The Analysis of Regularity and Synchrony of Parkinsonian Tremor Using Approximate Entropy and Cross-Approximate Entropy

Yao Liu
[1]Institute of Intelligent Machines, Chinese Academy of Sciences, Hefei, China
[2]Department of Automation, University of Science and Technology of China, Hefei, China

Nan Cheng
[3]Hospital Affiliated to Institute of Neurology, Anhui University of Chinese Medicine, Hefei, China

Shengqiang Xu, Yining Sun, Xianjun Yang
[1]Institute of Intelligent Machines, Chinese Academy of Sciences, Hefei, China

Abstract— **Parkinsonian tremor is one of the primary symptoms of Parkinson's disease. The current methods of objective assessment are mainly based on amplitude and frequency. In recent years, the ApEn and Cross-ApEn have been introduced as new methods of nonlinear analysis. They are used to assess the regularity and synchrony of time series. In this paper, a set of wireless data acquisition units were developed to collect 3-axis acceleration data. When PD patients group and the control group performed the instructed tasks, the acceleration signals of their thumb and index fingers were recorded at the meantime. We calculated the ApEn and Cross-ApEn for the acceleration signals and compared them respectively. The mean ApEn of Parkinson's patients were significantly lower than healthy subjects, both for resting tremor and postural tremor. In addition, the mean Cross-ApEn between thumb and index signals of PD were also lower than those of healthy people. The results revealed that the ApEn and Cross-ApEn are effective analysis methods to identify Parkinsionian tremor.**

Keywords- Parkinsonian tremor; objective assessment; Acceleration signal; Approximate Entropy (ApEn); Cross-ApEn

I. INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder in the world, after Alzheimer's dementia. The prevalence rate is 0.5% to 1.0% between the age of 65 to 69, and increases to 3.0% for people more than 80 years of age [1]. Although neurologists have studied a mass of relevant brain's mechanisms, the cause of this disease is still unknown. Even for an experienced neurologist, it is difficult to make an accurate diagnosis in the early stage. Among the PD patients, about 70% can appear the symptom of tremor. The presence of tremor is a fundamental diagnostic criterion used in the determination of PD onset and progression. Tremor is a kind of involuntary movements that body segments have rhythmic oscillation. It can also be observed in healthy people. To a certain extent, the physiological tremor in healthy people is similar with the pathological tremor in PD. So, the accurate quantification of tremor is important to diagnose PD and to determine the efficacy of therapeutic intervention.

There have been some investigations in quantitative analysis of physiological and pathological tremor. One of commonly used objective techniques is measuring the acceleration of the hand tremor [2,3,4,5]. Multiple parameters are calculated for quantitative measurements, most of which are based on the time domain (such as RMS amplitude, autocorrelation and cross-correlation), or converted into the frequency domain by applying the Fourier Transform (such as peak frequency, harmonic index, proportional power in a certain frequency range) [6,7]. However, amplitude and frequency characteristics do not always distinguish the Parkinsonian tremor from physiologic tremor, especially in the early stage of PD [2,3]. Compared to normal physiological tremor, Parkinsonian tremor has a more periodic morphology and contains some underlying indications of nonlinear dynamics. Classical time domain and frequency domain characteristics may not be sufficient to fully characterize individuals with PD, since they are most suitable for linear systems. They have some inherent limitations in addressing wide classes of nonlinear systems, typically biomedical signals [8].

In recent years, Approximate Entropy (ApEn), as an effective nonlinear measure developed by Pincus [9], has been introduced into quantitative discrimination and assessment of tremors [10,11,12]. It is a widely used method to provide a general description of the regularity and complexity of time series. The range of ApEn is 0~2. Smaller ApEn value indicates less complexity of the data, namely more regularity and predictability, whereas the larger ApEn indicates more complexity, i.e. more randomness and unpredictability. According to a universal point of view, the effects of aging and disease are associated with a loss of complexity of the physiological system [12]. Similar to a direct regularity measurement of single signal given by ApEn, Cross-Approximate Entropy (Cross-ApEn) was designed to quantify the synchrony between two signals [8]. It can determine the changes in the degree of synchrony in interconnected systems.

There are a few literatures concerning the ApEn analysis of tremor time series in PD. Vaillancourt et al displayed the resting and postural tremor accelerations of the PD subjects were more regular than healthy control subjects, though there

This work was supported by the Science and Technology Service Network Initiative of Chinese Academy of Sciences KFJ-SW-STS-161, and Science and Technology Project of Anhui Province 1501021042.

978-1-5090-3710-0/16/$31.00 ©2016 IEEE

is no significant difference in the amplitude and modal frequency for each subject group [10]. In another paper, they quantified the regularity of tremor by ApEn analysis of the grip force. A positive correlation between tremor regularity and the severity of PD symptom was shown [11]. Morrison et al analyzed the postural sway and finger tremor simultaneously using ApEn and Cross-ApEn [12]. These results suggest that analysis of the regularity and synchrony of tremor may improve the characterization of PD.

In this paper, we focused on the finger tremor. A set of wireless data acquisition unit was developed to detect 3D acceleration signals. When conducting the instructed tasks, the subjects' resting tremor and postural tremor are recorded respectively. The calculations of ApEn and Cross-ApEn are performed to the preprocessed signals. Statistics analysis results were used to compare the difference between patients and healthy people.

II. METHODS

A. Subjects

14 patients with PD (age, 48-77 years; mean±SD, 61±9.7 years), reported no other neurological disorders or any sensory, cognitive or physical impairment that could affect experimental result, were recruited from Hospital Affiliated to Institute of Neurology, Anhui University of Chinese Medicine. They are selected to ensure that everyone exhibited resting and postural tremor. 18 healthy adults (age, 45-76 years; mean±SD, 60±10.2 years) with physiological tremor also participated in the study as the control group. All subjects signed the informed consent to experimental procedures, which was explained in detail by examiners. All clinical testing was approved by Medical Ethical Committee of Anhui University of Chinese Medicine. PD patients were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) by an experienced neurologist. The UPDRS item 20 score for resting tremor and item 21 score for postural and action tremor were analyzed respectively. The most affected limb of the patients was determined by observation. Table 1 shows the clinical characteristic information of PD patient group.

TABLE 1. CLINICAL INFORMATION OF PD GROUP

Subjects	Age	UPDRS item 20	UPDRS item 21	The most affected side
PD01	49	2	2	L
PD02	71	3	3	R
PD03	70	2	1	R
PD04	67	2	2	L
PD05	77	3	3	R
PD06	52	2	2	R
PD07	53	1	1	R
PD08	65	3	2	L
PD09	53	1	1	L
PD10	63	1	1	R
PD11	51	1	2	R
PD12	48	3	1	R
PD13	71	2	1	R
PD14	64	1	1	R
Mean± SD	61±9.7	1.9±0.8	1.6±0.7	

B. Acceleration Signal Acquisition

We designed a wireless data acquisition unit (apparent size: 65×38×20 mm) for this study. Two 3-axis acceleration sensors (MPU6050, InvenSense, USA) packed in fingerstalls were used to measure acceleration signals of thumb and index finger respectively. They were connected to a wrist-worn component that contained the main circuit board. The sampling frequency was 100Hz. The collected data were transmitted by a Wi-Fi chip (EMW3161, MXCHIP, China) and forwarded to PC through a wireless router. The PC custom software was developed to receive and store the data in txt format. The whole unit was powered by a rechargeable lithium battery. Fig. 1 shows the data acquisition unit and the installation on a patient's hand.

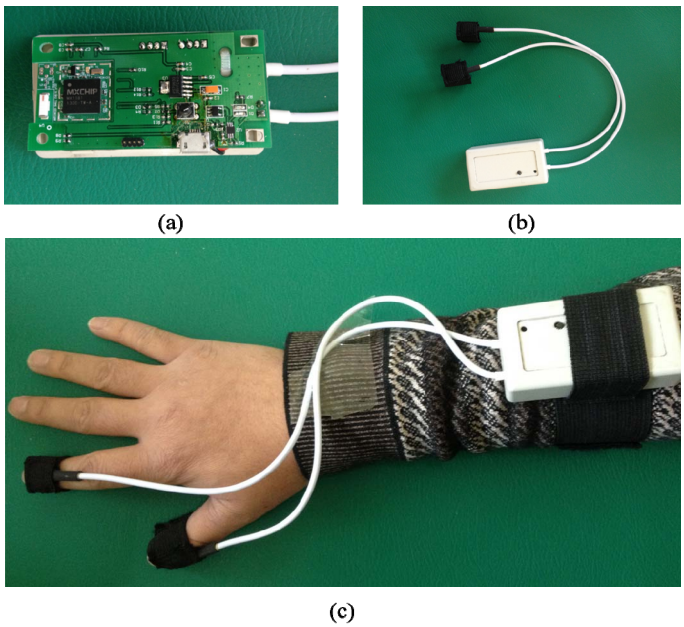


Figure 1. The data acquisition unit, (a) the main circuit board, (b) overall appearance of the device with two sensors packed in fingerstalls, (c) display a patient's hand wearing the device.

C. Experiment Protocol

At the time of testing, no subject was taking any form of anti-PD medication that could attenuate the tremor symptom. At the beginning, the acceleration module was mounted on the most affected side of upper limbs with a fixation belt. When holding the hand in the horizontal position, the direction of the three axes X, Y, Z were medial/lateral, anterior/posterior, and superior/inferior, respectively. The experiment was composed of two procedures. First, the subjects were instructed to sit in a chair with their hands putting peacefully and comfortably on their thighs to record resting tremor. Then, postural tremor were recorded when the subjects were standing still with their two arms stretched forward. Each procedure lasted about 30s. All clinical tests were completed under the supervision of two professional doctors.

The acceleration signals were preprocessed by ignoring the first 5s data and filtered by a second-order Butterworth low-

pass filter (cutoff frequency 30 Hz). The preprocessing work was performed by developing a custom software in Matlab.

D. Calculation of ApEn and Cross-ApEn

Given an equally spaced time series of N points u(1), u(2), ... , u(N), construct vector sequences $X_m(i)$ = [u(i), u(i+1), ... , u(i+m-1)], i=1, 2, … , N-m+1. These vectors represent m consecutive u values started with the ith point. Define the distance between vectors $X_m(i)$ and $X_m(j)$ as the maximum difference in their respective scalar components [8],

$$d[X_m(i),X_m(j)] = \max_{k=0,\ \ldots,m-1} |u(i+k)-u(j+k)| \quad (1)$$

Use the sequence $X_m(i)$ to construct

$$C_i^m(r) = \frac{1}{N-m+1}(\text{no. of } j \le N-m+1 \text{ such that } d[X_m(i),X_m(j)] \le r) \quad (2)$$

Define

$$\Phi^m(r) = \frac{1}{N-m+1}\sum_{i=1}^{N-m+1} \ln C_i^m(r) \quad (3)$$

where ln is the natural logarithm, then define the statistic

$$\text{ApEn}(m, r, N) = \Phi^m(r) - \Phi^{m+1}(r) \quad (4)$$

Two unknown arguments should be specified beforehand for the calculation of ApEn. The first argument, embedded dimension m, sets the length of the sequence to be compared, and typical value is 2. The second one r is the tolerance threshold for matching similarity between two segments. In other words, the difference between a pair of values is smaller than r is considered matching. In fact, r is essentially a filter whose type is determined by the choice of r. For example, a large r can be considered as an all-pass filter since the number of self-matches will be large, whereas a small r performs as a low-pass filter since it will lead to few self-matches and lost some detail information. Typical value is r = 0.2*std (std means standard deviation of the time series), but Chon et al suggested that r value should be chosen carefully, and the most appropriate r value that maximizes the ApEn should be explored [13]. Their work demonstrated that the maximum ApEn, which signifying the maximum complexity, is less arbitrary than using the recommended r = 0.2*std. However, finding the maximum ApEn is time-consuming since every ApEn should be computed using possible r value. In order to avoid the large computational burden, we introduced the automatic selection method of r developed by Sheng Lu, et al [14]. Based on nonlinear least squares fitting, they derived the general equations for determining the most appropriate r. The equations for m=2 are as follows,

$$r=(-0.036+0.26\sqrt{\text{std}_1/\text{std}_2})/\sqrt[4]{N/1000} \quad (5)$$

The calculation of Cross-ApEn is almost identical with ApEn, except that it is applied to two time series rather than a single one. Given two N length sequences u = [u(1), ... , u(N)] and v = [v(1), ... , v(N)], construct vector sequences $X_m(i)$=[u(i), ... , u(i+m-1)] and $Y_m(i)$=[v(i), ... , v(i+m-1)] respectively. Set

$$C_i^m(r) = \frac{1}{N-m+1}(\text{no. of } j \le N-m+1 \text{ such that } d[X_m(i),Y_m(j)] \le r) \quad (6)$$

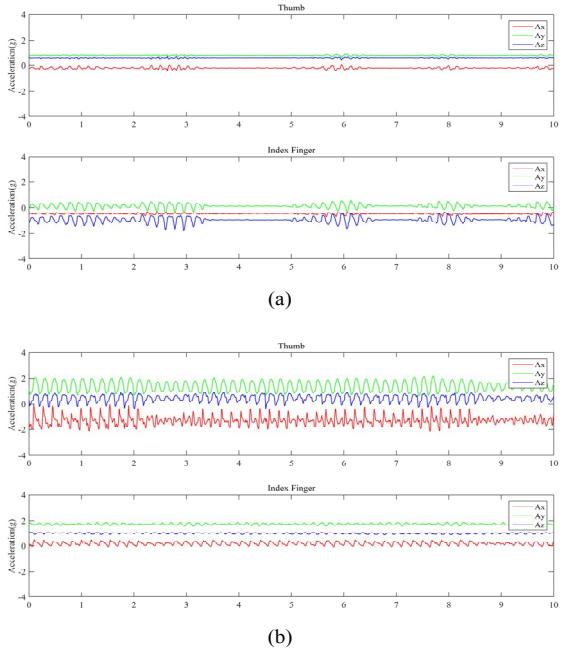
Where $d[X_m(i),Y_m(j)]$ is similar with the equation (1). Then define

$$\Phi^m(r) = \frac{1}{N-m+1}\sum_{i=1}^{N-m+1} \ln C_i^m(r) \quad (7)$$

Finally define

$$\text{Cross-ApEn}(m, r, N) = \Phi^m(r) - \Phi^{m+1}(r) \quad (8)$$

The arguments m and r take the same meaning as in the definition of ApEn. To eliminate the influence of different variances of two signals, we compute Cross-ApEn by normalizing the tremor signals of thumb and index finger and taking input arguments m=1 and r=0.2.



(a)

(b)

Figure 2. The comparison of original 3D acceleration signals of thumb and index finger for resting tremor. (a) Healthy subject (b) Patient with PD.

III. RESULTS

A. Comparison of Regularity for Resting Tremor and Postural Tremor

Fig. 2 illustrated an example of finger acceleration in the resting tremor of a PD patient and a control subject. From intuitional impression, there was an obvious increase in regularity of Parkinsonian tremor for all 3D accelerations compared with physiologic tremor. We calculated the ApEn

statistics of each signal (Ax, Ay, Az and A) for resting tremor and postural tremor respectively [15]. The resultant acceleration A was calculated by original 3D signals as follows:

$$A=\sqrt{A_x^2+A_y^2+A_z^2} \quad (9)$$

The ApEn values of resting tremor for PD subjects and control group were shown in Table 2. Data were presented as mean±SD. All ApEn mean values of PD group were lower than control group for the thumb and index finger, respectively. The t test confirmed the observations that the ApEn decreased significantly for thumb signals Ax, Az and A ($p<0.01$), and for index signals Ax ($p<0.05$), Az and A ($p<0.01$). This result supported the hypothesis that there are more regular oscillations in the resting tremor of PD patients, which is consistent with previous reports [16].

TABLE 2. APEN FOR RESTING TREMOR BETWEEN PD GROUP AND CO GROUP

Position	Group	Ax	Ay	Az	A
Thumb	PD	1.08±0.13	1.13±0.21	0.95±0.16	1.01±0.23
	CO	1.34±0.08	1.32±0.12	1.44±0.13	1.47±0.09
	Sig.	**		**	**
Index finger	PD	1.11±0.16	1.21±0.22	0.99±0.20	1.10±0.25
	CO	1.31±0.15	1.45±0.19	1.51±0.22	1.43±0.12
	Sig.	*		**	**

** p<0.01, * p<0.05

TABLE 3. APEN FOR POSTURAL TREMOR BETWEEN PD GROUP AND CO GROUP

Position	Group	Ax	Ay	Az	A
Thumb	PD	0.98±0.16	1.03±0.22	0.87±0.15	0.92±0.10
	CO	1.23±0.13	1.19±0.11	1.21±0.14	1.14±0.17
	Sig.	*		**	*
Index finger	PD	0.80±0.08	0.99±0.14	0.77±0.08	0.89±0.16
	CO	1.19±0.07	1.20±0.10	1.03±0.13	1.10±0.06
	Sig.	**		**	*

** p<0.01, * p<0.05

Table 3 presented the ApEn values of postural tremor for PD group and control group. Four acceleration signals had differences between the two groups for both thumb and index finger. These differences were characterized by decreased ApEn for patients with PD while higher values were observed for healthy subjects. Specifically, the mean differences were statistically significant for thumb signals Az ($p<0.01$), Ax, A ($p<0.05$), and for index signals Ax, Az ($p<0.01$), A ($p<0.05$). This result indicated that the postural tremor of PD patients had more regularity than the physiologic tremor of healthy subjects when they performed the same posture. Fig. 3 displayed the comparison for the resting tremor and postural tremor.

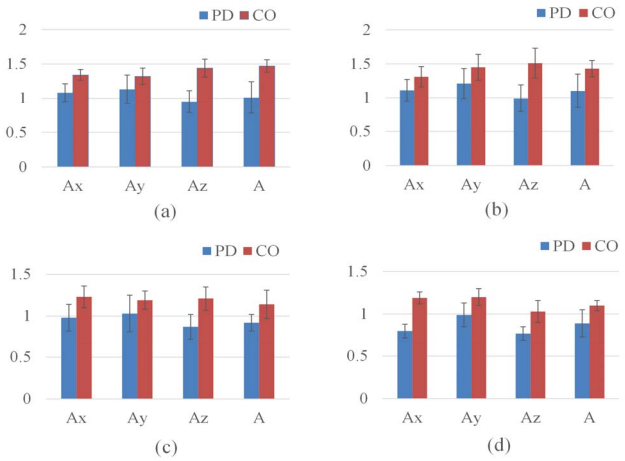


Figure 3. The comparison of ApEn values between PD group and control group. (a) Thumb and (b) index finger for resting tremor, (c) thumb and (d) index finger for postural tremor.

B. *Comparison of Synchrony between Thumb and Index Finger*

In order to investigate the relationship between thumb and index finger, we calculated Cross-ApEn of each pair of acceleration signals between the two fingers. Table 4 presented the results of Cross-ApEn for resting tremor between PD and control subjects. Table 5 presented the corresponding results for postural tremor. As stated in section I, Cross-ApEn measured synchrony between two signals and was independent of the amplitude of each signal. A lower Cross-ApEn value corresponded to an increased coupling between two signals whereas uncoupled signals tended toward a Cross-ApEn equal to 2 [10]. Fig. 4 showed that there was a significant reduction in Cross-ApEn for the PD subjects compared to controls. This result indicated that coupling between the thumb and index tremor activity increases from the controls to the PD patients. Furthermore, the PD group had a large lower Cross-ApEn than control group in the resting tremor condition, coupled with a relatively slight reduction in the postural tremor condition.

TABLE 4. CROSS-APEN OF TWO FINGERS FOR RESTING TREMOR

Group	Ax	Ay	Az	A
PD	1.33±0.15	1.48±0.26	1.36±0.15	1.41±0.19
CO	1.61±0.16	1.74±0.14	1.66±0.16	1.71±0.10
Sig.	**	*	**	**

** p<0.01, * p<0.05

TABLE 5. CROSS-APEN OF TWO FINGERS FOR POSTURAL TREMOR

Group	Ax	Ay	Az	A
PD	1.37±0.12	1.30±0.16	1.29±0.05	1.31±0.11
CO	1.56±0.10	1.49±0.09	1.53±0.13	1.55±0.15
Sig.	**	*	*	**

** p<0.01, * p<0.05

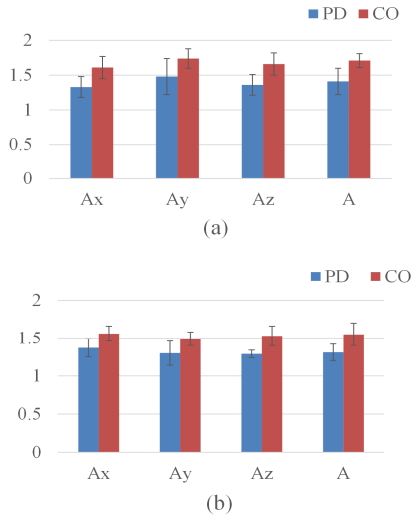


Figure 4. The comparison of Cross-ApEn between PD group and control group. (a) Resting tremor (b) Postural tremor.

IV. CONCLUSION

In this study, we designed a set of wireless data acquisition unit to investigate the regularity and synchrony of tremor by calculating the ApEn and Cross-ApEn. We demonstrated that the acceleration signals of Parkinsonian tremor is more regular than normal physiological tremor. The increased regularity of tremor is consistent with the hypothesis that there is a loss of the independent sources of control in PD tremor [16]. In addition, the synchrony of acceleration signals between the two fingers increases according to our results. This indicates that coupling between the thumb and index tremor activity increases in PD. Our results suggest that the ApEn and Cross-ApEn are effective tools to discriminate Parkinsonian tremor from normal physiological tremor. It has a potential use in assessing patients with PD. In future work, we will combine ApEn and Cross-ApEn with classical linear parameters as multidimensional feature vectors to assess the severity of tremor.

ACKNOWLEDGMENT

We thank Zheng Tang for his technical support in device development of hardware and software, and Dabing Xu and Xiaoyong Sun for assisting in data collection.

REFERENCES

[1] R. L. Nussbaum, and C. E. Ellis, "Alzheimer's disease and Parkinson's disease," N. Engl. J. Med, 2003, vol. 348, pp. 1356-1364.

[2] E. Roderick, and B. Anne, "Using time domain characteristics to discriminate physiologic and Parkinsonian tremors," J. Clin. Neurophysiol, 2000, vol. 17, pp. 87-100.

[3] E. Roderick, and B. Anne, "Using frequency domain characteristics to discriminate physiologic and Parkinsonian tremors," J. Clin. Neurophysiol, 1999, vol. 16, pp. 484-494.

[4] J. Timmer, M. Lauk, and G. Deuschl, "Quantitative analysis of tremor time series," Electroencephalography and clinical Neurophsiology, 1996, vol. 101, pp. 461-468.

[5] V. Rajaraman, D. Jack, S. V. Adamovich, W. Hening, and J. Sage, "A novel quantitative method for 3D measurement of Parkinsonian tremor," Clinical Neurophysiology, 2000, vol. 111, pp. 338-343.

[6] A. Y. Meigal, et al. "Linear and nonlinear tremor acceleration characteristics in patients with Parkinson's disease," Physiol. Meas, 2012, vol. 33, pp. 395-412.

[7] J. B. Gao, "Analysis of amplitude and frequency variations of essential and Parkinsonian tremors," Medical & Biological Enineering & Computing, 2004, vol. 42.

[8] S. M. Pincus, "Irregularity and Asynchrony in biologic networks signals," Methods in Enzymology, vol. 321, 2000.

[9] S. M. Pincus, "Approximate entropy as a measure of system complexity," Proc. Natl. Acad. Sci, 1991, vol. 88, pp. 2297-2301.

[10] D. E. Vaillancourt, and K. M. Newell, "The dynamics of resting and postural tremor in Parkinson's disease," Clin. Neurophysiol, 2000, vol. 111, pp. 2046-2056.

[11] D. E. Vaillancourt, A. B. Slifkin, and K. M. Newell, "Regularity of force tremor in Parkinson's disease," Clin. Neurophysiol, 2001, vol. 112, pp. 1594-1603,.

[12] S. Morrison, G. Kerr, K. M. Newell, and P. A. Silburn, "Differential time- and frequency-dependent structure of postural sway and finger tremor in Parkinson's disease," Neuroscience Letters, 2008, vol. 443, pp. 123-128.

[13] K. H. Chon, C. G. Scully, and S. Lu, "Approximate entropy for all signals," IEEE Eng. Med. Biol. Mag, 2009, vol. 28, pp. 18-23.

[14] S. Lu, X. Chen, J. Kanters, I. C. Solomon, and K. H. Chon, "Automatic selection of the threshold value R for approximate entropy," IEEE Tans. Biomed. Eng, 2008, vol. 55, pp. 1966-1972.

[15] G. Manis, "Fast computation of approximate entropy," Computer Methods and programs in Biomedicine, 2008, vol. 91, pp. 48-54.

[16] L. M. Gil, T. P. Nunes, F. Silva, A. Faria, and P. Melo, "Analysis of human tremor in patients with Parkinson Disease using entropy measures of signal complexity," 32nd Annual International Conference of the IEEE EMBS, 2010, pp. 2786-2789.