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Application of Fractal Dimension on Vestibular Response Signals for Diagnosis of Parkinson's Disease

Z. A. Dastgheib, B. Lithgow, Z. Moussavi

Abstract - **In this paper, a novel method based on analysis of dynamic response of vestibular system for diagnosis of Parkinson's Disease (PD) is introduced. Electrovestibulography (EVestG) signals are recorded from the ear canal in response to a vestibular stimulus. EVestG signals are in fact the vestibular response modulated by more cortical brain signals. We used EVestG data of 20 patients with PD and 26 age-matched healthy controls recorded in a previous study. We calculated the Katz Fractal Dimension (FD) of the extracted timing signal of firings during contralateral and ipsilateral stimuli of both left and right ear. We used multivariate analysis of variance (MANOVA) to select pairs of features showing the most significant differences between the groups. Then, Linear and Quadratic Discriminant (LDA, QDA) classification algorithms were applied on the selected features. The results have shown above 77.27% accuracy. Given the small population of the subjects and the patients were at different stage of disease, the results encourage continuing exploration of the application of EVestG for PD diagnosis and perhaps as a quick and non-invasive screening tool.**

I. Introduction

Idiopathic Parkinson's disease (PD) is the second largest neuro-degenerative disorder estimated to afflict approximately 3% of the population over the age 65 [1-3]. There is no way known to prevent or to cure PD. The end stage of the disease can lead to pneumonia, choking, severe depression, and death.

Parkinson's disease belongs to a group of conditions called motor system disorders. It occurs as the results of a slow and progressive loss of dopaminergic neurons. These are located in the midbrain region called substantia nigra pars compacta, which is a part of basal ganglia of the brain. The loss of dopaminergic neurons affects nigrostriatal neurons in the striatum, and results in a reduction in dopamine concentration [4]. The lack of dopamine neurotransmitters in neural pathways weakens the motor cortex signals that coordinate muscle movement [5].

Currently, no early detection method exists for PD [6] and its diagnosis is based on medical history and neurological examination. A definite diagnosis of PD requires autopsy [7]. The aim of this study is to investigate the possibility of PD diagnosis by analyzing the vestibular response to a tilting stimulus.

There is a clear link between dopamine and the vestibular system; dopamine receptors (D2) have been identified in medial vestibular nuclei and lateral vestibular nuclei [8]. Also, meaningful levels of dopamine have been detected in a region of the vestibular nuclei [9]. There is an evidence to suggest that dopamine might exert a modulatory action on the vestibular system, either by a direct action on the vestibular neurons or by modulation of GABAergic transmission [10]. Abnormalities in the vestibular system have been previously documented in PD, in relation to an abnormal vestibular-ocular reflex [11].

Electrovestibulography (EVestG) [12], a non-invasive technique to record neural activity from the vestibular apparatus and vestibular nuclei, has been previously applied to PD diagnosis [13]. EVestG measures a vestibular driven response stimulated from passively tilting a participant who is seated in a special hydraulic chair, placed in an electrically and acoustically shielded chamber. The EVestG signal is recorded during dynamic and static phases via an electrode resting proximal to the tympanic membrane [12]. The electrodes are simply and painlessly positioned and rested close to the left and right ear drums of the test subject. Figure 1, shows the recording system with the hydraulic chair.

In a previous study [13] on the application of EVestG signals for PD diagnosis, a biofeature extracted from the shape of the average field potential of EVestG signal was found significant between the two groups of patients and controls; the correlation of this biofeature with the severity of the disease was also shown to be significant [14].

In this study, we investigate whether the fractal dimension of the firing time pattern of the vestibular field potentials recorded by EVestG can be used for diagnosis of PD. Hence we used the data of the previous study [13] and applied the Katz fractal dimension among patients with PD and control subjects.

II. Materials and Method

A. Data

Data of this study was adopted from a previous study [14], [15] which included data of 20 PD patients and 26 age-

Z. A. Dastgheib is with Faculty of Electrical and Computer Engineering, University of Manitoba, Winnipeg, MB, Canada, R3T 5V6. (email: zeinab@ee.umanitoba.ca)

B. Lithgow, Senior Research Fellow, Monash Alfred Psychiatry Research Centre, Senior Lecturer ECSE Monash University and Research Affiliate of Riverview Health Center, Winnipeg. (e-mail: brian.lithgow@monash.edu).

Z. Moussavi is with Faculty of Electrical and Computer Engineering, University of Manitoba, and Research Affiliate, Riverview Health Center, Winnipeg. (e-mail: moussavi@ee.umanitoba.ca).

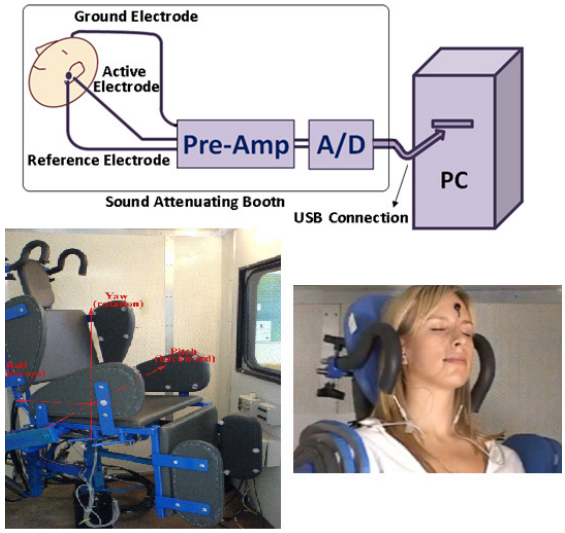

Fig. 1. The recording system with the hydraulic chair

matched healthy as controls. The PD patients were diagnosed by a neurologist. The patients were tested, while they had been off their medication (Levadopa preparations) for at least 4 hours and typically overnight. Among PD subjects, 6 subjects were evaluated to have Parkinson's symptoms as mostly on the right, 5 on the left and 9 on both sides of their body. The severity of the disease was assessed using the Modifed Hoehn and Yahr Parkinson's Disease Staging Scale [16]. Based on this scale, one patient was severely affected, while the others were in the mild to moderate stages. EVestG data, recorded at 44100 Hz, of the side-tilt trial was used in this study.

B. *EVestG Experiment*

The whole EVestG experiment [12] includes several tilting stimuli. The one that is used in this study is the side tilt stimulus. The side tilt stimulus takes 120 s; it begins with a 20 s background (steady state), while the subject is sitting in a still position without any inclination, followed by a 3 s tilt to the right (about 40 degrees), 17 s rest in the tilted position, 3 s moving back to center, 40 s rest at the center position, 3 s tilting to the left, 17 s rest at the left position, 3 s return to the center and 20 s rest at the center. Figure 2 shows the pattern of the chair movement during a side tilt trial. The periods of interest are 1.5 s before the movement and the 3 s tilting stimuli. Given that each movement has an acceleration and deceleration phases, assuming a minimum jerk movement, the first 1.5 s after the onset of the tilt is marked as OnAA and the next 1.5 s is marked as OnBB, representing acceleration and deceleration phases, respectively. Since the chair is tilting to both left and right while recording both right and left ears, there are both contralateral (CT) and ipsilateral (IP) stimuli.

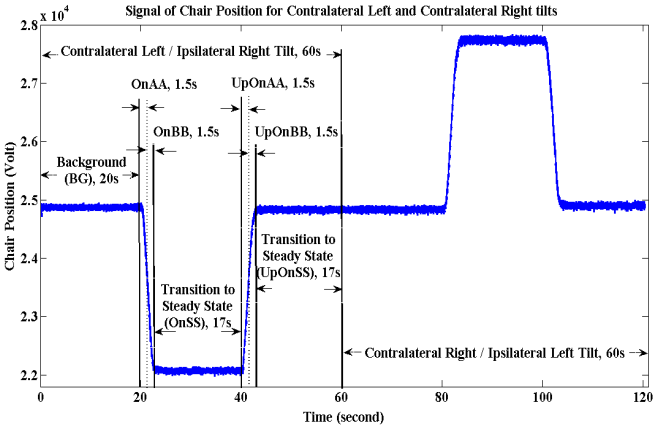

Fig. 2. The pattern of the chair movement during a side tilt trial.

The EVestG-evoked response field potentials were extracted using a Neural Event Extraction Routine (NEER) [17-18]. Furthermore, in the NEER Algorithm, the sample numbers of each detected field potential is registered and saved as the Field Potential Index vector (simply called firing time signal) for every segment in every tilt of the experiment.

C. *Signal Analysis*

We used the firing time signal of only the OnBB segments of the tilts from center to either side. Given that signals of both ears were recorded, for every subject we have 4 signals: contralateral left (CTL), contralateral right (CTR), ipsilateral left (ITL) and ipsilateral right (ITR). Figure 3 shows the probability distribution function of the time interval between the successive firing potentials for one control subject.

Basically, firing time signals are smooth increasing curves during 1.5s of OnBB segment. We excluded the firing time signals that had less than 1.36s duration due to corruption by artifact. In total 3 ITR, 2 CTR, 1 ITL and 1 CTL segments of entire data population were excluded.

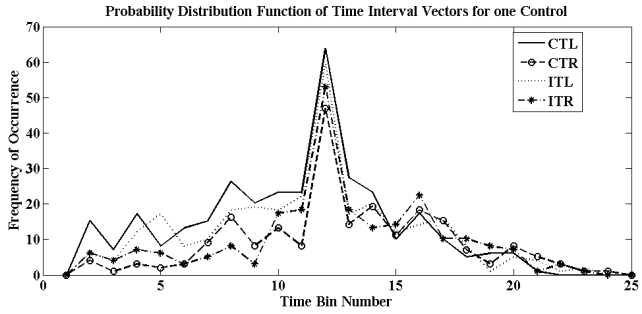

Fig. 3. The probability distribution function of time interval signal for ITL, ITR, CTL, and CTR tilts for one control subject.

D. *Katz Fractal Dimension*

Fractal dimension (FD) mathematically refers to a non-integer or fractional dimension of a self-similar (or a self-affine) object that exceeds its Topological dimension [19]. The self-similarity (or self-affinity) of the object is confirmed if a portion of the object is exactly (or statistically) a scaled down version of itself. FD values also indicate the complexity of a pattern, the degree of irregularity or the quantity of information embodied in a waveform pattern in terms of morphology, entropy, spectra

or variance [19]. FD is often used as a characteristic feature for diagnostic purposes using biological signals. In this study we used Katz algorithm to calculate the FD values due to its robustness respect to noise [20]. We also calculated FD values with Higuchi method [21] and Variance Fractal Dimension method [19] but none of them ended in significant results.

In Katz Method [22], the Dimension of a curve is defined as:

$$\frac{\log(n)}{\log(\frac{d}{L}) + \log(n)}. \quad (1)$$

where L is the total length of the curve or sum of distances between successive points, d is the diameter estimated as the distance between the first point of the curve and the point which provides the farthest (maximum) distance. To be independent of the measurement units, parameter $n = L/a$, is defined, in which a is the average step or average distance between successive points and n is the number of the steps in the curve. The FD compares the actual number of units that compose a curve with the minimum number of units required to reproduce a pattern of the same spatial extent.

We calculated the Katz FD of the normalized (divided by the total duration of each signal) firing time signals of ITL, ITR, CTL, and CTR for each subject, and investigated the significance of these 4 FD features using Analysis of Variance (ANOVA). Furthermore, we ran multivariate analysis of variance (MANOVA) to select pairs of features with most significant difference in 2 dimensions between the two groups [23]. In all statistical tests $p < 0.05$ was considered significant.

E. Linear and Quadratic Discriminant Analysis

Once the best pairs of features were selected, we applied the linear and quadratic discriminant classifiers (LDA & QDA) on the selected pairs of features, which are the standard approach to supervised classification problems. They estimate the likelihood probability of each class as a Gaussian distribution. LDA has an extra condition of assuming identical covariance matrices for all of the classes. Posterior distributions were used to estimate the class for a given test point. The Gaussian parameters for each class can be estimated from training points with maximum likelihood (ML) estimation [24]. Due to the small size of data we used leave-one-out method for training and testing the classifier. Leave-one-out routine uses all data except one for training and use the left-out data for test; this procedure is repeated till all data are being used as test data once. The misclassified subjects are found through testing these classifiers by using the Leave-one-out method [24].

III. RESULTS

Table I shows the results of ANOVA and MANOVA on the 4 FD features and the 6 pairs among the subjects. As shown, most significant pairs were CTL-CTR and CTR-ITR. Hence, these two pairs were selected for further analysis.

Table II shows the results of LDA and QDA classifications in terms of accuracy, sensitivity and specificity for each pair of features among the two groups of controls and PD patients. Figures 4 and 5 show the classification curves for the above mentioned pairs of features. As can be seen, QDA classification outperforms the LDA classifier in this population. Out of the two pairs of features, the CTR-CTL pair outperformed the other one.

IV. DISCUSSION

Fractal Dimension of the firing time signals was selected as a feature to represent a property of firing pattern of vestibular response. The FD values of the contralateral and ipsilateral tilts showed statistically significant difference between the two groups of PD and controls. The FD values of firing time signals of the controls were higher than that of the PD patients, implying a higher complexity of the signals of control group versus PD patients. This is an interesting result; because the average total number of firings in PDs was observed to be distinctively greater than that of controls. However, despite this observation, the number of firing points required to reproduce the pattern of firing is lower in PD patients compared to that of the controls. Furthermore, higher FD values in controls represent higher degree of self similarity in such curves in comparison to that in PD patients. This may imply a more synchronous firing among control subjects than in PD patients.

The overall performance of both of the classifiers was high, while QDA classifier outperformed the LDA. Three patients who were misclassified by QDA: one had PD symptoms on both side of the body with severity of 2 out of 7, the second had PD symptoms on left part of body with severity of 1 out of 7 and the third had PD symptoms on right part of body with severity of 1 out of 7. The highest severity degree for our PD patients was 5. This indicates that the method is capable of identifying moderate and severe PD cases but encounters errors when the patients are in mild level of the disease. Overall, the results are very encouraging. However, the method must be tested in a larger population. Also, the combination the two selected pairs for classification should also be investigated.

V. CONCLUSION

We applied Katz algorithm to calculate the FD values of the firing time signals to produce a new set of biofeatures for identification of PD subjects from age-matched control subjects. Higher FD values of the controls imply the difference of the groups in terms of complexity and the self-similarity of neural firings in the vestibular response. The high sensitivity of the QDA classification is encouraging to use this method on a larger population. However, other classification methods which do not assume normal

TABLE I
STATISTICAL ANALYSIS (ANOVA AND MANOVA) FOR SELECTED PAIRS OF FEATURES OF KATZ FD OF FIRING CURVES

Katz Fractal Dimension of firing time signals									
ANOVA				MANOVA					
CTL	CTR	ITL	ITR	CTL-CTR	ITL-ITR	CTR-ITR	CTL-ITL	CTL-ITR	CTR-ITL
0.021	0.003	0.38	0.006	0.002	0.036	0.004	0.072	0.02	0.013

distribution of the data can be applied. In this study we only used the deceleration phase (OnBB) of the tilts. The inclusion of the acceleration phases may also improve the accuracy of the classification.

Overall, the results of this study shows a new potential of EVestG signals towards generating an adequate set of biofeatures for diagnosis, monitoring, and perhaps measuring the efficacy of drug treatment during early PD stages. The results may lead to a simple, objective, and non-invasive clinical assessment of Parkinson Disease.

TABLE II
MESURES OF THE CLASSIFICATION PERFORMANCE
ACC: ACCURACY, SPEC: SPECIFICITY, SENS: SENSITIVITY

Katz Fractal Dimension of Firing Curves						
	QDA Classifier			LDA Classifier		
	Acc (%)	Spec (%)	Sens (%)	Acc (%)	Spec (%)	Sens (%)
CTL-CTR	81.81	72	94.73	77.27	72	84.21
CTR-ITR	73.8	65.21	84.21	71.42	60.86	84.21

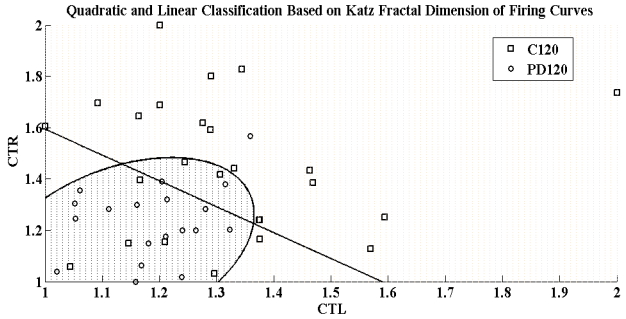

Fig. 4. The classification curves (Linear and Quadratic) using CTL-CTR features. C and PD represent controls and PD patients.

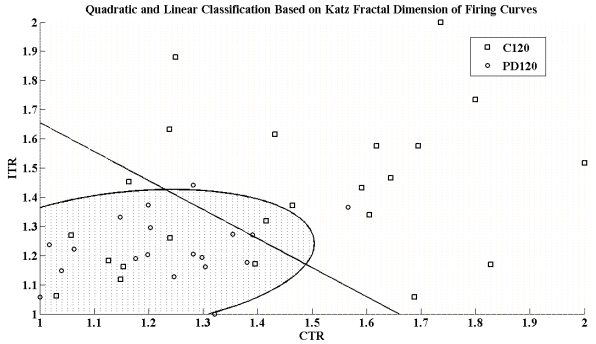

Fig. 5. The classification curves (Linear and Quadratic) using CTR-ITR features. C and PD represent controls and PD patients.

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