



An Improved Modeling of Parkinson's Tremor and Investigation of Some Approaches to Remove this Symptom

F. Ghoreishian, M. Pooyan*

Biomedical Engineering Dept., Engineering faculty, Shahed University, Tehran, Iran

PAPER INFO

Paper history:

Received 14 January 2020

Received in revised form 27 January 2021

Accepted 20 March 2021

Keywords:

Parkinson's Disease

Modeling

Tremor Removing

ABSTRACT

In this research, an improved model of Parkinsonian tremor is presented by using a mathematical and computational approach. In Parkinson's disease (PD), an abnormal signal is produced by basal ganglia (BG). This signal goes to the thalamus, then enters cortex and after interaction with peripheral system goes to muscle and finally appears as tremor. In the presented model, all of the mentioned process are simulated. Also, the skeletal muscle model as well as the central nervous system (basal ganglia, thalamus, cortex and supplementary motor area) and peripheral nervous system (spinal reflex) mechanisms are considered. In addition, two methods for tremor suppression are applied in this paper, 1) deep brain stimulation (DBS) which affects dopamine level in BG and 2) a mechanical method which is based on a negative feedback. The accuracy and efficiency of the presented simulation are demonstrated by comparison of the obtained results with those obtained by clinical tests.

doi: 10.5829/ije.2021.34.05b.20

1. INTRODUCTION

The Parkinson's disease was first described in 1817 by James Parkinson [1]. This disease is related to central nervous system and is caused by death of dopamine-generating cells in the substantia nigra pars compacta (SNc) which is a region of basal ganglia [2, 3]. PD develops gradually and can be recognized by four symptoms which are rest tremor, rigidity, bradykinesia and postural instability [1, 3]. Tremor is the most common and well-known symptom of disease which is usually a rest tremor. The frequency of rest tremor in PD is between 4 and 6 HZ [2, 3]. PD changes electrophysiological activities in basal ganglia-thalamocortical system (BGTCS) [4]. There are two primary treatments for PD which are Medical treatment and deep brain stimulation (DBS).

Researchers use mathematical models to analyze various objects [5-7]. A lot of mathematical and computational studies for PD are presented. MashhadiMalek et al. [3] investigated the relationship

between rigidity and tremor in PD. They considered central and peripheral nervous parts and muscle model. The result of their research demonstrates that rigidity and tremor are interdependent and simultaneous treatment of these two symptoms is more beneficial.

Haeri et al. [2] modeled the physiological and pathological behavior of BG; BG components were modeled as first-order systems. Hand tremor is the output of their model. Ghoreishian et al. [8] presented a mathematical model for tremor in Parkinson disease. The structures involved in tremor genesis are analyzed in their model. They used the largest lyapunov exponent, the correlation dimension and kolmogorov entropy to compare the model output with clinical results. A mechanical method for tremor suppression was designed by Pledge et al. [9]. This method is through impedance control of patient muscle. A resistive force applied on patient's limb in order to decrease tremor movements.

Nahvi et al. [1] examined the effect of DBS on PD. In their model, the DBS targets were subthalamic nucleus (STN), internal and external globus pallidus (GPi and

* Corresponding Author Institutional Email: pooyan@shahed.ac.ir (M. pooyan)

GPe). They used a mean field model for this purpose. The result of their research indicates that DBS of STN and GPe can reform the activity of thalamus relay neurons but GPi DBS will inhibit it. A model of BG which determines the inter-relation of BG's components was introduced by Parent et al [10]. In this model neurotransmitters and their excitatory and inhibitory characteristics are specified. In this paper, a mathematical and computational model of BGTCS is presented. This model is based on clinical and physiological information. In this study, the effect of DBS and medical treatment is investigated and also a mechanical method for tremor suppression is applied.

2. PHYSIOLOGICAL BACKGROUND

In BGTCS, the nuclei may exert an excitatory or an inhibitory influence upon each other. The inhibitory connections contain gamma amino butyric acid (GABA) and excitatory connections hold glutamate (GLU). Haeri et al. have used a first-order system for modeling the components of BG, the behavior of neurotransmitters were modeled by a gain between BG components. In this research, we applied these approaches for BG and thalamus.

Each neuron has three features: longitudinal resistance at axons and dendrites, membrane resistance and membrane capacitance. An exponential output will occur, when the input of membrane is step. It shows that the resistance and capacitance of neuron are joined in parallel and longitudinal resistance at axons and dendrites is in series with them, because the signal would pass along axons without any changes. So each neuron would be presented by a first-order system. It is notable that there are nonlinear characteristics in neurons. As mentioned above, SNc is the main component which generates tremor, so all nonlinearities are assumed to be in this block. There are a lot of parallel neurons in each component of thalamus and BG. So the whole behavior of each component can be presented by a first-order system [2].

For modeling the behavior of BGTCS the parameters of each block are needed. It is obvious from physiological literature that the quantity of components firing rate in Parkinson's disease is related to the components activity. Indeed, if component activity is more than normal state in PD, its firing rate is also more than normal and vice versa. So we used the relationship between component's firing rates to estimate the parameters of each first-order system of BGTCS blocks, in PD state. These firing rates are in physiologically realistic ranges detected from monkeys. Figure 1 shows the inter-relation of BGTCS in PD state. The hyperactivity and hypoactivity of blocks are indicated by thick and dashed lines respectively. In this figure the inhibitory and excitatory connections are presented too.

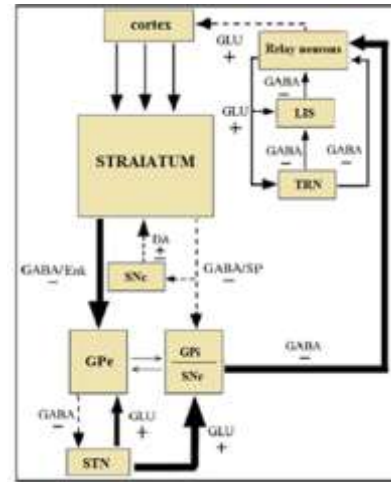


Figure 1. The inter-relation of BGTCS in PD state

3. MATHEMATICAL MODEL

3. 1. BG and Thalamus Model

As mentioned above, each block of BG and thalamus is considered as a first-order system. In this section the transfer function of the blocks are presented. The transfer functions are represented by $P_i(s)$. $P_1(s)$ represents the dynamics of striatum. This block has two outputs (So_1 and So_2). Its input has an excitatory effect on outputs.

$$P_1 : So_1(s) = g \times \frac{300}{s+30} SNco(s),$$

$$So_2(s) = \frac{1}{g} \times \frac{5500}{s+30} SNco(s) \tag{1}$$

$P_2(s)$ is the transfer function of SNc. So_2 is the input of this block which has an inhibitory effect on SNc. A nonlinear function (sign function) is in continuation of this block [2].

$$P_2(s) : SNco(t) = \text{sgn}(A(t)),$$

$$A(s) = \frac{1}{g} \times \frac{1}{s} \times \frac{-100}{s+40} So_2(s) \tag{2}$$

$P_3(s)$ represents the behavior of GPe. This component has an excitatory input and an inhibitory input.

$$P_3(s) : GPeo(s) = \frac{1}{g} \times \left(\frac{-1425}{s+10} So_1(s) + \frac{200}{s+10} STNo(s) \right) \tag{3}$$

$P_4(s)$ represents the transfer function of STN. This component has an inhibitory input.

$$P_4(s) : STNo(s) = g \times \frac{-4.7}{s+50} GPeo(s) \tag{4}$$

Transfer function of $P_5(s)$ represents the dynamics of GPi (and SNr) with one excitatory and one inhibitory input.

$$P_5(s) : GPio(s) = g \times \left(\frac{-40}{s+10} So_2(s) + \frac{11.5}{s+10} STNo(s) \right) \quad (5)$$

$P_6(s)$ models relay neurons (REN) of thalamus which has three inhibitory inputs.

$$P_6(s) : RENo(s) = \frac{1}{g} \times \left(\frac{-40}{s+30} GPio(s) + \frac{-35}{s+30} LISo(s) + \frac{-80}{s+30} TRNo(s) \right) \quad (6)$$

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

$$P_7(s) : TRNo(s) = \frac{96}{s+10} RENo(s) \quad (7)$$

Finally, $P_8(s)$ models local interneuron (LIS) with an inhibitory and an excitatory input.

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

The behavior of neurotransmitters is modeled as connection strength (gain). A direct relation is assumed for the amount of the gain and the quantity of neurotransmitters. So increment of neurotransmitter is modeled as gain of ‘g’ and the decrease is supposed as ‘1/g’. It should be mentioned that the signal from cortex is not considered, because the malfunction of BG is assumed to be the origin of PD.

3. 2. Cortex Model

The input of cortex is from thalamus and supplementary motor area (SMA) and its output goes to alpha motor neuron and muscle. SMA has an inhibitory effect on cortex in normal state. However, in PD state this inhibitory effect decreases and has an excitatory effect on cortex [3].

3. 3. SMA Model

The model of SMA contains 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 [3].

3. 4. Muscle and Peripheral System Model

In this study, the formulas of hand muscles which are presented by mains and Soechting [11] are used. The input of muscle is stimulation rate from cortex to muscle (α) and the output is Angular displacement (θ). The transformation function of $\theta(s)$ is as follows:

$$\frac{\theta(s)}{\alpha(s)} = \frac{m}{Is^3 + DIs^2 + (K+B)S + DB} \quad (9)$$

The complete model of this study is represented in Figure 2. The peripheral system is modeled by a long loop which begins from muscle, goes to peripheral part (spinal cord) and after passing SMA and cortex returns to the muscle [3].

4. TREMOR SUPPRESSION

Two tremor suppression methods are used in this study:

1. DBS.
2. A mechanical method.

4. 1. DBS

The exact mechanism in which tremor suppresses by DBS is still unknown [12]. However, it is mentioned in literature [13-15] that dopamine level in BG changes by DBS. It changes the system parameters which cause change in PD symptoms [2]. In this model, neurotransmitters variation is modeled by gains (g and 1/g). Before DBS g equals 10 and after that it will be 1. The model output without any treatment is represented in Figure 3, which is fairly like the clinical data presented in (www.physionet.org). The output of model with DBS treatment is shown in Figure 4.

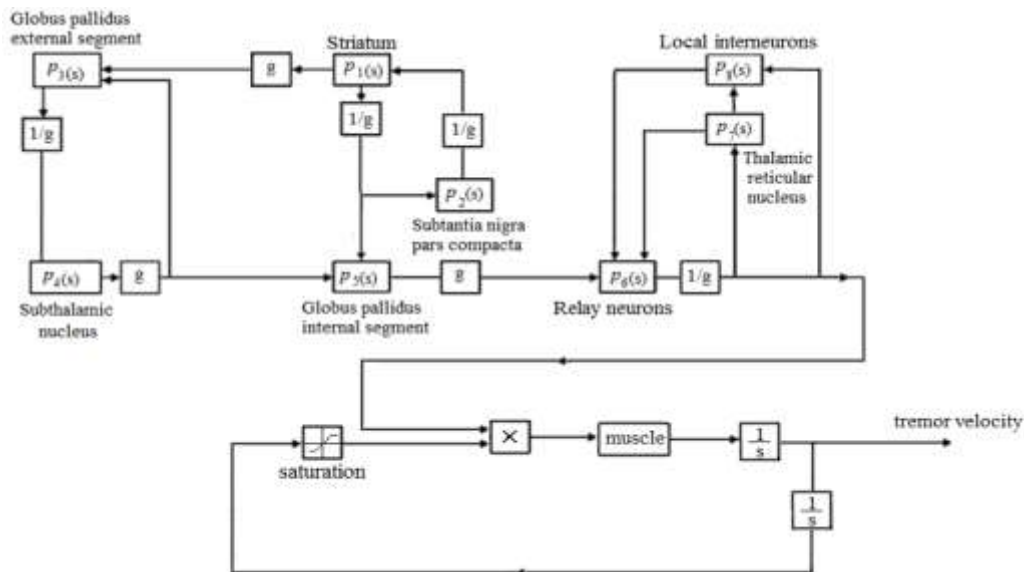


Figure 2. The complete model, used in this study

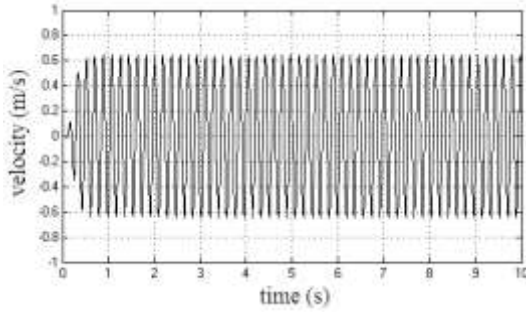


Figure 3. Model output with no DBS

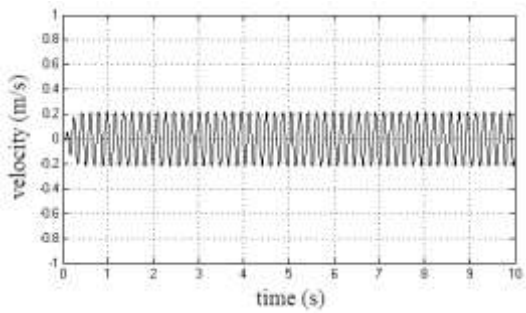


Figure 4. Model output after applying DBS

5. MECHANICAL METHOD

In this study, the experimental work of Pledgie et al. [9] is simulated as the second technique for tremor suppression to examine the efficiency and accuracy of presented model. In order to suppress the tremor, they have used an impedance control method that applies a resistive force to patient’s limb. To achieve this purpose, the patient should grasp the end-effector of a small robotic arm (PHANTOM). The manipulator of phantom applies force to muscle by a second order negative feedback. The feedback input is hand movement (X(s)) and the output is force (F(s)). The transfer function of the closed-loop is as follows:

$$T(s) = \frac{1}{(M + a_1)s^2 + (C + a_2)s + (K + a_3)} \tag{10}$$

The mass (M), damping (C), and stiffness (K) are the combined properties of human limb and the robotic arm. The nominal parameter values used for M, C and K are 1.3 kg, 5 Ns/m and 200 N/m, respectively. The negative feedback is a second order system which creates a closed-loop system.

As a matter of fact, the feedback coefficients (a₁, a₂, a₃) impact the closed-loop system coefficients in an additive fashion. The closed-loop system magnitude response can be estimated as follows:

$$R_{\omega} = \frac{1}{\sqrt{[K + a_3 - (M + a_1)\omega^2]^2 + (C + a_2)^2 \omega^2}} \tag{11}$$

The purpose of this method is decreasing the magnitude response of the closed-loop system in order to decrease the system output (hand movement). So the feedback coefficients are selected in a manner to increase the attenuation of magnitude response at tremor frequency. It is notable that by setting ω to zero (there is no tremor), feedback system shouldn’t have any effect on muscle (because there is no input). So a₃ is set to zero; otherwise it will cause undesirable attenuation in closed-loop system whereas there is no tremor. A method is presented to estimate a₁ and a₂ (acceleration and rate coefficients) which permits selecting one of them. At first step a desired level of closed-loop attenuation (R_{ω_t}) should be selected, and then by using the following expressions, feedback coefficients will be determined.

$$a_1 = \frac{1}{\omega_t^2} \left[K + \sqrt{\left(\frac{1}{R_{\omega_t}}\right)^2 - C^2 \omega_t^2} \right] - M \tag{12}$$

$$a_2 = \frac{1}{\omega_t} \sqrt{\left(\frac{1}{R_{\omega_t}}\right)^2 - (K - M\omega_t^2)^2 - C} \tag{13}$$

Figures 5 and 6 represent the model output after applying negative feedback with acceleration and rate coefficients, respectively. The model outputs are in accordance with clinical results obtained by Pledgie et al. [9]. It is visible that negative feedback will suppress tremor in an acceptable manner.

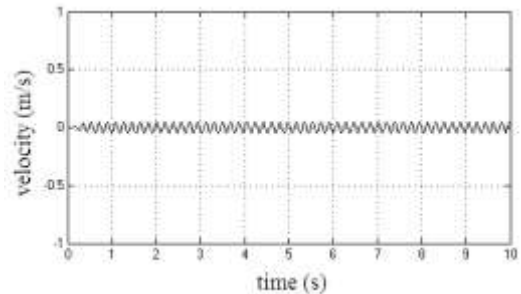


Figure 5. The model output after acceleration feedback (without DBS)

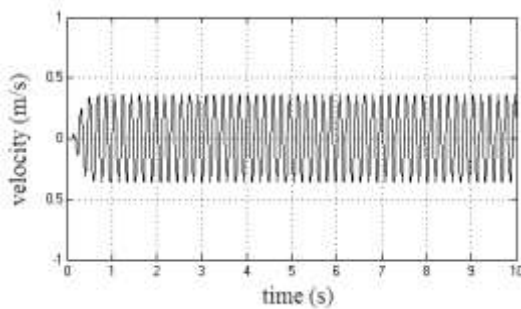


Figure 6. The model output after rate feedback (without DBS)

6. COCLUSION

Understanding the functions of the human brain is one of the most important goals of contemporary science. Mathematical medicine is a truly interdisciplinary area that brings together medical researches and engineering science. In this study a mathematical and computational model of PD tremor is presented to analyze the brain behaviour on tremor genesis. Two methods for tremor suppression is applied in this paper. These methods are deep brain stimulation (DBS) and a mechanical technique. Similar to real condition, the strength of block connections (gains) will change by variation in dopamine level. According to literature DBS affects dopamine level in BG; therefore, DBS effect is exerted by changing the connections' gain. The second method for tremor suppression is a mechanical method. This method is based on a negative feedback. The model results are in good agreement with the clinical results.

The presented model helps to have a better understanding of PD tremor. This model includes physiological information about tremor and some methods to control this disease.

7. REFERENCES

- Nahvi, A. R., Bahrami, F., Hemmati, S. "Investigating different targets in deep brain stimulation on parkinson's disease using a mean-field model of the basal ganglia-thalamocortical system." *Mechanics in Medicine and Biology*, Vol. 12, No. 2, (2011), 1-13. doi: 10.1109/MECBME.2011.5752089.
- Haeri, M., Sarbaz, Y., Gharibzadeh, Sh. "Modeling the Parkinson's tremor and its treatments," *Theoretical Biology*, Vol. 236, (2005), 311-322. doi: 10.1016/j.jtbi.2005.03.014.
- MashhadiMalek, M., Towhidkhah, F., Gharibzadeh, Sh., Daeichin, V., Ahmadi-Pajouh, M. A. "Are rigidity and tremor two sides of the same coin in Parkinson's disease?", *Computers in Biology and Medicine*, Vol. 38, (2008), 1133-1139. doi: 10.1016/j.compbiomed.2008.08.007.
- vanAlbada, S. J., Robinson, P. A. "Mean-field modeling of the basal ganglia-thalamocortical system. I Firing rates in healthy and parkinsonian states", *Theoretical Biology*, Vol. 257, (2009), 642-663. doi:10.1016/j.jtbi.2008.12.018.
- Dvoynikov, M., Kunshin, A., Blinov, P., Morozov, V. "Development of Mathematical Model for Controlling Drilling Parameters with Screw Downhole Motor", *International Journal of Engineering, Transactions A: Basics*, Vol. 33, No. 7 (2020), 1423-1430. doi: 10.5829/ije.2020.33.07a.30.
- Tehrani, F. T. "A Model of the Respiratory System in the Newborn Infant", *International Journal of Engineering*, Vol. 4, No. 3 (1991), 101-106.
- Zolfaghari, M., ghoreishi, M., tahmasbi, v. "Temperature in bone drilling process: Mathematical modeling and Optimization of effective parameters", *International Journal of Engineering, Transactions A: Basics*, Vol. 29, No. 7, (2016), 946-953. doi: 10.5829/idosi.ije.2016.29.07a.09.
- Ghoreishian, F., Pooyan, M. "A mathematical model for tremor genesis in Parkinson disease from a chaotic view", in 21st Iranian Conference on Biomedical Engineering, (2014), 353-357. doi: 10.1109/ICBME.2014.7043950.
- Pledgie, S., Barner, K., Agrawal, S. "Tremor Suppression Through Impedance Control", *IEEE Transactions on Rehabilitation Engineering*, Vol. 8, No. 1, (2000), 53-59. doi: 10.1109/86.830949.
- Parent, A., LeAvesque, M., Parent, M. "A re-evaluation of the current model of the basal ganglia", *Parkinsonism and Related Disorders*, Vol. 7, (2001), 193-198. doi: 10.1016/s1353-8020(00)00058-4.
- Mains, R. E., Soechting, J. F. "A model for the neuromuscular response to sudden disturbances", *Journal of Dynamic Systems, Measurement, and Control*, Vol. 93, No. 4, (1971), 247-251. doi: 10.1115/1.3426508
- Montgomery, J. r., Baker, K. B. "Mechanisms of deep brain stimulation and future technical developments", *Neurological Research*, Vol. 22, No. 3, (2000), 259-266. doi: 10.1080/01616412.2000.11740668.
- Figee, M., Koning, P., Klaassen, S., Vulink, N., Mantione, M., Munckhof, P., Schuurman, R., Wingen, G., Amelvoort, Th., Booij, J., Denys, D. "Deep Brain Stimulation Induces Striatal Dopamine Release in Obsessive-Compulsive Disorder", *Biological Psychiatry*, Vol. 75, (2014), 647-652. doi: 10.1016/j.biopsych.2013.06.021.
- Klanker, M., Feenstra, M., Willuhn, L., Denys, D. "Deep brain stimulation of the medial forebrain bundle elevates striatal dopamine concentration without affecting spontaneous or reward-induced phasic release", *Neuroscience*, Vol. 364, (2017), 82-92. doi: 10.1016/j.neuroscience.2017.09.012.
- Smith, G. S., Mills, K. A., Pontone, G. M., Anderson, W. S., Perepezko, K. M., Brasic, J., Zhou, Y., Brandt, J., Butson, Ch. R., Holt, D. P., Mathews, W. B., Dannels, R. F., Wong, D. F., Mari, Z. "Effect of STN DBS on vesicular monoamine transporter 2 and glucose metabolism in Parkinson's disease", *Parkinsonism & Related Disorders*, Vol. 64, (2019), 235-241. doi: 10.1016/j.parkreldis.2019.04.006.

Persian Abstract

چکیده

در این تحقیق، لرزش پارکینسونی با استفاده از روش‌های ریاضیاتی و محاسباتی مدل‌سازی شده است. در بیماری پارکینسون، سیگنالی غیرطبیعی توسط عقده‌های قاعده‌ای تولید می‌شود. این سیگنال وارد تالاموس شده و پس از تعامل با قشر مغز و سیستم عصبی محیطی نهایتاً در عضله به شکل لرزش ظاهر می‌گردد. در مدل ارائه شده در این مقاله، کلیه مراحل ذکر شده در بالا به کمک مدل‌سازی عضله و سیستم عصبی مرکزی (عقده‌های قاعده‌ای، تالاموس، قشر مغز و منطقه حرکتی مکمل) و سیستم عصبی محیطی (رفلکس نخاعی) شبیه‌سازی شده است. در نهایت دو روش برای کاهش لرزش مورد استفاده قرار گرفته است (۱) تحریک عمیق مغز که بر سطح دوپامین در عقده‌های قاعده‌ای تأثیر می‌گذارد و (۲) یک روش مکانیکی که بر اساس بازخورد منفی است. مقایسه نتایج مدل و نتایج آزمایشات بالینی نشان می‌دهد که مدل ارائه شده در این مقاله دقت و کارایی قابل قبولی دارد.