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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 applying an artificial neural network for the evaluation of the effects of deep brain stimulation (DBS) of the subthalamic nucleus (STN) on Parkinson disease (PD) patients with and without medication. A sample of 15 PD patients who have undergone STN DBS were evaluated under four test conditions: medication off and stimulation off (mof-sof), medication off and stimulation on (mof-son), medication on and stimulation off (mon-sof) and medication on and stimulation on (mon-son). A control group with 30 subjects was also evaluated. Principal component analysis (PCA) was applied on vertical ground reaction force (vGRF) and the first six principal component scores (PC score) were obtained in both groups. Those PCs scores were used as input in a probabilistic neural network (PNN). PNN presented satisfactory classification performance in the separation of controls and PD with 90.1% accuracy, 69.2% sensitivity and 100% specificity. The stimulation mof-son and mon-son conditions presented better results compared to mon-sof. In the mof-son condition, 41.7% were classified as normal, while further enhancement (63.3%) was given by the mon-son condition. These results indicated the potentiality of PNN to quantitatively evaluate treatment effects. Furthermore, STN DBS shows improvement on vGRF pattern in PD patients, most substantially when used with medication.**

Keywords – **Parkinson Disease, Deep Brain Stimulation, Artificial Neural Network**, **Gait analysis.**

I. Introduction

PARKINSON disease (PD) is a neurodegenerative disorder characterized by bradykinesia, rigidity, tremor and postural instability [1]. Gait hypokinesia is among the primary movement disorders associated with PD. The characteristic slow, short stepped, shuffling walking pattern results from a combination of constraints on locomotor control imposed by neurotransmitter imbalance [2].

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Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is widely performed in the treatment of advanced PD [3]. Many studies have showed the short-term effects of STN DBS [4]-[7]. More recently, four to five year follow-up studies were reported [8]-[11]. These authors found improvement in motor function including gait and posture. However, the effectiveness of the DBS in PD has been evaluated using clinical motor scores and few studies have quantitatively assessed the gait pattern of PD patients [12]-[14]. Quantitative measurements may provide a reliable and objective alternative in assessing the effects of STN DBS.

A constant challenge to clinicians is the knowledge of the extent and consequences of a disease and outcomes of potential interventions. Predictive models are used in a variety of medical domains for diagnostic and prognostic tasks. Among different modeling approaches, artificial neural networks (ANN) has been used with some success, including studies of human locomotion [15]-[18]. According to Hahn et al. [18] applications of ANN may be pursued in simulation of the effect on balance and gait control, as well as simulation of prospective outcomes from therapeutic interventions. However, no previously published work has addressed the ability of such models in the evaluation of the effects of STN DBS.

This paper aims at applying the ANN technique as a mathematical tool for developing classifiers in the evaluation of the effects of DBS of the STN on PD patients with and without medication.

II. Materials and Methods

Fifteen PD patients (three women and twelve men) with ages of 56.4 ± 8.3 years participated in the study. All subjects 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. A control group with 30 subjects (20 women and 10 men), with ages of 50.1 ± 7.8 years, without history of neurological illness, degenerative conditions or any general disease that might interfere with normal gait was also evaluated. Each subject signed an informed 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 his/her usual doses of PD medications and stimulators were turned "on". The gait assessment was first conducted in the medication "on" and

stimulation "on" (mon-son) condition. After the test, the stimulator was turned off for 30 minutes, and the measurements were repeated in the medication "on" and stimulation "off" (mon-sof) condition. In the second visit, the subjects came to the laboratory without having taken any PD medication for at least 12 hours and with the stimulator turned "on". Gait analysis was first conducted in the medication "off" and stimulation "on" (mof-son) condition. Again, the stimulators were turned off for 30 minutes and the tests were repeated in the medication "off" and stimulation "off" (mof-sof) condition. As not all subjects could walk with step length enough to reach each force platform, some subjects did not present all conditions assessed. Then, were evaluated 13 subjects on mof-sof, 12 on mof-son, 14 on mon-sof and 11 on mon-son conditions. Subjects from control group came to the laboratory just once for the gait test.

Two force platforms (AMTI, Watertown, MA) were used to evaluate the vertical ground reaction forces (vGRF) of both feet during walking. The vGRF signals were collected at a frequency of 100 Hz for 10 seconds to ensure the complete data set of ground reaction forces during stance phases of two feet. All subjects practiced the walking trial on the walkway at least five times before the experiment. The subjects walked at their self-selected speed, while barefoot, and repeated the walking trial five times during the evaluation. For each subject, the vGRF was normalized by his/her body weight.

The averaged vGRF data of the five walking trials was filtered using a low pass Butterworth filter, with a cut-off frequency of 30 Hz [19]. The data were interpolated and re-sampled with 101 samples according to the stance phase duration of each foot. Thus, 202 vGRF samples from two complete stance phases were used in the analysis.

Principal Component Analysis (PCA) method, as described in [20] was applied to the covariance matrix of vGRF from 43 subjects (controls and PD mof-sof condition). The broken stick test [20], [21] criterion was used for choosing the relevant PCs for the analysis.

All PC scores chosen by the broken stick test were used as input variables in a probabilistic neural network (PNN), a feed-forward neural network developed by Specht [22], in which the response to an input pattern is processed from one layer to the next with no feedback paths to previous layers. This network often has three layers: input, hidden, and output layers. PNN is one of the most powerful networks commonly used in solving classification/discrimination problems [23]. Results in the training set (controls and PD mof-sof condition) were tested by computing the accuracy, sensitivity and specificity values using the leave-one-out cross-validation approach.

The PC scores of PD subjects from treatment conditions (mon-sof, mof-son and mon-son) were calculated for comparing the effects of treatments. Those data were used as a validation set to evaluate the effect of the treatment in the PNN model obtained by the training set (controls and PD in mof-sof condition).

All signal processing, statistical and data analysis were implemented with the software Matlab 6.5 (The Mathworks, USA). The probabilistic neural network was also carried out using the 'Neural Network Toolbox' of MATLAB 6.5.

III. Results

The averaged vGRF from PD subjects showed an improvement in the peaks of force in the conditions where the stimulation was turned on (Fig. 1). The baseline (mof-sof) showed the worst condition (Fig. 1a) and increased force peaks towards the pattern of the control group was observed in mon-son conditions (Fig. 1 d).

The broken stick test indicated that the first six PCs should be included in the analysis. Those PCs explained 91.1% of the total variation.

PNN presented satisfactory classification performance in the separation of training set (controls and PD mof-sof condition). In this set, there was 90.1% accuracy, 69.2% sensitivity and 100% specificity. In the validation set, the stimulation conditions (mof-son and mon-son) presented better results (Table I) than just medication (mon-sof). In the mof-son condition, 5 of 12 subjects (41.7 %) were classified as normal, while further enhancement was given by the mon-son condition, with 63.6% of subjects classified as a normal. These results are indicative that STN DBS improves the GRF pattern of gait.

Table I
PNN classification

	Normal	Patient	Total
mof-son	5 (41.7%)	7 (58.3%)	12 (100%)
mon-sof	2 (8.3%)	12 (91.7%)	14 (100%)
mon-son	8 (63.6%)	3 (36.4%)	11 (100%)

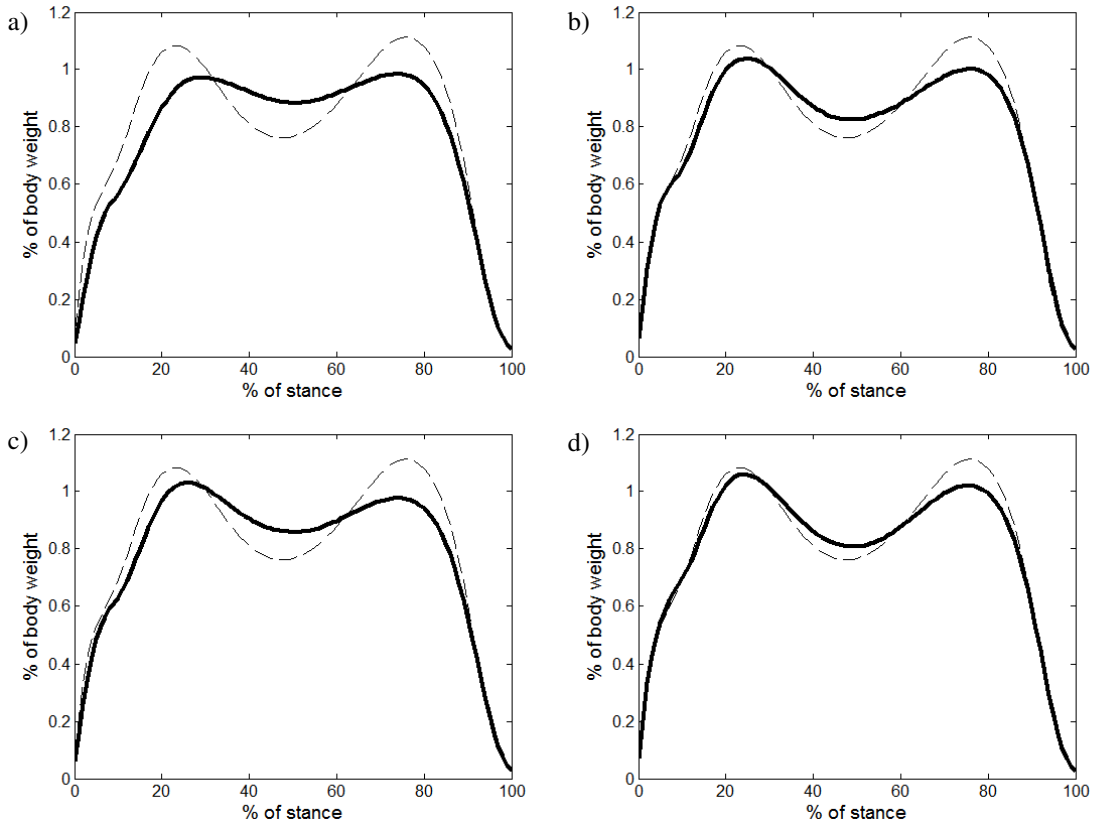

Fig 1 - Averaged vertical ground reaction force from controls (dotted line) and PD (bolded line): a) mof-sof, b) mof-son, c) mon-sof and d) mon-son conditions.

IV. Discussion

The averaged shape of the vGRF showed qualitative changes in all treatment conditions. However, such descriptive approach represents only the first step in gait analysis [24], since it did not allow a clear separation between controls and PD subjects in different conditions.

Given the relatively small size of the data set, the PNN designed with the six first PC score as inputs performed reasonably well. PNN is useful for automatic pattern recognition and has been considered the most appropriate form of ANN for classification approaches [22], [25]-[26]. Some recent applications of PNN demonstrated their predictive superiority over logistic regression [23], [26]. In gait analysis, the use of ANN techniques for decision making in certain applications is more effective than conventional statistics [27]. According to Hahn et al. [18] 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 results in the validation set indicated a greater effect on vGRF patterns with stimulation alone compared to medication alone, since the former was responsible for 41.7% of patients classified as a normal compared to just 8.3% with medication (Table I). Faist et al. [28] and Ferrarin et al., [13] stated that STN stimulation induced changes towards a normal gait pattern. However, Faist et al. [28] reported almost identical mean values comparing supra-threshold dose of levodopa and STN stimulation. Krystkowiak et al. [29] found better results with levodopa than STN stimulation on major gait parameters. A possible explanation for this disagreement is differences in the experimental protocols, since in the present study the medication "on" condition means the usual daily dose of each subject. Thus, this condition may not have represented the best medication "on" state. Nevertheless, it was established to better represent a daily living condition of patients [12].

A further improvement in vGRF was observed with both STN stimulation and medication (mon-son) with more subjects classified as normal. Similarly, past studies [13], [29]-[31] have reported a further enhancement in gait performance with combined stimulation with medication. Some authors [28], [30], [32] suggested a synergistic effect of STN stimulation and levodopa for axial PD symptoms.

The objective of the modeling phase in this application was to develop classifiers capable of identifying an input combination into either one of the two classes: normal or PD to evaluate the effects of STN DBS. 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. [33] to optimize the efficacy and efficiency of rehabilitation interventions, it

is also important to identify the benefits of a specific treatment.

ANN modeling is a technique that is gaining increasing interest in clinical research. Although many applications have shown some benefit over conventional modeling techniques, several considerations remain. The development of an artificial neural network is largely empirical, and there are no established guidelines for the development of an optimal artificial neural network. According to Chau [34] further improvements and innovations are necessary to improve reliability of classifying pathological gait.

As a conclusion, the presented results pointed to the potential power of a probabilistic neural network in discriminating between normal and PD vGRF and objectively evaluating the effects of STN DBS. Furthermore, STN DBS shows improvement on vGRF pattern in PD patients, particularly when used in conjunction with medication.

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