) = \frac{d\theta}{dt} \tag{2}$$

$$a(t) = (x(t)^2 + y(t)^2)^{1/2} \tag{3}$$

where

$$\theta(t) = \arctan \frac{y(t)}{x(t)} \tag{4}$$

$$y(t) = \frac{1}{\pi} P \int \frac{x(t-\tau)}{\tau} d\tau \tag{5}$$

where $\omega(t)$ is the instantaneous frequency (IF), $a(t)$ is the instantaneous amplitude (IA), $\theta(t)$ is the instantaneous phase, $y(t)$ is the Hilbert Transform of $x(t)$, P indicates the Cauchy principle value, and $x(t)$ is the time series. By means of the combination of the IA and the IF of each IMF, it is possible to obtain the resulting time-energy-frequency representation of the signal.

$$H(f,t) = Re \sum_{j=1}^{n} a_j(t) e^{j2\pi \int \omega_j(t) dt} \tag{6}$$

Here $r_n(t)$ is left behind because is either the mean trend of the data or a constant. Once the IA and the IF have been calculated they can be combined graphically in a 3D plane, similar to those obtained with the wavelet transform. It is called the Hilbert Spectrum (HT) show in Fig. 3.

III. Automatic identification system

The automatic identification system can be summarized as shown in Fig. 4. It is composed of four steps: (i) raw data preprocessing, (ii) time-frequency analysis, (iii) feature extraction, and (iv) classification.

A. Raw data preprocessing

Prior to MER signal analysis, raw data is amplified by a preamplifier located near the electrode to reduce electrical noise. After these preconditioning steps, the signal is sampled with an analog-to-digital converter with a sampling rate of at least 24 kHz. Then an artifacts detector is used to eliminate wrong entries presented in the MER signal due to patient

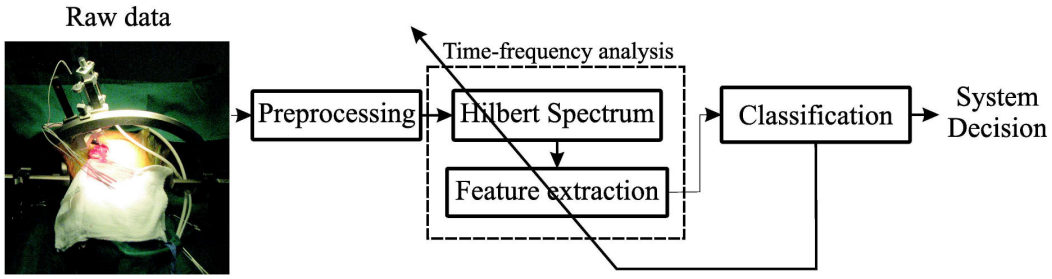

Fig. 4. General structure of the proposed automatic identification system of various nuclei in the BG. The feedback arrow represent the selection of the most discriminating features by the classifier in the training step, using the combination of features which presented the highest accuracy rate.

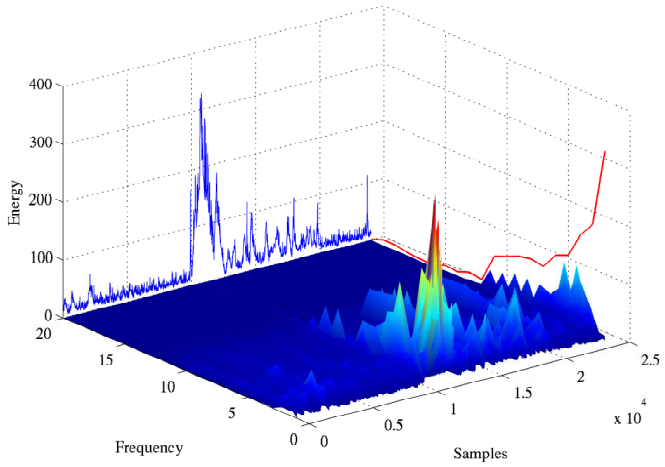

Fig. 3. Hilbert Spectrum. Time contour (blue), frequency contour (red). Contours are computed to extract discriminating informacion from the HS.

movements. Each MER signal is segmented with a window of 1s, time considered enough for identification of brain zones [3].

B. Time-frequency analysis

Once the signal is free of artifacts and normalized in time, HS is calculated using the Hilbert-Huang transform presented in Sect. 2. First empirical mode decomposition is used to extract nine IMF that contain most of the frequencies of interest of the MER signal, then HT is computed for each IMF in order to obtain the instantaneous amplitude and frequency. After that the HS can be constructed.

C. Feature extraction

Statistical moments are calculated from the time contour of the HS, its first derivative and its second derivative, which also present discriminating information about the dynamic of the MER signal (Fig. 5). The follow measures are calculated:

$$m(a) = max(|a|) \tag{7}$$

$$\sigma^2(a) = \frac{1}{N-1}\sum_{n\in C_k}(a_n - \overline{a})^2 \tag{8}$$

$$E(a) = \frac{1}{2}\sum_{n\in C_k} a_n^2 \tag{9}$$

$$E1(a) = -\sum_{n\in C_k} a_n^2 \log(a_n^2) \tag{10}$$

$$E2(a) = \frac{1}{N}\sum_{n\in C_k} |a_n| \tag{11}$$

$$\gamma_1(a) = \frac{\frac{1}{N}\sum_{n\in C_k}(a_n-\overline{a})^3}{\left(\frac{1}{N}\sum_{n\in C_k}(a_n-\overline{a})^2\right)^{3/2}} \tag{12}$$

$$\gamma_2(a) = \frac{\frac{1}{N}\sum_{n\in C_k}(a_n-\overline{a})^4}{\left(\frac{1}{N}\sum_{n\in C_k}(a_n-\overline{a})^2\right)^{2}} - 3 \tag{13}$$

where a_n is the nth sample of the Nth MER record, $\overline{a}$ is the mean value, N is the number of records of each BG nuclei and $k = 0, 1, 2, ..., C$, with C the number of BG nuclei; σ is the standard deviation and σ^2 de variance, $E(a)$ is the energy, $E1(a)$ is the Shannons entropy, $E2(a)$ is the mean of the absolutes elements on each BG nuclei, $\gamma 1(a)$ is the third standardized moment around the mean called Skewness and

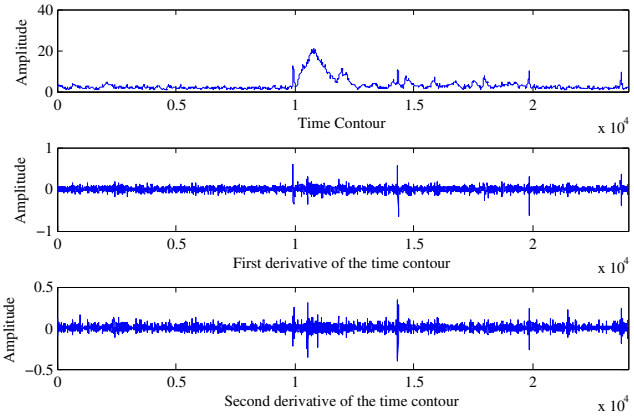

Fig. 5. (From Top-to-Bottom) Time contour, first derivative, and second derivative.

TABLE I
CLASSIFICATION RESULTS

Database	%TAL	%STN	%SNR	%ZI	%Total
UPV-BD	86.00 ± 8.10	83.75 ± 15.65	75.83 ± 15.44	98.15 ± 1.95	88.81 ± 2.56
UTP	-	91.43 ± 5.52	87.27 ± 8.24	-	90.00 ± 3.77

$\gamma 2(a)$ is the fourth moment around the mean called Kurtosis. Each of these measures is calculated from the three contours to obtain a set of 21 features. Later in the classification step, five features will be selected as discriminating characteristics because they maximized the classification accuracy among all the possible combinations of the initial feature set.

D. Classification

Dynamic classification is based on Hidden Markov Models (HMM). Once the discriminating features has been selected, the classification task begins with the generation of an HMM model for each nuclei, the HMM parameters are obtained by the Expectation- Maximization algorithm (EM) [11] and the parameters of the model is given by the BIC-Pruning algorithm [10]. In the validation step a new HMM model is generated for the unknown MER recording in the same way than in the training step and then it is compared model-to-model with the Kullback-Leibler distance [12]; the selection of the class to which the new data belongs is made based on the minimum distance.

IV. RESULTS AND DISCUSSION

A. MER Database

In order to validate the proposed system two different sets of MER recordings are used in this paper. The first one is the Polytechnic University of Valencias database (UPV-BD). The surgeries were carried out in the University General Hospital of Valencia, and labeled by both specialists in neurophysiology and electrophysiology, according to the affected region. The equipment used in the acquisition was the LEADPOINTTM Medtronic, with a sampling rate of 24 kHz and 16-bit resolution. In total there are 177 records discriminated in 43 TAL signals, 25 STN signals, 24 SNr signals, and 85 ZI signals. The second set of MER signals correspond to five interventions carried out locally in the city of Pereira where the authors participated. All the subjects gave their informed consent allowing the use of the neural signals recorded to research. The acquisition equipment used is the ISIS MER of Inomed, neural signals were labeled by two specialists in neurosurgery and neurophysiology; the sampling rate was 25 kHz and 16-bit resolution. There are 160 neural signals divide in two groups, STN signals and non-STN signals.

B. Results

A final set of five characteristics obtained the highest classification rate among the possible combinations of the feature set, those were: (7), (9), and (10) from the time contour; (7) from the first derivative, and (7) from the second derivative. Table I presents the classification results for the databases. As shown the system can recognized the different nuclei with a high classification rate for both databases, also due to the flexibility of the Hilbert-Huang transform a reduce space of feature can represent the dynamic of the MER signals, which is an advantage in the classification stage. As shown the system can recognized, with low classification error, the STN nuclei which is a common target in the PD neurosurgery.

In future work, further study is necessary in order to improve classification accuracy of some nuclei that were not well discriminated with the features selected (SNR), also the inclusion of more nuclei and more patients is necessary. In a final stage, the proposed system could be implemented in a computational platform for operating online, to give intraoperatory support to the specialists in the surgery for PD.

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