A mathematical model for tremor genesis in Parkinson disease from a chaotic view

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***Abstract*—A mathematical model of Parkinsonian tremor is presented in this research. This model contains structures involved in tremor genesis from brain to muscle. The result of this study is compared with physiological parkinsonian tremor by using the correlation dimension, the largest Lyapunov exponent and the Kolmogorov entropy. The correlation dimension represents the complexity and the largest Lyapunov exponent and the Kolmogorov entropy indicates the chaoticity of the system. This comparison shows that the obtained result based on the purposed model is close to experimental data, so the presented model is an accurate and applicable model.**

Keywords-Parkinson's disease; Tremor; Modeling; chaos.

I. INTRODUCTION

The Parkinson disease (PD) was described by James Parkinson in 1817 for the first time [1]. PD is characterized by loss of dopaminergic cells of the substantia nigra pars compacta (SNc), which is a part of the basal ganglia (BG) [2]. PD causes different changes in the basal ganglia-thalamocortical system (BGTCS) discharge rates. The disease increases the mean firing rates in subthalamic nucleus (STN) and internal globus pallidus (GPi). On the other hand, the disease decreases the mean firing rates of external globus pallidus (GPe), thalamic reticular nucleus and the relay nucleus of thalamus [3]. Tremor is the most common symptom of PD with a frequency of 4-6 HZ. The system complexity can be estimated by correlation dimension and the Lyapunov exponent.

There are many computational and mathematical studies which investigate PD. A mathematical and pathological model of BG is presented by Haeri et al [2]. In that study each component of BG is modeled by a first-order system. Connection strength is used for modeling the variation of neurotransmitters quantity. In this research we applied these approaches to model the BG and thalamus. The relationship between rigidity and tremor is investigated by MashhadiMalek et al [4]. They considered the central and peripheral nervous system and muscle model. The peripheral system (spinal and long-loop reflex) begins from muscle, passes spinal cord and CNS and finally returns to muscle. The central system consists of cortex, basal ganglia and supplementary motor area (SMA). Cortex inputs are from BG and SMA. A gain is used for modeling the amount of cortex command to muscle. The SMA is modeled by an absolute function, a gain and a saturation function. When the antagonist muscle is active, the agonist is in rest and vice versa. This behavior is simulated by two gains in the spinal cord. Parent et al [5] presented a model of BG and determined the inter-relation of its components. They specified the excitatory and inhibitory characteristic of neurotransmitters.

Merrikh-Bayat [6] studied the (clinical) time-series data of Parkinson's disease, Amyotrophic Lateral Sclerosis and Huntington's disease. In that research, the time series data are embedded in a vector space and the correlation dimension of the diseases is estimated. The 0-1 test is used for studying the existence of chaos in these diseases. The simulations show that none of them are chaotic. Stam et al [7] investigated the EEG nonlinearity in dementia and Parkinson's disease. They investigated that, using different embedding method and the largest Lyapunov exponent and the Kolmogorov entropy in addition to the correlation dimension, can distinguish the EEG form linearly filtered noise.

A computational and mathematical model of BGTCS is presented in this paper. The model of peripheral system, antagonist and agonist muscles are considered too. This research is based on clinical and physiological information. Also the purposed model contains a path from brain to muscle. We used the correlation dimension, the largest Lyapunov exponent and the Kolmogorov entropy to compare the results of this study with physiological parkinsonian tremor. This comparison shows that the results of the presented model is close to experimental data, so the purposed model is an almost accurate and applicable model which can be useful for simulating the PD.

II. PHYSIOLOGICAL BACKGROUND

A first-order system is considered for BG and thalamus components. Each neuron has three features: longitudinal resistance at axons and dendrites, membrane capacitance and membrane resistance. When the input of membrane is a step function, an exponential output will occur. So it can be found that the resistance and capacitance of neuron are joined in parallel, in fact membrane resistance and membrane capacitance are parallel. The signal would pass along axons without any changes; it shows that the longitudinal resistance at axons and dendrites is in series with them. So each neuron would be presented by a first-order system [2].

ISBN: 78-1-4799-7417-7

The quantity of components firing rate in Parkinson disease is related to the components activity. The firing rate of each component is used to estimate the parameters of BGTCS blocks in PD state. These firing rates are in physiologically realistic ranges detected from monkeys [3]. These rates are presented for illness and healthy states in table 1. The excitatory and inhibitory connections, hypo activity and the hyperactivity of blocks are shown in Fig. 1.

TABLE I. FIRING RATES OF BGTCS BLOCKS IN ILLNESS AND HEALTHY STATES [3].

component	*illness*	*healthy*
Cortex	12	12
D1	2.2	7.4
D2	12	3.5
Gpi/SNr	110	69
GPe	47	48
STN	36	28
Relay nuclei	10	14

III. MATHEMATICAL MODEL

A. BG and thalamus model

In this section the first-order system of each block is presented. $P_1(s)$ is the transfer function of the striatum. This block has two outputs and one input. The input has an excitatory affect on outputs. These outputs are nominated as So1 and So2.

$$P_1 : So1(s) = g \times \frac{22}{s+30} SNco(s), \quad So2(s) = \frac{1}{g} \times \frac{1}{s} \times \frac{14500}{s+30} SNco(s) \tag{1}$$

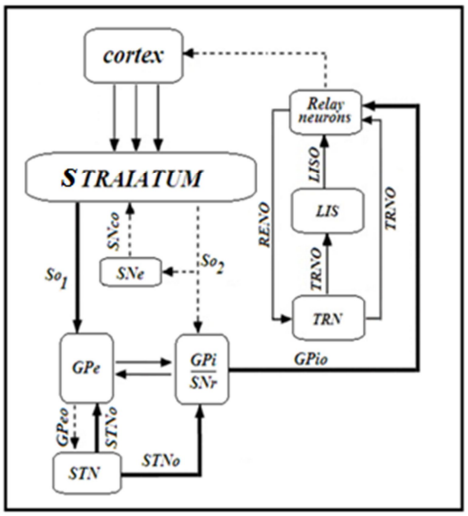

Figure 1. The inter-relation of BGTCS in PD state. The thick lines show hyperactivity and dashed lines show hypo activity.

$P_2(s)$ represents the dynamics of SNc. So2 is the input of this block and has an inhibitory affect on SNc. A nonlinear function (sign function) is at continuation of this block [3].

$$P_2(s) : \text{sgn}(A(s)), \quad A(s) = \frac{-50}{s+40} So2(s) \tag{2}$$

This block has an inhibitory input and an excitatory input.

$$P_3(s) : GPeo(s) = \frac{1}{g} \times \left(\frac{-3500}{s+10} So1(s) + \frac{20}{s+10} STNo(s)\right) \tag{3}$$

$P_4(s)$ represents the behavior of STN. The input of this component has an inhibitory affect on the output.

$$P_4(s) : STNo(s) = g \times \frac{-4.8}{s+50} GPeo(s) \tag{4}$$

$P_5(s)$ represents the dynamics of GPi (and SNr) which has an excitatory and an inhibitory input.

$$P_5(s) : GPio(s) = g \times \left(\frac{-1}{s+10} So2(s) + \frac{11}{s+10} STNo(s)\right) \tag{5}$$

The transfer function of $P_6(s)$ represents the thalamus Relay neurons dynamics. This component has three inhibitory inputs.

$$P_6(s) : RENo(s) = g \times \frac{-40}{s+30} GPio(s) + \frac{-40}{s+30} LISo(s) + \frac{-40}{s+30} TRNo(s) \tag{6}$$

$P_7(s)$ models the thalamic reticular nucleus (TRN) which has one excitatory input.

$$P_7(s) : TRNo(s) = \frac{135}{s+10} RENo(s) \tag{7}$$

Finally, $P_8(s)$ represents the dynamics of local interneuron (LIS). It has one excitatory and one inhibitory input.

$$P_8(s) : LISo(s) = \frac{1}{s+20} RENo(s) + \frac{-20}{s+20} TRNo(s) \tag{8}$$

The neurotransmitters behavior is modeled by connection strength (gain). A direct relation is assumed for the quantity of neurotransmitters and the amount of the gain. So the decrement of neurotransmitters is modeled as gain of '*1/g*' and the increase is supposed as '*g*'. It is notable that the signal from cortex is not considered, because it is assumed that the malfunction of BG is the origin of PD.

B. Cortex model

The input of cortex comes from BG and SMA and the output goes to alpha motor neurons and the muscles. There are two gains nominated as g_a and g_{an} which control the amount of cortex command on muscles. g_a is related to agonist muscle and is 0 when this muscle is inactivated and equals 1 when it is activated. g_{an} is for antagonist muscle which is -1 and 0 when it is activated and inactivated, respectively [4].

C. SMA model

The SMA input comes from thalamus and spinal cord and the output goes to cortex. In normal state, SMA has an inhibitory affect on cortex and it has an excitatory affect in PD state. SMA is modeled by a saturation function and a gain. The quantity of saturation function is assumed to be 1-2 in PD and 0.5-1 in normal state [4]. Changing the amount of the gain will

ISBN: 78-1-4799-7417-7

change the output of SMA. The model of cortex and SMA is represented in Fig. 2.

D. Muscle and peripheral system model

The muscle model which is used in this paper is based on Hill model. The input of muscle is from cortex and the output is hand movement velocity. The peripheral system is modeled by a long loop. This loop begins from muscle, passes BGTCS and alpha motor neurons and finally returns to the muscle. When the agonist muscle is activated the antagonist muscle is in rest and vice versa. This behavior is modeled by two gains (g_{af} and g_{anf}). g_{af} equals 0 when the agonist muscle is inactivated and is 1 when it is activated. g_{anf} is 0 when the antagonist muscle is inactivated and is 1 when it is activated [4]. The complete model which is simulated in SIMULINK is shown in Fig. 3.

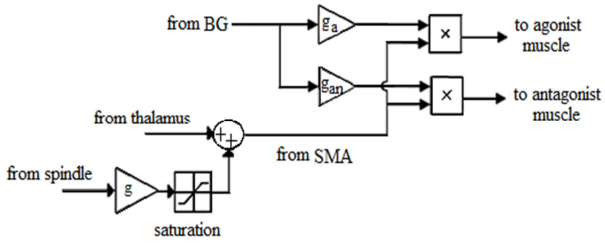

Figure2. The model of cortex and SMA [4].

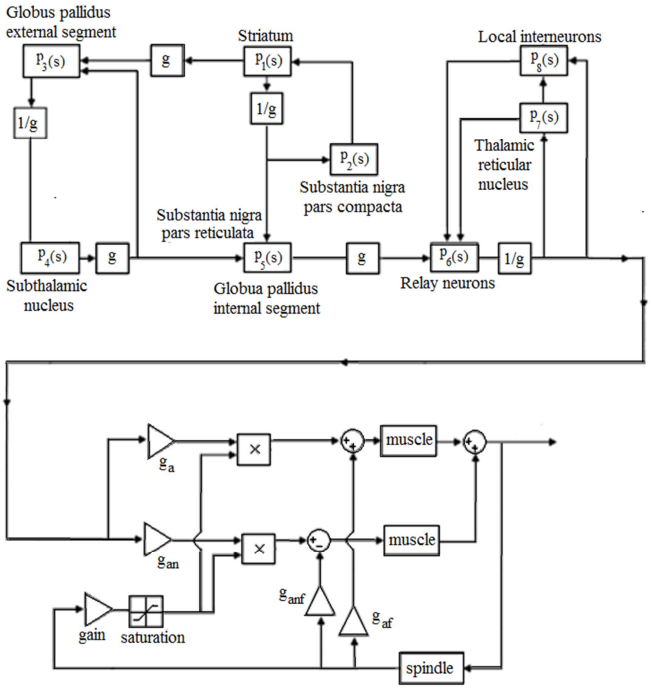

Figure 3. The complete model simulated in SIMULINK.

Fig. 4 represents clinical data of hand movement obtained from www.physionet.org.

Fig. 5 represents the output of presented model. The output of our model is the velocity of hand movement.

IV. Comparison between clinical data and model result

To investigate the accuracy of model result, we compared the correlation dimension, the largest Lyapunov exponent and the Kolmogorov entropy of clinical data and the result obtained from this study.

A. Correlation dimension

3 steps are needed to calculate the correlation dimension:

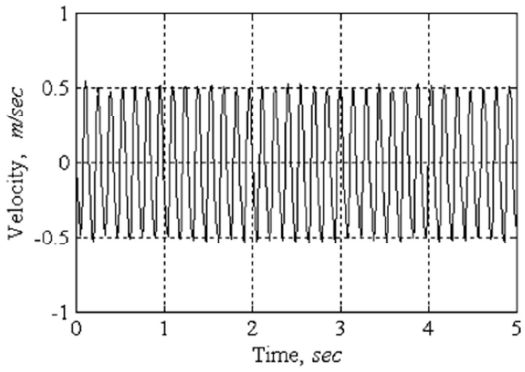

Figure 4. The clinical data obtained from www.Physionet.org.

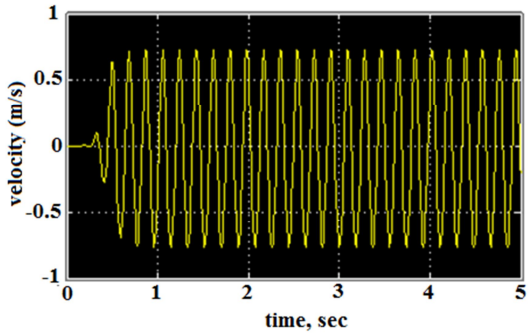

Figure 5. The output of presented model.

(1) Estimation of the Euclidian distance between pairs of points.

(2) Estimating the correlation integral *C(R)* for different distances of *R*. *C(R)* is determined as follow:

$$C(R) = \lim_{N\to\infty} \frac{2}{N(N-1)} \sum_{i=1}^{N} \sum_{j=i+1}^{N} \theta(R - |x_i - x_j|) \tag{9}$$

N is the number of points, x_i and x_j are points and θ is the Heaviside step function which is defined as follow:

$$\theta(\varepsilon) = \begin{cases} 1 & if\ \varepsilon <= 0 \\ 0 & if\ \varepsilon > 0 \end{cases} \tag{10}$$

(3) Determining the slop of the linear region of the *logC(R)/log(R)* curve.

$$CD = \lim_{R\to 0} \frac{\log C(R)}{\log R} \tag{11}$$

ISBN: 78-1-4799-7417-7

Fig. 6 and Fig. 7 show the plot of log *C(R)/log (R)* for clinical data and model result respectively. The slope of the following curves indicates that the correlation dimension of clinical data and model result are close to each other.

B. *The largest Lyapunov exponent*

Positive Lyapunov exponent and positive Kolmogorov entropy are expected to be in chaos. The first step to calculate the largest Lyapunov exponent is the election of one point as the original point. The second step is estimating the distance between this point and other points, this distance is nominated as d_i. i shows the number of original point.

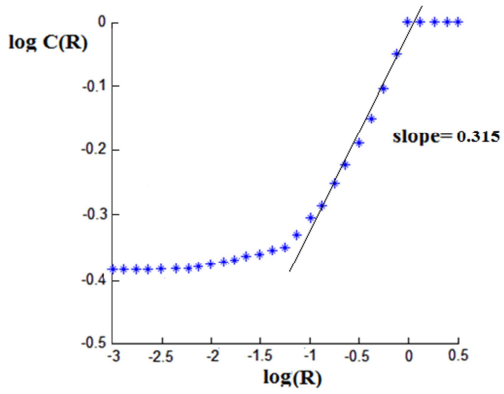

Figure 6. The logC(R)/log(R) plot for clinical data.

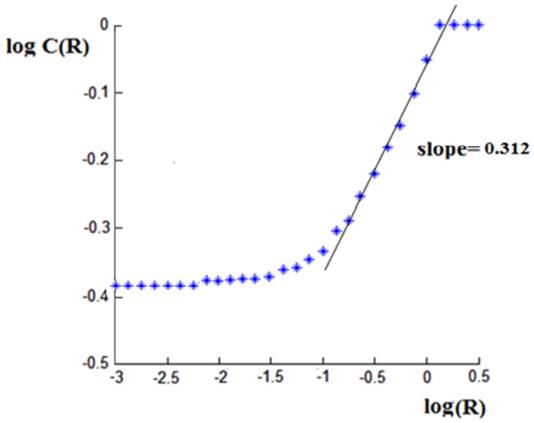

Figure 7. The logC(R)/log(R) plot for model result.

This procedure should be repeated for some other original points. The slope of $ln(d_i)/N$ would be measured in each stage and finally the mean of these slopes results the largest Lyapunov exponent.

$$LE = \frac{1}{N} \times \frac{1}{n} \sum_{i=1}^{n} \ln \frac{d_i}{N} \tag{12}$$

N is the number of points and n is the number of iterations. In this study n is equal to 10. The largest Lyapunov exponent for clinical data and model result is obtained as -0.087 and -0.072, respectively. According to Merrikh-Bayat [6] Parkinsonian tremor is not chaotic. The result obtained from this study also shows that none of the clinical data and model result is chaotic.

C. *Kolmogorov entropy*

To estimate the order 2 Kolmogorov entropy, we should calculate $C_d(R)$ and $C_{d+1}(R)$ which are correlation integral of two consecutive embedding dimensions. The relation between $C(R)$ and Kolmogorov entropy is given by:

$$KE = \frac{1}{\Delta t} \log \frac{C_d(R)}{C_{d+1}(R)} \tag{13}$$

Δt is the time between successive samples and is equal to 1. Kolmogorov entropy is calculated for d=5 and $d+1$=6. The quantity of $C_d(R)$, $C_{d+1}(R)$ and Kolmogorov entropy for model result and clinical data are represented in table 2. As it is shown, the Kolmogorov entropy for both model result and clinical data is negative and also their quantity is very close to each other.

TABLE II. The quantity of $C_d(R)$, $C_{d+1}(R)$ and Kolmogorov entropy.

	Clinical data	***Model result***
$C_d(R)$	0.46	0.26
$C_{d+1}(R)$	0.6	0.33
Kolmogorov entropy	-0.109	-0.096

V. CONCLUSION

In this study a computational model of PD tremor is presented which includes BGTCS, peripheral system and the muscles model. To investigate the accuracy of model result, the correlation dimension, the largest Lyapunov exponent and the Kolmogorov entropy of clinical data and the result obtained from this study are compared. The comparison shows that the correlation dimension of the real system and the model presented in this study is very close to each other which indicate that the complexity of the model and the real system is similar. The largest Lyapunov exponents and the Kolmogorov entropy which obtained from presented model and clinical data are both negative which shows that none of them are chaotic. These results demonstrate that our model is close to real system and can be used for simulating the PD tremor in an accurate way.

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ISBN: 78-1-4799-7417-7