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A Gray-Box Neural Network Model of Parkinson's Disease Using Gait Signal

Yashar Sarbaz[1], Shahriar Gharibzadeh[1,*], Farzad Towhidkhah[1], Masood Banaie[2], Ayyoob Jafari[3]

1. Neuromuscular Systems Laboratory, Biomedical Engineering Faculty, Amirkabir University of Technology (Tehran Polytechnic), Tehran, Iran.
2. Department of Biomedical Engineering, College of Engineering, University of Tehran, Tehran, Iran.
3. Department of Biomedical Engineering , Islamic Azad University, Qazvin Branch, Qazvin, Iran.

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ABSTRACT

In this study, we focused on the gait of Parkinson's disease (PD) and presented a gray box model for it. We tried to present a model for basal ganglia structure in order to generate stride time interval signal in model output for healthy and PD states. Because of feedback role of dopamine neurotransmitter in basal ganglia, this part is modelled by "Elman Network", which is a neural network structure based on a feedback relation between each layer. Remaining parts of the basal ganglia are modelled with feed-forward neural networks. We first trained the model with a healthy person and a PD patient separately. Then, in order to extend the model generality, we tried to generate the behaviour of all subjects of our database in the model. Hence, we extracted some features of stride signal including mean, variance, fractal dimension and five coefficients from spectral domain. With adding 10% tolerance to above mentioned neural network weights and using genetic algorithm, we found proper parameters to model every person in the used database. The following points may be regarded as clues for the acceptability of our model in simulating the stride signal: the high power of the network for simulating normal and patient states, high ability of the model in producing the behaviour of different persons in normal and patient cases, and the similarities between the model and physiological structure of basal ganglia.

1. Introduction

Parkinson's disease (PD) is the most common neurological disorder after Alzheimer. This neurodegenerative disease is progressive and disabling andIts main symptoms are tremor, rigidity, bradykinesia, and gait disturbance. The destruction of Substantia Nigra Pars Compacta of basal ganglia with an unknown cause leads to PD [1].

One important symptom of PD is gait disorder. It is often presented in the primary stages of the disease. Gait disorder is progressive in all stages of the disease and is caused by muscle rigidity, bradykinesia, abnormal rhythmicity, asymmetry of the left and right parts of the body, and abnormal scaling of pace length. The gait disorder in PD patients includes slowed gait, shortened length of stride, decreased rhythm and cadence, increased time of double support in the stance phase, shuffling and festinating gait, decreased swing of the arms,

**** Corresponding Author:***
Shahriar Gharibzadeha,
Tel.: +98 21 6454 2364; fax: +98 216649 5655.
Email: gharibzadeh@aut.ac.ir

and disturbed regulation of the stride length. 5 minute walking uncovers the disturbances in patients [1].

Mathematical modeling in PD has been done by different researches in recent years. A mathematical model can produce a global understanding of complex biological systems. PD is a common neurodegenerative disease with unknown etiology. This mysterious behavior increases the importance of modeling approach.

In 1965, Austin et al. presented a simple model for PD tremor which was based on Van-Der-Pol oscillator. They argued that tremor is the result of altering the input of an internal oscillator in human body. However, their model had not included most physiological findings [2]. In 1995, Beuter and Vasilakos postulated the PD to be an apparent dynamic disease and claimed that tremor is the result of altered parameters of a control system in the patient. Their mathematical model included a linear combination of two nonlinear coupled oscillators. This study had not used real physiological data for validating the model [3].1n 1999, Edwards et al. presented an artificial neural network model with a parameter for attenuating the connections of neurons to simulate the decreased dopamine level in PD. The relation between this parameter and dopamine level was unclear [4]. In 2003, Asai et al. presented a model based on "central pattern generator" for PD pedaling. The change in the input of the model was supposed to be the cause of disturbed patient behavior. Although the roles of lower motor parts are considered in this research, the brain function is neglected for the purpose of simplicity [5]. In 2005, Haeri et al. focused on BG structure and presented a mathematical model for tremor. While being a simple model and accepting some assumptions as considering the tremor to be simple sinusoidal signal, the role of drugs and DBS treatments were simulated fairly suitable and clinically plausible [6]. In 2006, Niktrash supposed that there are some tremor-like oscillations in internal globus pallidus. They introduced a network model and chose the model parameters from a random Gaussian distribution. The role of different parameters was evaluated, but the response of the model was not compared with clinical data [7]. In 2006, Cutsuridis and Perantonis presented a network model for bradykinesia of PD. They tried to make error vector and desired velocity vector for monoarticular hand movement, although there was no physiological clue for these vectors. In this model, attention was paid to downstream levels of BG and the role of BG was presented only as a model input [8]. In 2008 MashhadiMalek et al. presented a model of BG structures based on Central Pattern Generator (CPG) in each block. They showed that rigidity and tremor are correlated. However, the presence of oscillations in the BG internal parts contradicts this hypothesis [9]. In 2009, Guthrie et al. introduced a conceptual neural network to model action selection of dopaminergic neurons. The role of dopamine signal on phasic rise & fall and tonic level and its effect on reward were showed. They tried to discuss the role of changing dopamine signal on cognitive deficit. The behaviour of L-dopa was implemented on the model [10].

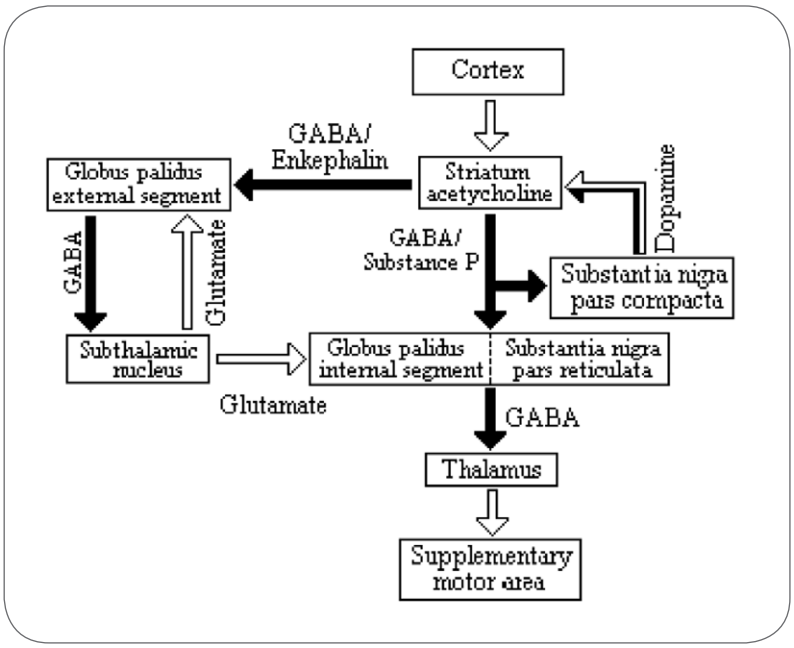

Figure 1. Basal ganglia and their components [6].

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Table 1. The mean of differences between real and model features in normal and PD cases

	Mean	Variance	Petrosian Dimension	1st Spectral Feature	2nd Spectral Feature	3rd Spectral Feature	4th Spectral Feature	5th Spectral Feature
Parkinonian	0.077564	0.003914	0.001143	0.162065	0.080369	0.064878	0.068935	0.104781
Healthy	0.07111	0.002074	0.000871	0.115247	0.042811	0.029832	0.029826	0.026804

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It is worth noting that one important symptom of PD is gait disturbance and different studies have evaluated the difference between normal and PD gait. Some studies have concentrated on the differences between PD and normal gait in time domain [11, 12]. Some other researchers have observed the fractal changing behaviour in PD patients [13, 14, 15]. Meanwhile, few models are presented for PD gait, which are generally based on CPG theory [16, 17].

As it was noted, most approaches have modeled the PD as black-box, and few physiological findings have been used and most models have compared the overall behavior of the model with real plants. On the other hand, different studies show that gait analysis has a good capability for PD evaluation and it can be used for modeling purposes, more than previous studies. In this study we try to present a comprehensive model, based on physiological findings, for all the members of our database. It is obvious that having such a model can help researchers in analyzing, diagnosing, controlling, and predicting the behavior of PD.

In this study, we present a model for basal ganglia in order to generate stride time intervals for healthy and PD states. Physiological findings show a feedback structure for dopamine modulatory effect in basal ganglia that has a critical role in PD. Because of this important effect, we had to consider it in our modelling strategy. Elman network is a neural network structure which is based on a feedback relation inside each layer. The remaining parts of the basal ganglia and the neuromuscular system involved in gait production are modelled with feed-forward neural networks. Hence, the proposed model consists of an Elman network and some feed forward neural networks.

In order to produce healthy and PD states in our model, we first trained our model with the data from one healthy and one PD person. However, it seems better to have a model which can simulate the behaviour of a great number of patients. Therefore, first it was necessary to extract some proper features of stride signal. Then, considering 10% tolerance in presented neural network weights and using multi object genetic algorithm, we found proper parameters to simulate the features of every person in our database.

2. Methods

In this section, we describe a physiological background about the structure of basal ganglia and the gait behavior of PD. Then, clinical data and the overall structure of the proposed model will be described. We have a brief review on Elman and feed forward neural networks. Finally, feature extraction stage and model training will be explained.

2.1. Physiological Background

BG are involved in motor control. When the person decides to do a certain movement, this willing is con-

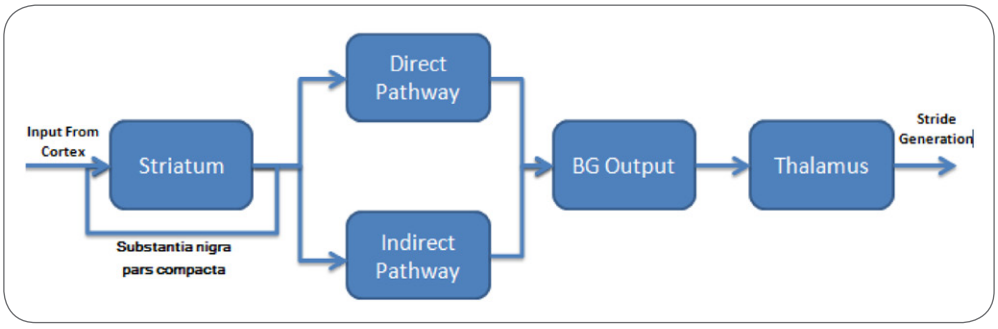

Figure 2. BG structure considering direct and indirect pathways.

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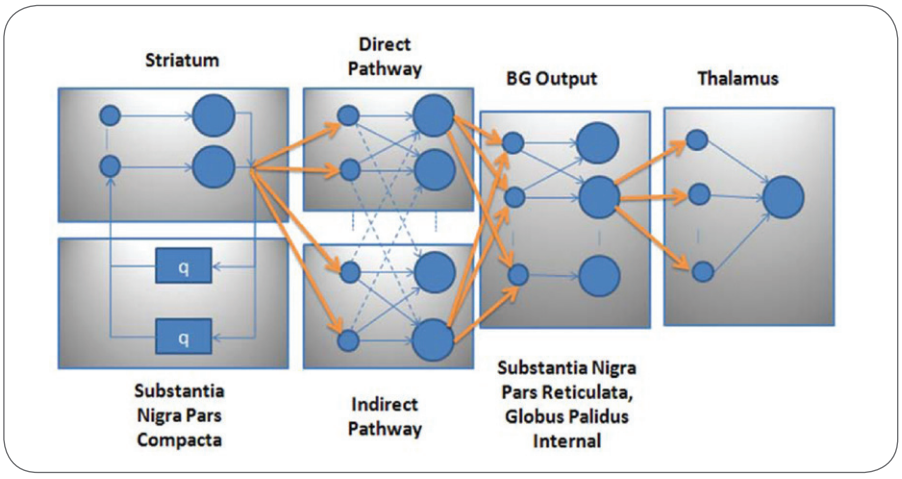

Figure 3. Schematic representation of the presented model.

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verted to motor commands, mainly by cerebellum, BG and cortex. These commands pass from spinal cord and reach the motor end plate. BG are responsible for regulating the quality of motion. Therefore, defects in BG do not cause movement cessation; instead, they cause disturbed movements, i.e. loss of smoothness, abnormal timing, and additional movements. It is suggested that BG have key roles in timing, initiation of voluntary movement, controlling the speed and acceleration of movement, regulation of muscle tone and etc.

BG input is from cortex and BG output is relayed through thalamus to supplementary motor area (SMA). Based on neuronal structure and neurotransmitters released, BG are supposed to be composed of 5 neuronal blocks: substantia nigra (SN), globus pallidus (GP), subthalamic nucleus (STM), putamen and caudate. Putamen and caudate act as BG inputs and are called collectively "striatum" (Str). Based on the mechanism of action, SN is divided into two functionally different parts: Substantia Nigra pars reticulata (SNr) and Substantia Nigra pars compacta (SNc).

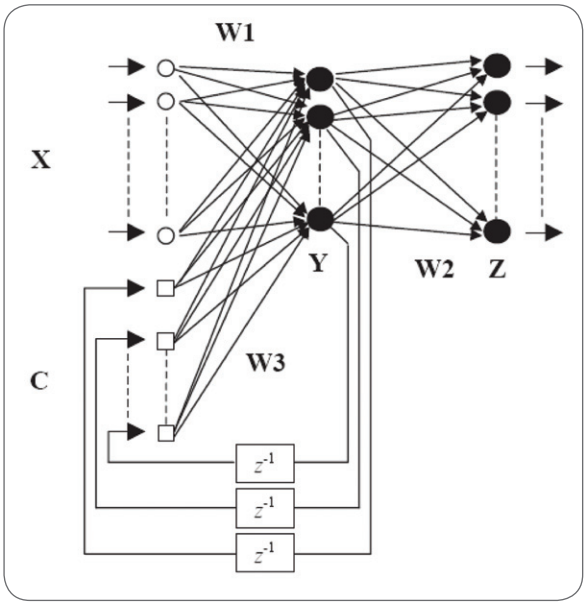

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Figure 4. A schema of Elman neural network.

Globus pallidus is similarly divided into two parts: external (GPe) and internal (GPi). SNr and GPi constitute the output of BG. The relations between BG blocks as well as the kinds of neurotransmitters are depicted in Fig. 1. As it is shown, BG inputs and outputs are related to each other by two different pathways: The first, which connects Str to BG output, is called direct pathway. The second, which connects Str to BG output through STN and GPe, is called indirect pathway. These two pathways are controlled by dopamine signal via the modulatory effect of SNc. The direct pathway has a simple and fast processing on the BG input, but the indirect pathway fulfils more complex processing on the BG input. The balance between these two pathways is regulated by SNc. In PD, because SNc is destructed, dopamine output is reduced and the balance between the two pathways is disrupted. The hypothetical schema that we used as the basis of our model is shown in Fig. 2 [1, 6].

2.2. Clinical Data: We used the data presented in www.physionet.org [13]. This database includes 14 Parkinsonian patients and 16 healthy persons as controls. Objects were able to walk independently for 5 minutes. In this database, time intervals of stride, swing, and stand are presented for both legs. Objects were asked to walk for 5 minutes in a 77 meter direct path. Patients didn't show falling or freezing of gait (FOG). Normal subjects

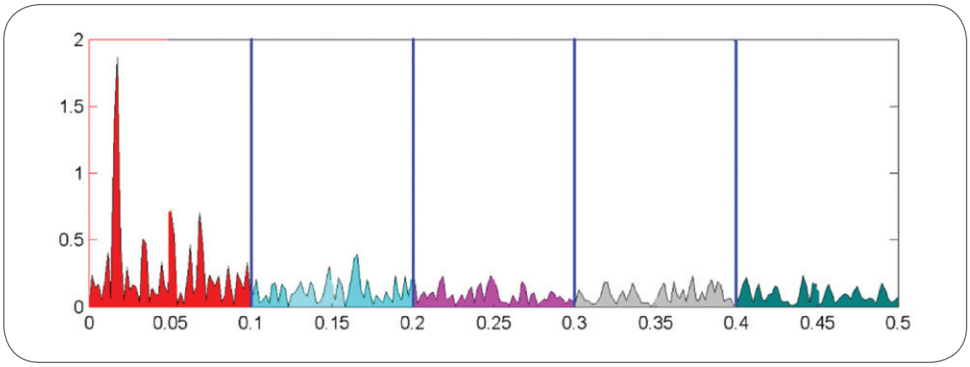

Figure 5. Feature extraction from spectral analysis.

had no previous neural disease or gait disorder. The gait data of the first 20 seconds were deleted in order to omit the effect of movement initiation. For measuring time intervals, plantar force sensors were used. The plantar force signal was sampled with the frequency of 300Hz.

2.3. Overall Structure of the Proposed Model

Because of its importance in PD, the role of SNc and its dopamine output is in the core of attention in our presented model. Because of the dopamine feedback and its role in the disease, the Elman structure is considered for this part of BG. Elman network contains feedback and can be easily trained by the back-propagation algorithm. Elman network is really powerful for producing and modelling periodic and semiperiodic signals. In this model, since the final output is stride time intervals, we are prone to semiperiodic signals. Therefore, Elman network is useful for producing the final output signal. For modelling other parts of BG, we used feed-forward neural networks to have a model similar to physiological findings. Therefore, we finally used an Elman network with one layer and a feed-forward network with two layers. The role of dopamine was considered in the feed-back of first layer (Elman network). Because the input of cortex to BG is intact in PD patients, the input of the model (input of the cortex to BG) was chosen as a constant signal which was not different between normal and patient states.. However, model parameters (BG) are changed in PD state in comparison with normal persons. The model structure, according to physiological structure of BG, is shown in Fig. 3.

2.4. Artificial Neural Networks

The structure of an Elman's Recurrent Neural Network is illustrated in Fig. 4. Here, X, Y, C, Z, and z-1 are input layer vector, hidden layer vector, context layer vector, output layer vector, and unit delay element, respectively.

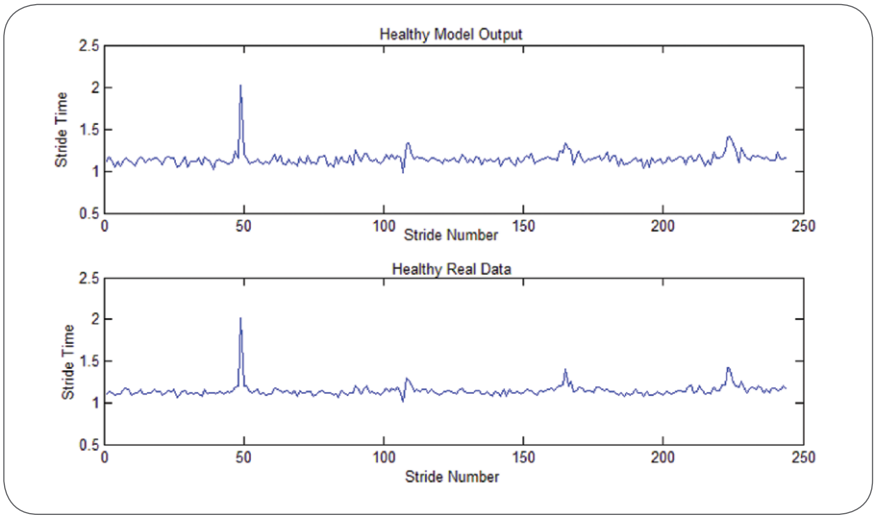

Figure 6. Real and simulated signals of a normal person.

Weight matrices are as follows: W1 is the weight matrix between input layer and hidden layer, W3 the weight matrix between context layer and hidden layer and W2 is the weight matrix between hidden layer and output layer.

The outputs of the neurons in the hidden layer and output layer for sth iteration can be computed as:

$$y_j^{(s)} = f(\sum_{i=1}^{n} w1_{ij}\, x_i^{(s)} + \sum_{j=1}^{m} w3_{ij}\, y_j^{(s-1)})$$

$$z_k^{(s)} = f(\sum_{j=1}^{m} w2_{jk}\, y_j^{(s)})$$

Where f is the activation function of each neuron [18].

Feed-forward structure does not contain the recurrent part of Elman structure. The relation between different parts of the network is similar to Elman relations without feedback part. If we put W3=0 in Fig. 3, we can find the schema of feed-forward structure.

In our model, the numbers of neurons are 30, 30, and 15 in the first, second and third layers, respectively. The activation function of all layers is sigmoid. Output of the network's third layer passes through a pure-line function and produces the final network output. There were 20 inputs to the system, which were supposed to be constant in healthy and PD state. Since the nature of this signal is complicated and immeasurable, we used a random 20 point time series as an initial assumption.

2.5. Feature Extraction

Previous studies usually have focused on statistical analysis of mean and variance. Significant differences have usually been seen between the mean and variance of stride in normal cases and patients [13]. Therefore, we used these two features in our study. Because of the semi-periodic behaviour of gait (stride) as well as the results of our previous studies, power spectra seem to be proper. These studies show that normal persons have more regular behaviours and their spectra have high energy in definite ranges. In contrast, patients had irregular behaviours and their spectra were distributed irregularly in all ranges. Therefore, the features extracted from spectral analysis can be useful for making the model responses similar to the real signals.

For calculating the power spectra of signal, we used Fast Fourier Transform (FFT) to convert our original signal to frequency domain. Then, we calculated the absolute value of FFT to produce the power spectra density [19].

For this purpose, the power spectra range was divided into 5 equal parts. The amount of energy (the area under the curve) in each part was calculated and chosen as a feature (Fig. 5).

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Figure 7. Representation of real and simulated signals of a normal person simultaneously.

In the disease situation, the state of the person is changed with respect to the normal conditions. Chaotic features are proper for showing the state changes. Different studies including EEG processing have evaluated the state change with chaotic features. For this reason, we used these features in our study. Fractal dimension is fairly proper for showing the state change. One method for fractal computation is Petrosian's Algorithm. Petrosian uses a quick estimate of the fractal dimension which can be done by extracting a time series from the present signal with different methods. Then this relation is used [20]:

$$D = \frac{\log_{10} n}{\log_{10} n + \log_{10}\left(\frac{n}{n + 0.4N_{\Delta}}\right)}$$

Where N is the length of the sequence (number of points) and NΔ is the number of sign changes (number of dissimilar pairs) in the generated binary sequence.

2.6. Training Stages

We first trained our model based on the data of one healthy and one PD person by back-propagation method. To isolate the direct and indirect pathways in 2nd layer, we divided the neurons in two groups and cleared the connection weights between the neurons of the two groups (i.e. we set them to zero). The cleared connections are shown as dashed connections in Fig. 3. We wanted to use this structure as the base model for simulating different healthy and PD states. In order to evaluate the ability of the model to produce healthy and PD states, we tried to produce the behaviour of other persons which are not used in training process (healthy and PD patients). For this purpose, we tried to correct some weights of the network. For modelling the behaviour of other normal humans, we decided to let the input signal and some of the weights of different parts of model to change in a 10% range. The signals from cortex to BG may differ among different persons, because of physiological differences between people. Also, the weights of BG are more or less different between individuals. For patients, we chose the weights of network only from SNc and input signal, because the main difference of patients depends on the amount of defect in SNc. The weights of SNc in our network were related to Elman layer feedback.

For choosing proper weights, genetic algorithm was used. We tried to have the same features of real cases in the outputs of our model. Genetic algorithm was used in multi-object manner and each of the features approached to the real ones, separately. The chosen features for stride signal were mean and variance of the strides, Petrosian Dimension of strides and power spectra features. For the purpose of clarification, we explain the genetic algorithm optimization method briefly:

Genetic algorithm (GA): Genetic algorithm, which is a randomized searching method, mimics evolutionary natural processes. Using a stochastic optimization meth-

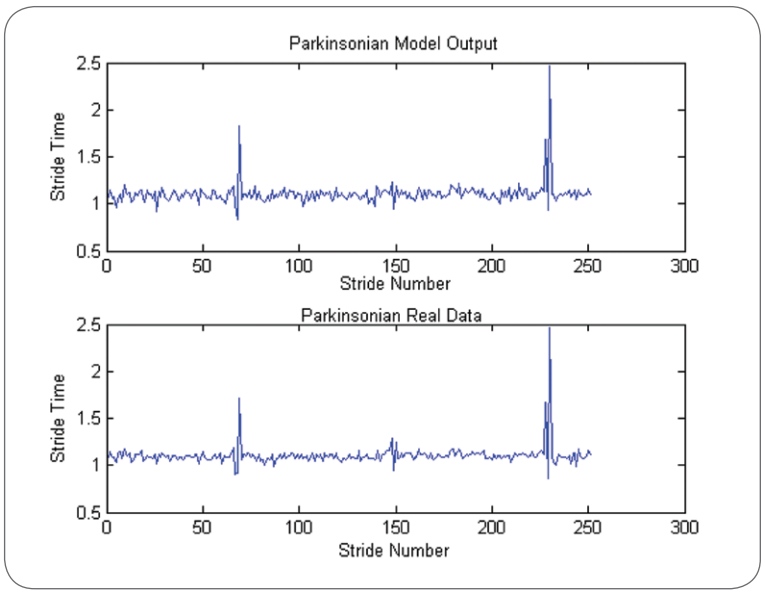

Figure 8. Real and simulated signals of a PD patient.

od, it can find and guide the searching space for optimization. It can also adjust the search direction adaptively without special rules.

In nature, weak species become extinct in their environment due to natural selection. The reason is that strong species are more likely to pass their genes to future generations through reproduction. Consequently after several generations, the species with proper gene combination become dominant in the population. This algorithm is valuable for solving multi-objective problems.

Since our goal was producing all the features of model response similar to real cases, we considered each feature of the signal as one object and used GA in multi-object manner. Therefore, each of the features of the model approached the real features of the stride.

3. Results

We pointed out that model response is the stride time intervals of normal and PD patients. Real and simulated signal of a normal person are shown in Fig 6. In Fig. 7, we show modelled and real data simultaneously. Also, Fig. 8 shows the real and simulated signal of a PD patient. In Fig. 9, we show modelled and real data simultaneously. As it is shown in these figures, the real signal and model output are clearly similar. The considerably good ability of the model in generating a response similar to real recorded data shows the high potency of the model structure.

The power spectra of normal and PD persons are shown in Fig. 10 and their difference is seen apparently: normal ones have their most energy in low ranges of the spectrum, while the energy of PD patients is distributed in all ranges of the spectrum. We tried to produce the behaviour of normal and PD persons who were not used in training process. For each person, we corrected the model with up to 10% change in selected weights. Features of model response in each person were calculated and compared with the real features. The difference of real and model features in each normal and disease state were calculated and its mean was computed. Table 1 shows this mean difference of features in normal and PD states. This table shows how these features are similar, which means that model response is very similar to the real signal.

4. Discussion

PD is a common neurological disease and the core of attention of researches. Different researchers have focused on symptoms, etiology, behaviour and treatment of PD. Meanwhile, some researchers have tried to find

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Figure 9. Representation of real and simulated signals of a PD patient simultaneously.

out and analyse the cardinal symptoms of PD and model them in order to understand BG behaviour. Such models help us in identifying the disease behaviour and state the changes in BG. The brain structure is so complex that it is impossible to recognize its performance in different states exactly. In disease states, this complexity is usually increased. Computational models present a global understanding of a specific brain function in PD and normal states. There are different computational models for PD, most of which are black boxes that have considered some details of physiological findings. Most of the models are implemented for tremor and few proper models are presented for gait disorder. The gait behaviour and its disorders are complex and for this reason, designing a model based on physiological findings may be useful in understanding the disease and finally to diagnose and control it in earlier stages.

In this study, based on reliable physiological findings, we tried to introduce a model which can include key roles of BG and produce the stride of normal cases and patients. For this purpose, in accordance with BG structure, a three layer ANN with feedback in the first layer (Elman structure) was designed. The feedback in the first layer of ANN simulates the modulatory effect of SNc on striatum (by dopaminergic signal). We tried to match the fraction of neurons in each layer of ANN with physiological findings. The excitatory and inhibitory relations were simulated by the sign of weights between different layers. The final response of the ANN was assumed to be the real stride. At first step, the ANN was trained for a normal person and a PD patient. This was used in the remaining parts of our study as the preliminary model. It must be noted that the final model of our study must be able to produce the behaviour of all normal cases and patients. For achieving such a general simulation power, we executed several steps: 1) the main features of the stride time intervals were chosen and extracted for each subject. 2) The weights of the preliminary ANN were allowed to select proper amount in 10% tolerance of the initial values. 3) A multi object GA was implemented to find the proper chromosome (proper set of ANN weights), so that proper features of each subject, can be generated by the model. This means that our model is now able to simulate each of the subjects in our database.

It must be noted that with choosing the above mentioned features, the signals are analyzed from three different views, i.e. time domain, frequency domain, and complexity.

In a general view, the following points may be regarded as clues for the acceptability of our model in producing the stride signal: the high power of the ANN when training it for normal and PD states, high ability

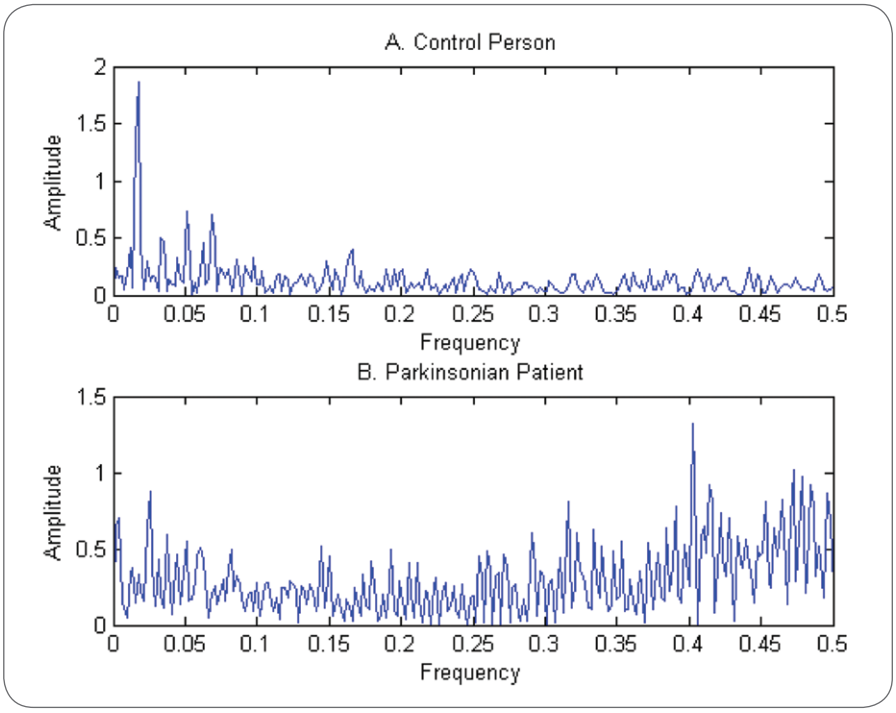

Figure 10. The power spectra of normal and PD persons.

of the ANN in producing the behaviour of different persons in normal and PD cases (with maintaining a unique structure and minute change of some parameters), and the similarities between the model and physiological behaviour of BG.

We suggest that based on physiological plausibility of this novel model, it can be used as a proper primary template for future PD studies. We think that our model is capable of testing different treatment routes in PD.

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