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Assessment of the Effects of Subthalamic Stimulation in Parkinson Disease Patients by Artificial Neural Network

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***Abstract*—This study aims at using a probabilistic neural network (PNN) for discriminating between normal and Parkinson disease (PD) subjects using as input the principal components (PCs) derived from vertical component of the ground reaction force (vGRF). The trained PNN was further used for evaluating the effects of deep brain stimulation of the subthalamic nucleus (STN DBS) on PD, with and without medication. A sample of 45 subjects (30 normal and 15 PD subjects who underwent STN DBS) was evaluated by gait analysis. PD subjects were assessed under four test conditions: without treatment (mof-sof), only with stimulation (mof-son) or medication (mon-sof), and with combined treatments (mon-son). PC analysis was applied on vGRF, where six PC scores were chosen by the broken stick test. Using a bootstrap approach for the PNN model, and the area under the receiver operating characteristic curve (AUC) as performance measurement, the first three and fifth PCs were selected as input variables. The PNN presented AUC = 0.995 for classifying controls and PD subjects in the mof-sof condition. When applied to classify the PD subjects under treatment, the PNN indicated that STN DBS alone is more effective than medication, and further vGRF enhancement is obtained with combined therapies.**

***Index Terms*—Neural Network, Classification, Ground Reaction Force, Parkinson Disease, Deep Brain Stimulation.**

I. INTRODUCTION

PARKINSON disease (PD) is a neurodegenerative disorder leading to difficulty in the performance of skilled motor tasks, such as walking, writing and speaking [1]. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an approved treatment for advanced PD patients with disabling motor fluctuations and dyskinesia. This procedure has been shown to relieve the primary motor symptoms and often allows a significant reduction in dopaminergic medications [2]. Various studies have demonstrated the effects of DBS using clinical motor scores [3]–[5] and only a few studies have quantitatively assessed gait patterns of PD patients [2], [6].

A constant challenge to clinicians is the knowledge of the extent and consequences of a disease and the outcomes of potential interventions. Predictive models are used in a variety of domains for diagnostic and prognostic tasks. Artificial neural network (ANN) modeling has been used in human locomotion investigations focusing on gait pattern recognition [7], and gait pattern classification between normal and pathological subjects [8]. Probabilistic neural network (PNN) is an optimum classification approach [9] that can minimize the risk of wrongly classifying an object. However, none of past studies used PNN for classifying gait patterns. Furthermore, there were no studies evaluating the effect on GRF as prospective outcomes from therapeutic interventions in PD patients.

This paper aimed at evaluating a PNN model developed to discriminate PD subjects from the normal. The model inputs were the principal components derived from vertical ground reaction force (vGRF) recorded during gait. The effects of STN DBS on vGRF with and without medication were also evaluated using the model.

II. MATERIALS AND METHODS

A. Subject Selection and Data Acquisition

The subject pool (n = 45) consisted of 30 healthy subjects (20 women) and 15 PD subjects (three women). The healthy subjects with an average age of 50.1 ± 7.8 (mean ± SD) years had no history of neurological illness, degenerative conditions or any other disease that might interfere with body sway or gait. The PD subjects with an average age of 56.4 ± 8.3 years had undergone bilateral STN DBS and were stable when the study was conducted. Averaged time since surgery was 15.05 ± 9.47 months and duration of the disease was 12.23 ± 4.3 years. Each subject signed an in-formed consent approved by the Institutional Review Board of the University of Kansas Medical Center.

Each PD subject came to the gait laboratory on two different days for repeated quantitative gait measurements. In the first visit, the subject had taken the usual dose of PD medications and stimulators were turned "on". The gait assessment was first conducted with both medication and stimulation (mon-son condition). After turning stimulator off for 30 minutes, the measurements were repeated (mon-sof). In the second visit, the subjects were without medication for at least 12 hours. Gait analysis was first conducted with stimulation (mof-son), and repeated after 30 minutes without

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stimulation (mof-sof). Due to experimental problems, some subjects did not complete all tests. Therefore, 13 subjects were evaluated on mof-sof, 12 on mof-son, 14 on mon-sof and 11 on mon-son conditions. Subjects from the control group were evaluated only once. The quantitative analysis for the control group and for PD subjects in the baseline condition (mof-sof) was used to develop the PNN models. The other three conditions for the PD group were applied into the developed model to evaluate the STN DBS effect in PD treatment.

Two force platforms (AMTI, USA) were used to record the vGRF of both feet during walking. All subjects practiced the walking trial on the walkway at least five times before the experiment. The subjects walked at their self-selected speed in barefoot, and repeated the walking trial five times. The vGRF signals were collected for 10 s at a frequency of 100 Hz, filtered using a low pass Butterworth filter with a cut-off frequency of 30 Hz, and normalized by subject´s body weight.

B. Data Analysis

The averaged vGRF data of the five walking trials was interpolated with cubic splines and re-sampled with 101 samples according to the stance phase duration of each foot. Thus, 202 vGRF samples from the complete stride (right and left side) were used in the analysis.

Principal component analysis (PCA) method, as described in [10] was applied to a covariance matrix of vGRF data from 30 healthy subjects and 13 PD subjects at mof-sof condition.

PNN is a feed-forward neural network developed by Specht [9], in which the response to an input pattern is processed from one layer to the next without feedback paths to previous layers. A typical PNN has four layers: input, pattern, summation and output. This network is one of the most powerful networks commonly used in solving classification/discrimination problems [11].

The broken stick test [10] criterion was used for choosing significant principal components (PCs) for the analysis. Moreover, it is then necessary to evaluate which scores are more relevant for the classifiers modeling [10], since there is no guarantee that the components with the larger eigenvalues contain useful information for classification [12]. PNN also requires the selection of the optimal value for the spread (σ^2) of the radial basis function. For selecting the input variables and the spread constant of the PNN, the models considered each possible combination of scores and varied the values σ^2 in the interval from 0.1 to 1, using the bootstrap approach [13]. The developed model with the bootstrap samples was tested with those subjects not included in the bootstrap by the area under receiver operating characteristic (ROC) curve (AUC) [14].

For a small sample size, the recommended approach is to apply a resampling technique to estimate the performance of the classifier [15]. The 0.632+ bootstrap approach was chosen because it is suitable to reduce the variability of error rate prediction and the AUC [14]. The prediction success of the classifier was also evaluated using the negative likelihood ratio (NLR), i.e. ratio between false negatives and true negatives.

For quantifying the effects of treatments, the PC scores from PD subjects in the mon-sof, mof-son and mon-son conditions were calculated. Similarly, those data were used as inputs in the developed PNN classifier.

III. Results

The avareged vGRF from CG evidenced normal pattern; conversely, PD subjects in mof-sof condition presented a smothly averaged vGRF pattern (Fig. 1a).,The broken stick test indicated that the first six PC, which explained 91.1% of the total variation, should be considered in the analysis. These PC were presented in Fig.1b, c d. The magnitude distribution of each eigenvector could be interpreted as the loading factor in the calculation of the respective PC score.

The PNN model that presented the highest averaged AUC has only four PC scores as input, including the first three and the fifth scores. Therefore, these input variables were adopted for the final PNN.

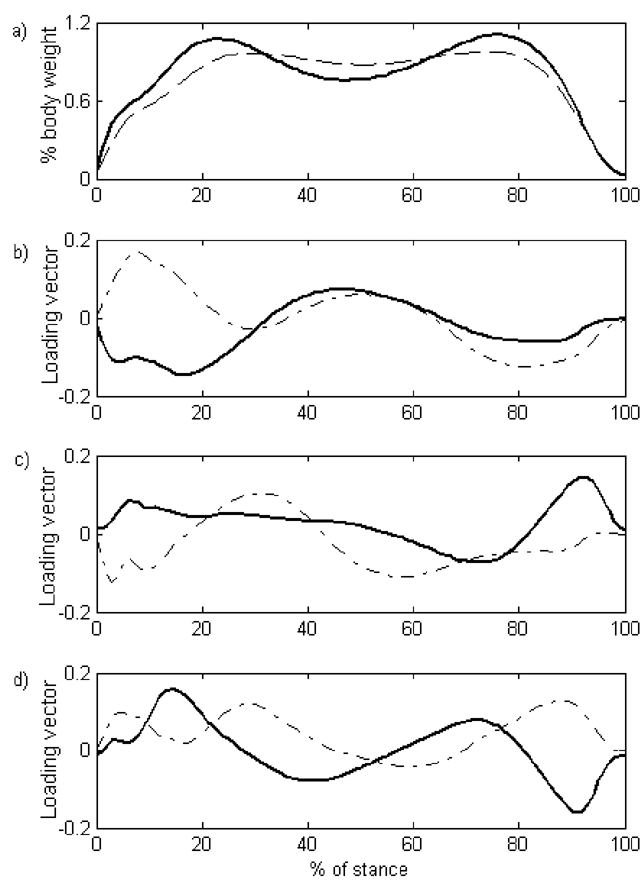

Fig. 1a) Average vertical GRF of control group (continuous) and PD subjects (dashed), b) the loading vector of the first principal component (PC) (continuous) and the second PC (dashed), c) the loading vector of the third PC (continuous) and fourth PC, d) the loading vector of the fifth PC (continuous) and sixth PC.

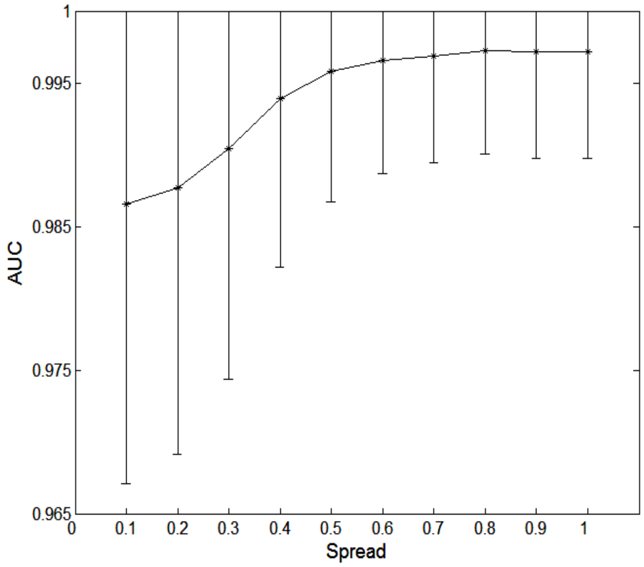

Fig. 2 The area under the ROC curve for each spread for the PNN with four PC scores. The maximum AUC was reached by the spread 0.7.

The analysis of mean and 95% confidence bands for AUC in one thou-sand bootstrap training and testing samples as a function of the spread constants for the selected inputs (Fig. 2) indicated that AUC reached its maximum for $\sigma^2 = 0.7$.

The estimated area ± standard error under the ROC curve at this spread constant over all one thousand bootstrap samples was 0.995 ± 0.011. The NLR for such model was 0.067 ± 0.13.

In the validation set, the stimulation conditions, mof-son and mon-son, presented better results than just medication (mon-sof) (Table I). In the mof-son condition, 10 of 12 subjects (83.3 %) were classified as presenting normal vGRF, while further enhancement was given by the mon-son condition, with 90.9% of subjects with normal vGRF pattern. These results are indicative that STN DBS improves the vGRF pattern of gait, mainly when associated with medication.

TABLE I
PNN CLASSIFICATION OF PD PATIENTS UNDER DIFFERENT TREATMENTS

	Normal	Abnormal	Total
mon-sof	7 (50.0%)	7 (50.0%)	14 (100%)
mof-son	10 (83.3%)	2 (16.7%)	12 (100%)
mon-son	10 (90.9%)	1 (9.1%)	11 (100%)

each cell contains the raw number (and % of total) of patients presenting Normal and Abnornal vGRF

IV. DISCUSSION

The averaged shape of the vGRF showed qualitative difference between controls and PD subjects (Fig. 1). PCA applied in the vGRF waveform allowed reducing the vGRF to only six PCs (Fig. 1), extracting essential information about normals and PD subjects gait pattern. The six PCs selected by the broken stick method accounted for 91.1% of the data variance. The corresponding PC scores carried information from entire vGRF curve rather than parameterization techniques, which extract only instantaneous values of amplitude and time from the gait curves [16], [17], thereby using a fraction of the available data. Additionally, it can be difficult to identify the required peaks and valleys in some clinical waveforms, which present abnormal profiles, far from normative data. Moreover, such methods do not address information that may lie in the pattern of the waveform.

The small number of PC scores allowed using the bootstrap techniques for selecting the most important inputs in searching for the appropriate spread value for this network model. Indeed, not all of them were important in the vGRF classification. Using bootstrap in the PNN model the AUC indicated that the first three PCs and the fifth one should be used as inputs variables, with the best PNN performance being obtained with 0.7 spread. The AUC has been described as one of the best summary measures to evaluate a classifier's performance [15], [18].

Given the relatively small sample size, the PNN model with the four PC scores as inputs performed reasonably well with 0.995 ± 0.011 AUC. The bootstrap approach is considered as a robust method for problems of classifier performance prediction under the constraint of a limited dataset. The 0.632+ bootstrap method was chosen because it provides the lowest bias with better accuracy [15]. Another performance index is the NLR that describe the discriminatory properties of negative test results. In this study, such value was 0.067 ± 0.13. According to Deeks [19], NLR bellow 0.1 have been noted as providing convincing diagnostic evidence.

PNN is useful for automatic pattern recognition and has been considered the most appropriate form of ANN for classification approaches [9], [20]. Some recent applications of PNN presented better performance than logistic regression [11], [20]. In gait analysis, the use of ANN techniques for decision making in certain applications can be more effective than conventional statistics [21]. According to Hahn et al. [7] applications of ANN may be pursued in the evaluation of the effects on balance control during locomotion, as well as outcomes from a given therapeutic intervention.

The use of the trained PNN for PD subjects with treatments indicated that STN DBS induced changes towards a normal gait pattern, showing a greater effect on vGRF patterns than medication. Other studies confirmed the positive effects of STN DBS [2], [22]. Faist et al. [22], however reported almost identical mean values comparing supra-threshold dose of levodopa and STN stimulation. A further improvement in vGRF was observed with both STN stimulation and medication (mon-son) with more subjects classified as normal. Similarly, past studies [2], [23] have reported an enhancement in gait performance with combined stimulation with medication, suggesting a synergistic effect of STN stimulation and levodopa for axial PD symptoms.

PNN has shown to be an efficient clinical diagnostic tool to evaluate the effects of both treatments applied in the PD subjects (DBS and medication). According to Masiero et al. [24] to optimize the efficacy and efficiency of rehabilitation interventions, it is also important to identify the benefits of a specific treatment.

Results obtained in the classification between control group and PD subjects, as well as on the effects of treatment are only indicative that these subjects presented a vGRF pattern similar to normal or abnormal subjects. This measure can not be extended to the whole gait pattern, which may include others kinematic and kinetic variables. On the other hand, the use of a whole vGRF waveform present more information than using only isolated measures, such as velocity or step length, that are still been used in the gait analysis of patients with DBS STN [2], [22], [23].

V. CONCLUSION

Results pointed to the potential power of PNN model for classifying between normal and PD subjects using PC scores derived from vGRF. Moreover, the obtained classifier allowed indicating that STN DBS improves the vGRF pattern in PD patients, particularly when used in conjunction with medication.

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