

Modeling the Parkinson's tremor and its treatments

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Abstract

In this paper, we discuss modeling issues of the Parkinson's tremor. Through the work we have employed physiological structure as well as functioning of the parts in brain that are involved in the disease. To obtain more practical similarity, random behaviors of the connection paths are also considered. Medication or treatment of the disease both by drug prescription and electrical signal stimulation are modeled based on the same model introduced for the disease itself. Two new medication strategies are proposed based on the model to reduce the side effects caused by the present drug prescription.

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1. Introduction

Parkinson's disease (PD) is a central nervous system disorder with vast symptoms. The disease is caused by degeneration or malfunctioning of basal ganglia (BG). This portion is composed of different parts and its main function is movement control. PD is caused by decreased dopamine secretion from "substantia nigra pars compacta". The common symptom is tremor, which can be subdivided into physiological and pathological tremors. Physiological tremor is a low-amplitude oscillation that, with suitable recording techniques, can be demonstrated in almost all normal subjects (Moises et al., 2003).

Parkinson's tremor is an involuntary tremble, with frequency of 4–6 Hz and high amplitude along the voluntary movement or at rest, especially in hands (Guyton and Hall, 2001).

There are two principal routes in PD treatment: medical treatment and deep brain stimulation (DBS).

A brief introduction to these two routes is essential for identifying treatment strategies.

(a) *Medical treatment*: Many researchers offered to increase dopamine in the brain in order to treat PD. The most important drug used for this purpose in the primary stages of PD is a dopamine derived substance, Levodopa, which passes through the blood-brain barrier and is converted to dopamine in the brain. Levodopa ameliorates the symptoms in primary stages but chronic application may cause drug resistance and aggravation of the symptoms.

(b) *DBS*: This method is a novel treatment for PD, obtained on the basis of previous experiences on improvement of the patients by destruction of some parts of the brain. In this route, bilateral electrodes are put permanently in one of the three parts of the brain:

1. The ventro-intermediate nucleus of the thalamus.
2. The internal globus pallidus.
3. The subthalamic nucleus (Limousin et al., 1998).

The electrodes are stimulated by pulse shaped electrical signals. The stimulation site and characteristics are obtained experimentally and differ among different

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patients (Klostermann et al., 2003). The exact mechanism of tremor suppression by DBS is still unknown (Montgomery and Baker, 2000). It is worth noting that these stimulations do not have destructive effects on the brain, because ceasing DBS causes recurrence of PD symptoms, especially tremor, as powerful as the pre-treatment state.

DBS, in essence, affects dopamine level in the BG. Owing to the previous hypotheses, it changes the parameters of the system, which in turn change the PD symptoms and causes damping of the tremor.

A lot of models for PD are present, most of them being conceptual or emphasizing mostly on reinforcement learning. There are a few computational simulations, concerned with the main symptoms as tremor (Titcombe et al., 2001; Edwards and Beuter, 1999; Asai et al., 2003). Titcombe et al. have designed a Hopf bifurcation model which had a response similar to tremor behavior under DBS. Although they had modeled DBS effects precisely, but there was no significant similarity between model and the plant neural structure. In addition, they have postulated the tremor as a simple sinusoidal signal, which in reality is not so. Edwards and Beuter have presented a neural network based model, the response of which could simulate the normal and PD subject responses, for some values of a postulated parameter. This parameter was not continuous and mechanism of transition from normal to diseased state was not discussed. Again, there was no considerable similarity between the body system and the presented model. Asai et al. have evaluated pedaling in PD. After classification of clinical data, they have designed a model, whose response classification is near to the clinical data classification. However, the model was designed regardless of nervous system structure. Hacisalihzade et al. have analysed Levodopa behavior precisely in two fields: pharmacodynamics and pharmacokinetics. They have offered an optimization method for the drug usage but numerical results are not included and PD behavior itself is not studied (Hacisalihzade et al., 1989). It seems that taking nearly all physiological information and structural characteristics to develop a holistic model is a necessity for better understanding of PD. It must be noted that most of the previous researches analysed the response of the system but they had few comments for controlling the disease.

We are to give a computational model based on experimental and physiological findings. Different parts of the brain involved in PD are all considered in our model. Hence, most features of the tremor have been completely shown in the model. Our mathematical model has considered the involved parts of the brain in a fairly accurate way, explaining the behavior and mechanism of the disease according to physiological information.

2. Physiological background

The internal relationships among the BG components as well as the relationships with external blocks are shown in Fig. 1 (Guyton and Hall, 2001).

From a physiological point of view, it is worthy noting whether a connection is excitatory (increasing the input would increase the output and vice versa) or inhibitory (increasing the input would decrease the output and vice versa).

As a matter of fact, information about the interior of each block is needed for modeling purposes. Since distinction of the blocks is not essentially according to their behaviors and physiological literatures do not provide a detailed function of each block in BG, obtaining mathematical relations representing dynamics of each block is tough and time consuming.

Here, some neural behaviors are presented, which are used as a basis for representing the internal behaviors of blocks.

Neurons create electrical signals by transporting ions into and out of the cell. In this regard, each neuron has three passive features: membrane transverse resistance, membrane capacitance and longitudinal resistance at axons and dendrites. There is a linear relation between current and steady-state polarization of neuron (represented by input resistance). The amount of polarization is determined from Ohm's law. The input resistance depends on membrane surface area as well as specific resistance of membrane itself. The above-mentioned points show only the steady-state behavior of the cell. The response of membrane for step input is exponential. Hence, existence of a capacitor is considered too. This capacity is also dependent to cellular surface area of membrane. The capacity of membrane and input resistance are joined in parallel. When the signal is

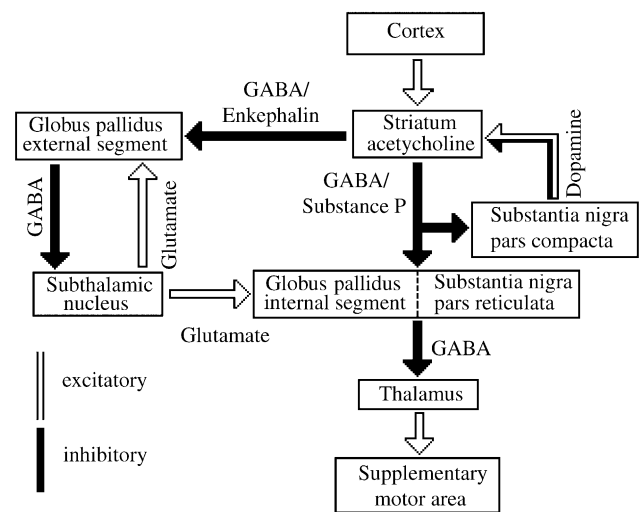


Fig. 1. Conceptual model of BG (data obtained from Guyton and Hall, 2001).

produced, it passes along axon without any changes and therefore axon acts similar to a resistance (Kandel et al., 2000). In each neuron, the relation between output (polarization) and the input (current) is a first-order dynamic system. In each block of BG, a lot of these neurons are working parallel together. So the whole behavior of block, in regard to its input, can be estimated with a first-order system. The parameters of the model for a single neuron are somewhat determined in the literature, but for a population of unknown number of neurons, the parameters are not apparent. We have tried to select the parameters considering the ultimate response, the tremor of disease. It is worth noting that neurons have certain nonlinear characteristics as well, including “threshold voltage effect”. Since substantia nigra pars compacta is the main component in generating the tremor, all the nonlinearities are lumped into this block in our model. It seems that although this assumption can fulfill all demands about PD, modeling other features of BG may need to impose different nonlinear parts in the model (Kandel et al., 2000).

3. Mathematical model

In compliance with the above discussion, the effect of each block was considered as a first-order system. The inhibitory and excitatory characteristics of the connections are considered on the transfer functions of the blocks.

The connection of substantia nigra pars compacta and striatum is almost only dopaminergic. We have assumed that the variation of the quantity of neurotransmitters (e.g., dopamine) acts like a connection strength (gain) between the blocks. It should be mentioned that because simple systems can oscillate easier with increasing the gain, the relationship of the quantity of neurotransmitter and the amount of the gain is taken as reverse. To this end, we used a gain between the substantia nigra and striatum. With this approach, the difference between dopamine amounts in health and disease is modeled. In physiological literature, it is mentioned that in addition to dopamine, other neurotransmitters are also changed during PD (Titcombe et al., 2001). Using different gains, our model includes other neurotransmitter changes as well. Since physiological knowledge about changes of neurotransmitters is not numeric and even the ratio of changes are not determined, we have taken into account all similar changes with the gain ‘*g*’. Decrement of neurotransmitter is designated with ‘*g*’ and the increase is modeled as gain of ‘ $1/g$ ’.

Nomenclature of the connecting signals is depicted in Fig. 2. The signal from cortex to BG contains “decision for movement”. Since the tremor origin is assumed to be

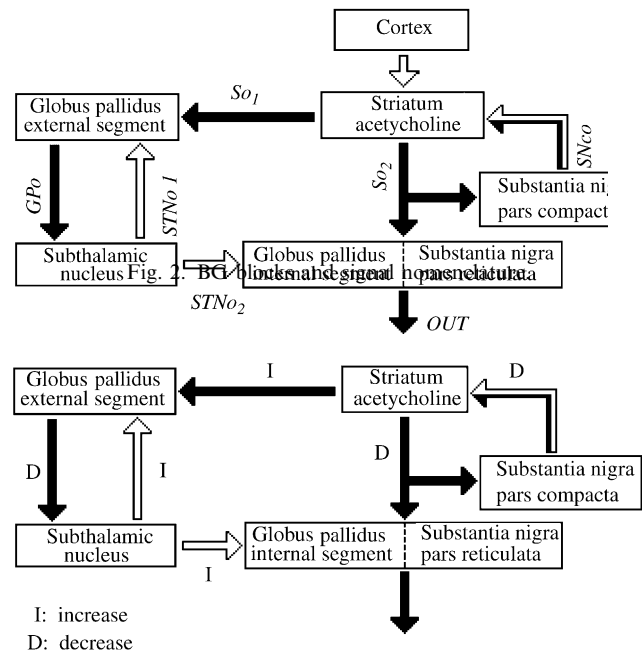


Fig. 3. Increase and decrease of connections’ strength in PD (data obtained from Kandel et al., 2000; Ganong, 2003).

the malfunctioning of BG due to degeneration of neurons of the substantia nigra pars compacta, in the simulation of the PD tremor, cortex signal is not considered.

The ultimate response of the model is the PD tremor, which is defined as “rest tremor”. In Fig. 3, changes in the block connections are illustrated for illness state.

In Fig. 4, a control block diagram similar to BG is presented. Here, a transfer function is assigned for each block, which is often multivariable. They are designated as $G_i(s)$ only for representation purposes.

$G_1(s)$ represents dynamics of the substantia nigra pars compacta. This part is taken as a first-order system. At the continuation of this transfer function, a nonlinear element (sign function) is imposed. Input signal has inhibitory effect over the output signal, which has been taken into account.

$$G_1(s) : SNco(t) = \text{sgn}(A(t)),$$

$$A(s) = \frac{-10}{s + 40} g \times So2(s). \tag{1}$$

$G_2(s)$ represents behavior of striatum. This component has two outputs and its input has an excitatory effect over them.

$$G_2(s) : So1(s) = \frac{1}{s + 30} SNco(s),$$

$$So2(s) = \frac{10}{s(s + 30)} SNco(s). \tag{2}$$

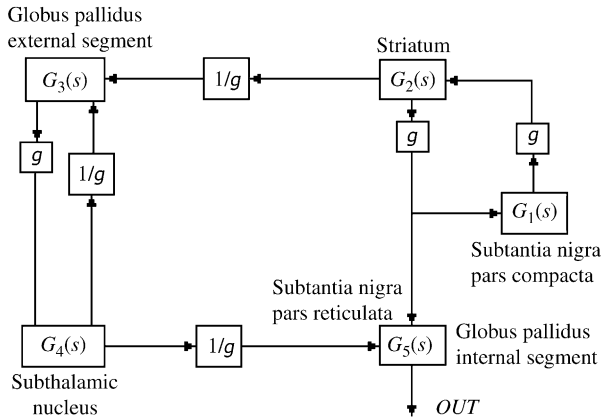


Fig. 4. Computational model of BG, producing tremor.

$G_3(s)$ models the globus pallidus external segment. Here, there is an inhibitory input and an excitatory input with a single output.

$$G_3(s) : GPO(s) = \frac{-1}{g} \times \frac{10}{s+10} STNo_1(s) + \frac{1}{g} \times \frac{50}{s+10} STNo_2(s). \quad (3)$$

Transfer function of $G_4(s)$ models the subthalamic nucleus. This part has one inhibitory input with two outputs. A first-order transfer function was considered for each output.

$$G_4(s) : STNo_1(s) = g \times \frac{-0.1}{s+40} GPO(s),$$

$$STNo_2(s) = g \times \frac{-1}{s+40} GPO(s). \quad (4)$$

Finally, transfer function of $G_5(s)$ models the globus pallidus internal segment and substantia nigra pars reticulata, which produce the output of the BG. It has one excitatory and one inhibitory input with only one output which is the final output of the BG. Transfer function of each input is considered a first-order system.

$$G_5(s) : OUT(s) = \frac{1}{g} \times \frac{200}{s+10} STNo_2(s) - g \times \frac{200}{s+10} So_2(s). \quad (5)$$

In Fig. 5, a sample recorded clinical data which is presented in (www.physionet.org), is drawn. In Fig. 6, the model response is plotted for two values of ‘ g ’. Response for $g = 10$ is the simulation of patient behavior (which is fairly like Fig. 5) and for $g = 1$ is the state after the treatment. As it is shown, the tremor is suppressed in an acceptable manner but has not been disappeared completely. This is very similar to real conditions.

The results of comparing “frequency content” between model response and clinical data are presented in Figs. 7 and 8. It is obvious that the frequency content of

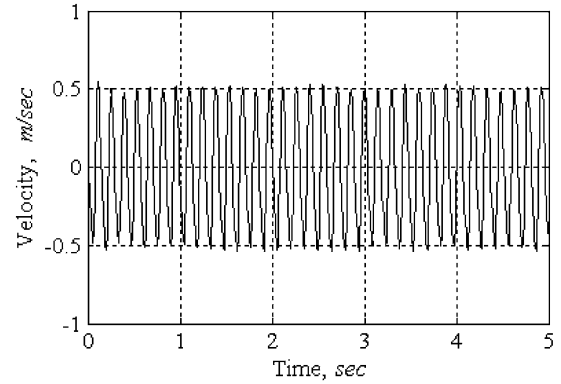


Fig. 5. Drawing of clinical data (raw data obtained from www.physionet.org).

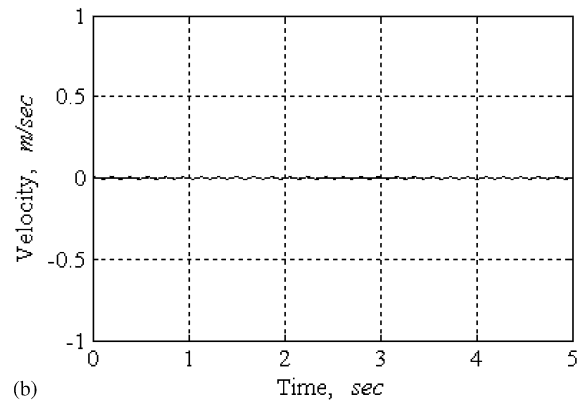
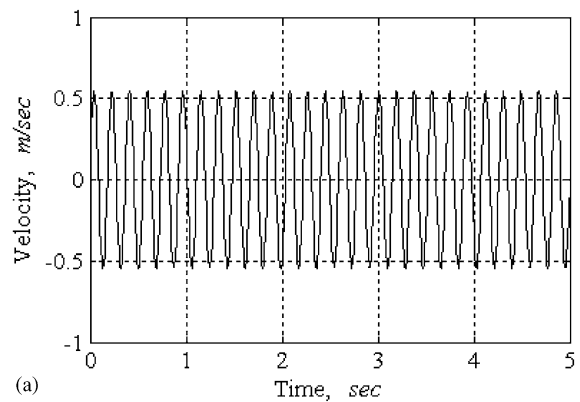


Fig. 6. The model response for two values of g (a) $g = 10$; (b) $g = 1$.

the two signals is similar. Of course, clinical data has more disordered spectrum around the peak frequency, which is related to the nature of noisy behavior of the tremor.

4. Modeling the treatment

4.1. Drug treatment modeling

Since chronic drug treatment will cause resistance against the medication, it is very important to determine

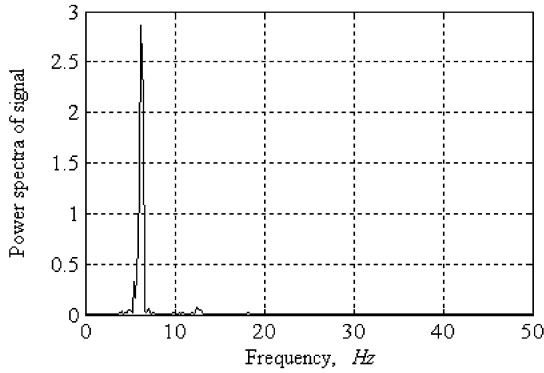


Fig. 7. Power spectra of clinical data (raw data obtained from www.physionet.org).

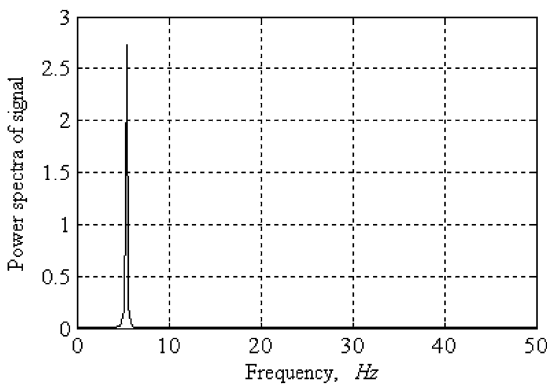


Fig. 8. Power spectra of simulated signal.

the proper dose of drug in primary stages of the disease. On the other hand, due to individual differences, it seems necessary to adapt drug dose distinctly for each patient. These purposes can be achieved by the presented model and optimizing its response.

According to clinical findings, drug affects 10–15 min after injection. Then, the PD disorders decrease and reach a minimum. Nearly after 2–2.5 h, beneficial drug effects begin to reduce. Finally after 4 h, all drug effects are disappeared.

Hacisalihzade et al. have modeled the pharmacokinetics of the drug (the relation between the drug dose and its plasma level) as a second-order system with the following transfer function (Hacisalihzade et al., 1998):

$$G(s) = \frac{k}{(1 + sT_1)(1 + sT_2)}, \quad (6)$$

where k denotes amplification factor, T_1 and T_2 are time constants in hours and s denotes the complex frequency. They measured the level of Levodopa in blood several times after administration of a 125 mg capsule, in order to identify the above parameters. They exerted an important correction on the equation by considering the

delay of drug effect initiation:

$$G(s) = \frac{ke^{-T_0s}}{(1 + sT_1)(1 + sT_2)}. \quad (7)$$

In which T_0 is the delay time. (Hacisalihzade et al., 1998). Parameters of the identified model are given as (Hacisalihzade et al., 1998):

$$k = 1418, \quad T_1 = 0.05473, \quad T_2 = 0.6073, \\ T_0 = 0.2461.$$

We considered the results of the second-order system in Eq. (7) with the given parameters. Then, impulse input with amplitude of drug dose (125 mg) was exerted to the system. The obtained response differed from what was given by Hacisalihzade. However, applying a constant gain of 910 is enough to correct the results.

Now it is necessary to model the pharmacodynamics (drug effect on disease symptom). For this purpose, input is plasma drug concentration and output is the gain of dopamine change (g). We divide pharmacodynamics effects into two parts: a linear dynamic and a nonlinear static relation between blood concentration and g . We have assumed that increment of drug concentration above 1500 mg/L will cause suppression of the tremor.

The concentration above 1500 mg/L is substituted by a horizontal line. In other words, saturation nonlinearity is applied. The following first-order system is used for simplicity:

$$G(s) = \frac{0.1}{s + 0.1}. \quad (8)$$

The scaled variation of parameter g in response to drug prescription is shown in Fig. 9.

Now, the determined signal should be converted to g with a proper scale for our main model in Fig. 4. A linear transformation mechanism is considered. Zero value of the signal was assumed for $g = 10$, because this amount of g simulates the illness properly. $g = 1$ is introduced for value of 1500 mg/L in signal, because this

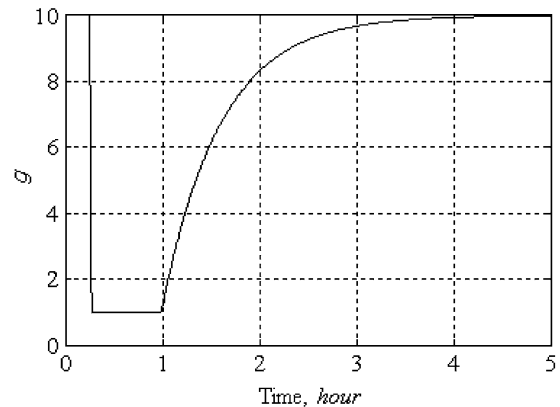


Fig. 9. Variation of g magnitude after drug prescription.

amount of g can simulate the treated state. Result of the transformation is shown in Fig. 9.

We now exert the equivalent g that represents the drug prescription on the main model of tremor in Fig. 4. Tremor behavior against time, after prescription of the drug is depicted in Fig. 10.

4.2. DBS treatment modeling

There is some controversy about relevancy of animal models for evaluating neurological deficits as Parkinson’s tremor (Cenci et al., 2002). Therefore, the clinical data recorded from four PD patients receiving DBS is used in this study. These data are obtained from the (Titcombe et al., 2001), which has focused on transient state, i.e., switch from on to off and vice versa. Amplitude and pulse width of DBS was constant in each patient, but differed among different patients. DBS parameters needed for optimizing suppression of tremor was determined clinically by performing different experiments. In general state, the amplitude of stimulation voltage was nearly $3v$, pulse width was almost $90 \mu s$ and the exerted frequency was greater than 100 Hz . Table 1 summarizes characteristics of the stimulation in each patient. Recorded clinical data indicate that there is a few seconds of delay between DBS and tremor suppression. This delay is seen exactly in Fig. 11 which illustrates 15 s of a tremor recording. Stimulation is exerted in time 0. Similarly, another delay is seen when

Table 1
DBS characteristics for each of the subjects

Subject	Effective frequency (Hz)	Pulse duration (ms)	Pulse intensity (v)	Stimulation mode
A	135	0.09	2.8	Continuous
B	185	0.09	5.3	Continuous
C	160	0.12	3.7	Cycle
D	185	0.09	2.4	Cycle

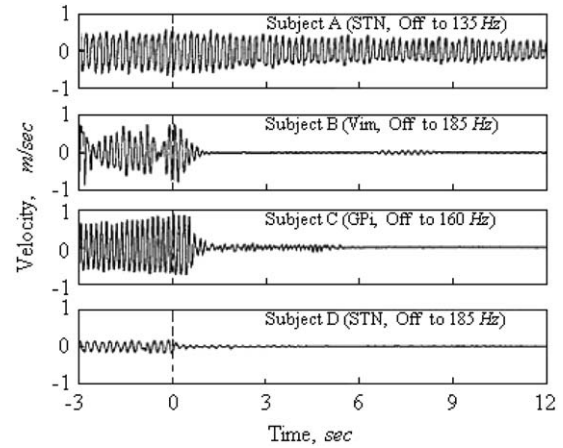


Fig. 11. Rest tremor in subjects after DBS exertion (www.physionet.org).

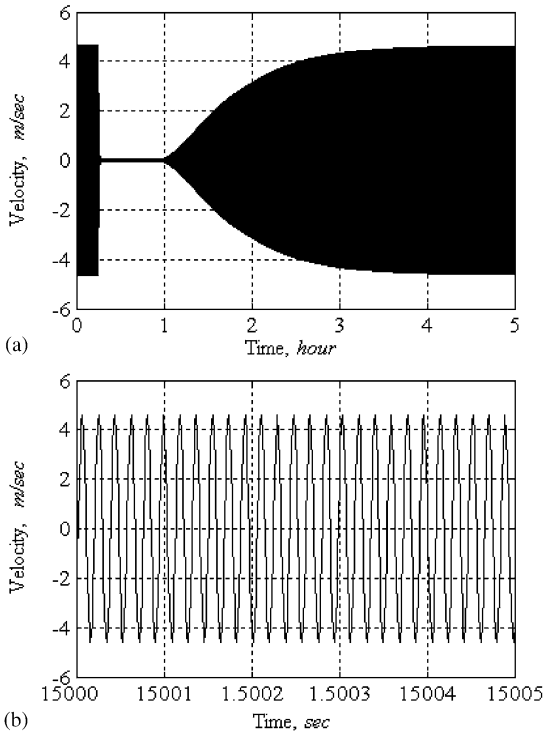


Fig. 10. Tremor behavior under drug medication: (a) whole time-scale; (b) short time-scale.

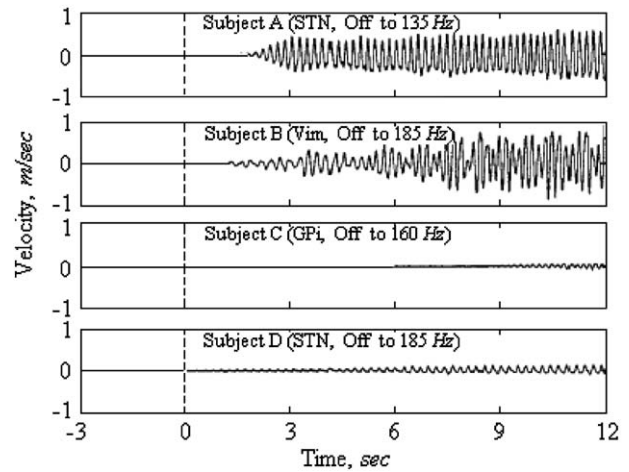


Fig. 12. Rest tremor in subjects after DBS stoppage (www.physionet.org).

stimulation is switched off. Fig. 12 shows tremor of the four subjects, while previous stimulation was turned off at time zero. In all the subjects, gradual increment of tremor amplitude was observed.

Beuter and Titcombe showed that no changes in tremor were observed across conditions in subjects with little or no tremor. However, in subjects with moderate

to large amplitude tremor, DBS decreased tremor amplitude to near normal values within a few seconds. Generally, transitions were progressive and occurred with a varying time delay. Occasionally, tremor escaped from control regardless of the stimulation condition considered (Beuter and Titcombe, 2003).

In general, two points are worthy noting: (1) there is a delay between DBS exertion and its effect. (2) Amplitude of tremor has gradual rather than sudden changes (Titcombe et al., 2001; Limousin et al., 1998).

Parameter g , the main model parameter, is controlled by DBS. In order to model the effects of DBS, it is supposed that each DBS releases a quantal amount, δ , of assumed substance z (Titcomb et al., 2001). Amount of z dies with a time constant t_c . Some studies have suggested that along DBS exertion, the amount of neurotransmitter is increased (Lee et al., 2004). Dopamine is one of these neurotransmitters. So it seems that DBS causes change in dopamine content of brain, which in turn affects tremor amplitude directly. τ is DBS period and we have $f = 1/\tau$. Without stimulation, substance z will damp toward zero with a time constant of t_c .

It should be noted that frequency of DBS, as well as amplitude, can be changed for tremor controlling. We suppose that the amplitude changes are represented by increase or decrease in δ . Now we consider the effect of DBS on the main model of Fig. 1. δ is supposed to be 1. Frequency of DBS is considered 125 Hz. In order to model different behaviors of subjects, t_c is changed in accordance with different behaviors of patients. Considering the acceptable range of g (between 1 and 10), in order to obtain g equal to 1, t_c is chosen 0.076 s. Larger t_c results in the smaller steady-state g . Since the non-positive values of g are not defined in the model and have no physical interpretation, the final value of g should not be 0 or negative. In Fig. 13, changes of g due to DBS application are depicted. Stimulations are exerted in second 5 and stopped in second 10. After stimulation, amount of g decreases and finally reaches 1.

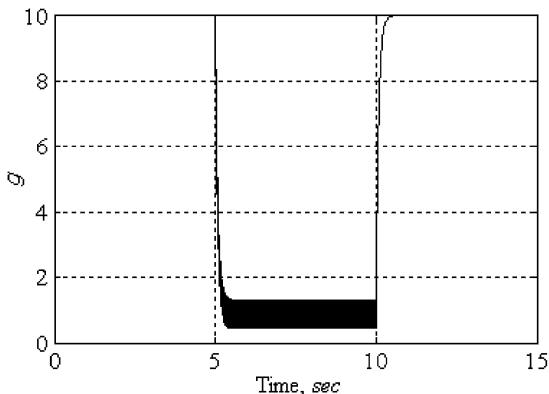


Fig. 13. Variations of g due to DBS exertion ($t_c = 0.076$ s).

After stoppage of stimuli, g increases again and approaches to its initial value of 10. The response of the proposed model is plotted in Fig. 14.

Since t_c is dependent on the subject, the effectiveness of DBS can be modeled by this parameter. For example if $t_c = 0.05$ s, the subject will not completely benefit from this particular DBS. In this case, the tremor amplitude is decreased, but not suppressed enough. In Fig. 15, variation of g is plotted when $t_c = 0.05$ s. In Fig. 16, response of the model is depicted for these

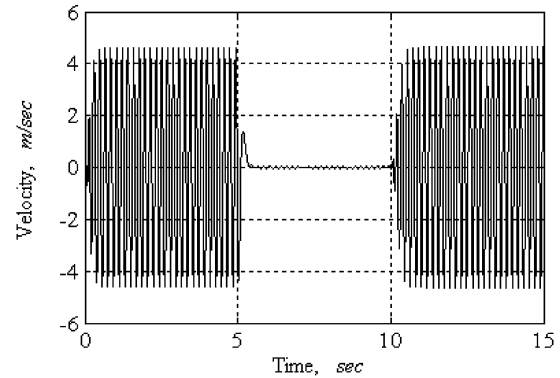


Fig. 14. Response of the model to DBS exertion ($t_c = 0.076$ s).

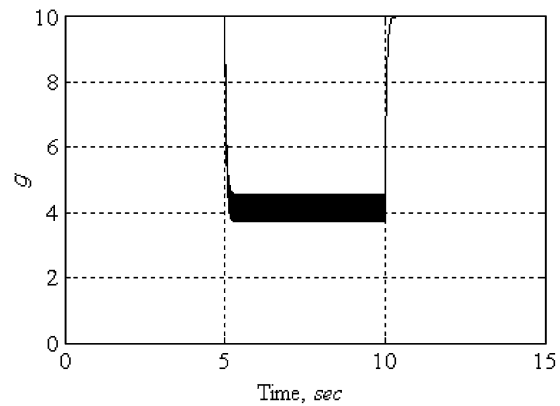


Fig. 15. Variations of g due to DBS exertion ($t_c = 0.05$ s).

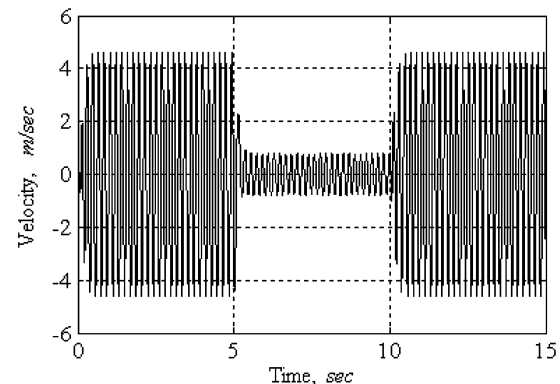


Fig. 16. The model response due to DBS ($t_c = 0.05$ s).

changes of g . It is obvious that during this DBS exertion, amplitude of the tremor is decreased, but is not suppressed adequately.

5. Predictions based on the proposed model

5.1. Optimization of the Levodopa usage

It is sometimes observed that Levodopa not only causes different side effects in different patients, but also its chronic prescription reduces the therapeutic advantages so that more amounts of the drug should be used. In the primary stages of the disease, less amounts of drug have more delayed onset of side effects. Now we calculate the optimum dose of the drug according to the mathematical formulas mentioned earlier.

5.1.1. Determining cost function of drug usage

Drug usage has two parameters, dose and time of prescription, which are considered as parameters of cost function. Decrement of the dose and increment of the time interval between successive doses is beneficial. In addition, daily dose cannot be greater than a definite amount. So, cost function is defined as

$$F(\delta, T) = b \times \delta + \frac{c}{T} \tag{9}$$

in which δ is the dose in each prescription and T is the time interval between two successive drug consumptions. Minimizing F will produce the optimum state, because it means decreasing δ and increasing T .

5.1.2. Relation between drug dose and time of prescription

The relation between drug prescription and its plasma level is an impulse response of a second-order system with delay. The amplitude of the impulse is determined by the drug dose. Plasma levels above 1500 mg/L can effectively suppress the tremor. So, we have regulated the time of prescriptions in a manner that after reaching the concentration of 1500 mg/L, the effect of second dose is initiated. If an impulse with amplitude of δ is implemented, the time response of system will be:

$$y(t) = 40.89 \times \delta(e^{-1.6466(t-0.2461)} - e^{-18.2715(t-0.2461)}), \tag{10}$$

The main constraint will be obtained by considering critical concentration (1500 mg/L):

$$1500 = 40.89 \times \delta(e^{-1.6466(T-0.2461)} - e^{-18.2715(T-0.2461)}), \tag{11}$$

where T is the time between consecutive drug prescriptions and δ is drug dose in each prescription. Since the maximum daily allowable dose of this drug

is 2500 mg then:

$$\frac{24}{T} \times \delta \leq 2500. \tag{12}$$

5.1.3. Optimization

This optimization problem has two constraints. We have simplified the formulas by the following variable alterations:

$$x_1 = \delta, \quad x_2 = \frac{1}{T - 0.2461}. \tag{13}$$

Then we have

$$F(x_1, x_2) = ax_1 + bx_2 \tag{14}$$

and the constraints will be

$$1500 - 40.89 \times x_1(e^{-1.6466/x_2} - e^{-18.2715/x_2}) = 0, \tag{15}$$

$$2500 - 24x_1x_2 + 615.25x_2 \geq 0. \tag{16}$$

Since both time of prescription and dose of the drug are fairly important, we considered equal weights for two parameters (x_1 and x_2) i.e., ‘ a ’ and ‘ b ’. This optimization problem was solved using Lagrange method with MATLAB software. Answers are as follows:

$$x_1 = 58.613, \quad x_2 = 2.7977. \tag{17}$$

Returning to the main parameters, we have

$$\delta = 58.613, \quad T = 0.6035. \tag{18}$$

These amounts will suppress the tremor completely.

5.2. Offering a new medical treatment

Now on the basis of our model, we attend to evaluate the role of another neurotransmitter, gamma amino butyric acid (GABA), on PD. GABA is an important neurotransmitter in BG, which accompanied with substance P, is the main input to substantia nigra (Fig. 1). Since the output of substantia nigra is dopamine, it seems that GABA may be effective in PD treatment. So, we have examined the effects of GABA changes on the model.

5.2.1. Evaluating the effects of GABA changes on model response

Since GABA increment is an external factor, we have modeled this increment with a gain in pathways having GABA as their neurotransmitter. Fig. 17 shows the same model as Fig. 4, except that the gains of GABA are included as k . k is supposed to be 1 in a patient who has not used external GABA. In a person who has used the maximum allowable external dose of GABA, k is considered to be 0.1. In Fig. 18a, the response of the system is depicted when g is 10 and k is 1. This simulates

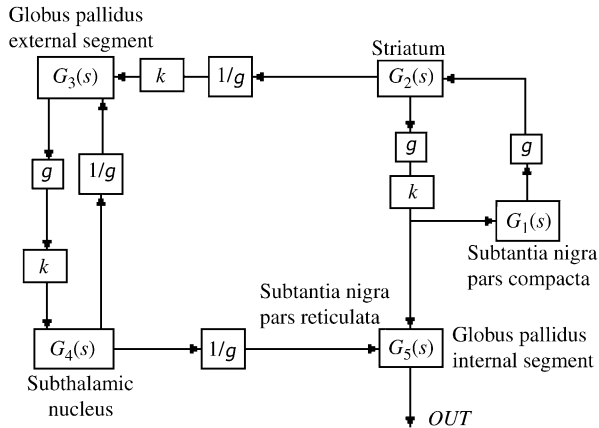


Fig. 17. Computational model for producing tremor, including GABA gains.

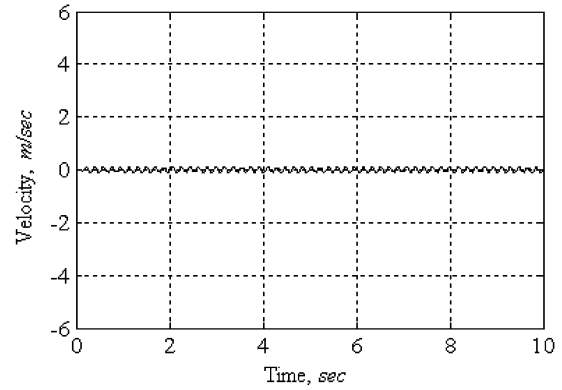


Fig. 19. Exerting dopamine and GABA changes on the model simultaneously.

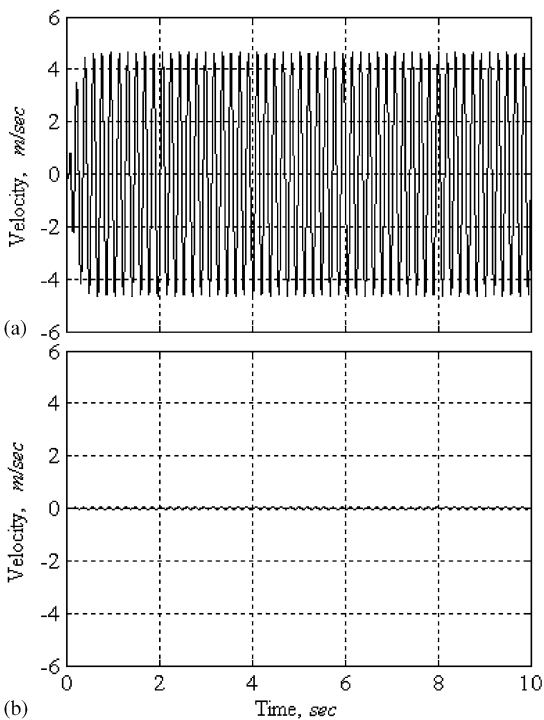


Fig. 18. Model response when (a) $g = 10$ and $k = 1$ and (b) $g = 10$ and $k = 0.1$.

a PD patient who has not used any medication. In Fig. 18b, g is 10 and k is 0.1, equivalent to a patient who has used maximum allowable dose of GABA. It is obvious in this figure that amplitude is decreased. However, this effect of GABA is weaker than the effect of lowering g from 10 to 1.

5.2.2. Using GABA as a complementary treatment

It seems that since GABA is effective on tremor, and minimizing the dose of dopamine will decrease its side effects, using GABA with dopamine will have better

effects on PD tremor than each of these two substances separately. For this purpose, we have converted g from 10 to 5 which correspond to less prescription of dopamine (Levodopa) and k from 1 to 0.1, which corresponds to maximum allowable GABA prescription. Results of such situations are depicted in Fig. 19.

Nowadays, a drug named Gabapentine is introduced, which increases GABA in the brain. Although it has been used in some neural diseases as multiple sclerosis, it has not been used yet in PD (Gray, 2004). On the basis of presented model, we think that using it in PD, along with less doses of Levodopa, will be a proper treatment for tremor. It is worthy to evaluate this comment clinically on PD subjects.

6. Completing the model

During transmission of signals between neurons, several noise sources can be considered: (1) voltage gated ion channels, (2) amount of calcium ion in the neurons, (3) diffusion of neurotransmitters between two neurons and (4) opening of ion channels in response to released neurotransmitter in the destination neuron. Probable additional noise sources in PD are: decreased uptake of dopamine in synapses of striatum and dopamine receptor upregulation (increment of dopamine receptors in striatum, following decreased dopamine release).

Applying these sources of noise to the model will really complete the primary model. Because of the nature of noise sources, we considered them in the connections. Since the noises are greater in PD, we considered the dependence of noise to g parameter and replace parameter g of the simple model by $g + g \times c \times n(t)$. $n(t)$ is a white noise having mean of 0 and variance of 1. 'c' is a free parameter to model the difference among patients. Power spectra are used for comparing clinical and simulated data.

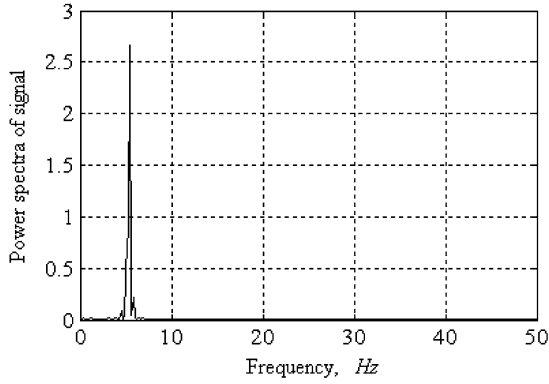


Fig. 20. Power spectra of noisy response.

Noisy response, which is shown in Fig. 20, has a wider width than non-noisy state of Fig. 8, and is similar to clinical data (Fig. 7). Some clinical recordings show frequency contents besides the peak frequency. So, another noise source must be considered just near the output of model, which simulates noises from sources other than BG (as muscles). A white noise is passed through a low pass filter which corresponds to muscles response. The final response of the model is as follows:

$$OUTo(s) = OUT(s) + dgG_{lp}(s)n(s), \tag{19}$$

$$G_{lp}(s) = \frac{50}{s + 50}. \tag{20}$$

6.1. Drug modeling

We now exert the g magnitudes of Fig. 9 (corresponding to drug prescription) to the complete model. Tremor behavior against time, after prescription of the drug is depicted in Fig. 21.

6.2. Modeling of DBS on the complete model

In Section 4.2, the effects of DBS on parameter g of the model was mentioned. We exerted the same effective and ineffective g on the complete model and obtained Figs. 22 and 23. As it is seen, the behavior is more similar to the real conditions.

7. Discussion

We believe that the mathematical models of brain physiological performance have a great role in elucidating medical knowledge and have expanded our attitude about the illness states. The increase in effectiveness of mathematical models is manifested by two factors: The complexity of brain structure itself, and greater com-

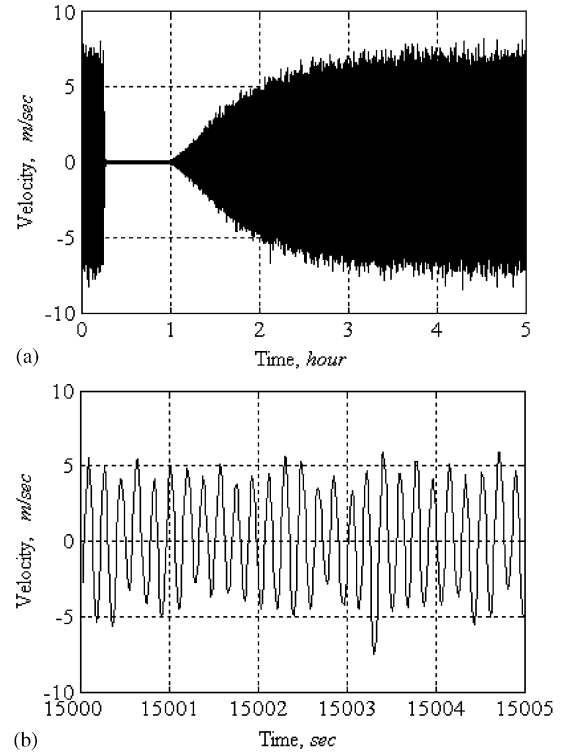


Fig. 21. Tremor behavior under drug medication: (a) whole time-scale, (b) short time-scale.

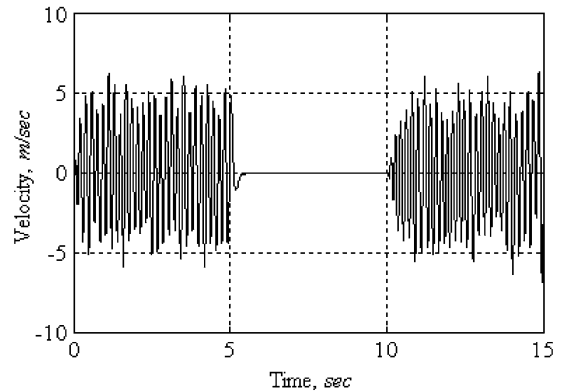


Fig. 22. Response of the model to effective DBS exertion.

plexity of pathological conditions. Meantime, certain neurological disorders such as PD have a particular importance and have gained attention of many researchers.

There are a few computational simulations, done by other researchers concerned with the main symptoms of PD (Fukumoto 1986; Asai et al., 2003; Edwards and Beuter, 1999; Titcombe et al., 2001). Fukumoto assumes that fatigue of intrafusal fibers, which results from chronic stimulation by the gamma system, is the main cause of Parkinsonian tremor and presents a mathematical model based on this assumption. Using a computer

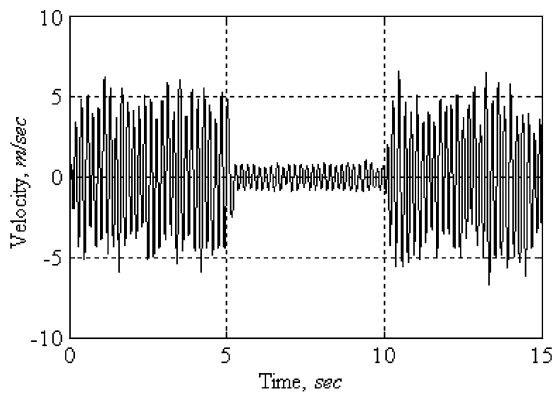


Fig. 23. Response of the model to ineffective DBS exertion.

simulation of the model, he shows that both physiological tremor and Parkinsonian tremor can be caused by the varying contractivity of the intrafusal fibers. Titcombe et al. have modeled only DBS. They designed a Hopf bifurcation model which had a response similar to a simple sinusoidal tremor under DBS, but there was no significant similarity between model and the body structure. Edwards and Beuter have designed an artificial neural network, the response of which modeled the normal and PD subject responses, for some values of a postulated parameter. This parameter was not continuous and mechanism of transition from normal to diseased state was not discussed. Asai et al. have evaluated pedaling in PD. Their model was designed regardless of nervous system structure. Hacısalihzade et al. have analysed Levodopa behavior, but they have not studied behavior of PD itself. Le Cavorzin et al. have presented a model for Parkinson's rigidity. They have designed a computer model of spinal proprioceptive input processing and showed that as the "threshold parameter" was much lowered, their model generated typical features of Parkinsonian resting tremor, endorsing the hypothesis of a participation of a spinal oscillator in this disorder. Their model does not evaluate the central nervous circuits in this disease (Le Cavorzin et al., 2003).

De la Fuente-Fernandez et al. have presented a probabilistic model for dystonia, dyskinesia and motor fluctuations of PD, but have not evaluated tremor directly (de la Fuente-Fernandez et al., 2004).

Here, we have modeled the tremor behavior of PD as a system similar to the structure of the body. We have attempted to increase the similarities of the model and the actual system as much as possible. Physiological researches have shown that the weakening of the substantia nigra pars compacta connection to striatum due to a decrease in dopamine secretion leads to PD and all the complexities of disease is due to lower dopamine secretion. Just as similar to brain, certain gains for connections were proposed in our model, which would

change with dopamine variation. Using gain to indicate the connection strength is the best method of modeling the decrease and increase of neurotransmitters, and simulates the real function as it is taking place.

In addition to a fairly accurate modeling of the effect of dopamine as a cause of disease, the proposed model has simulated the other parts of BG well enough. In each section of BG, inputs and outputs are included exactly and in addition, the inhibitory and excitatory parts are considered and modeled distinctly. Finally the differences of strength of connections at health and illness states were considered as well.

Then, drug and DBS therapeutic behaviors on the PD tremor were evaluated. The effects of both methods were represented based on the mathematical model. In PD treatments, amount of the neurotransmitters, especially dopamine should be increased. In drug medication, this increase is done by adding an external drug directly. In DBS, although some researches have modeled its effect as increasing firing rates of target cells, but it is verified that the neurotransmitters are also increased (Rubin and Terman, 2004; Titcomb et al., 2001). Our model considered nearly all pharmacodynamical and pharmacokinetical aspects in prescribing Levodopa. The model not only is able to represent the characteristics of routinely used treatments on the outcome of PD, but also can predict the effects of altered treatment parameters on the recovery.

Beuter and Titcombe showed that no changes in tremor were observed across conditions in subjects with little or no tremor. However, in subjects with moderate to large amplitude tremor, DBS decreased tremor amplitude to near normal values within a few seconds. Generally, transitions were progressive and occurred with a varying time delay (Beuter and Titcombe, 2003). Referring to Section 4.2, it is evident that our model represents nearly all of these findings.

On the other hand, although the exact mechanism of action of DBS is not yet understood, parameters of the stimulation including frequency, amplitude, pulse width, etc. can be evaluated with the proposed model. Examining these parameters in the model before implementing them on the patients is recommended.

The proposed optimal dose and optimal time of prescription, can suppress the tremor exactly and it might be the best way of drug prescription. It is worthy to examine these quantities experimentally.

An important novel drug, Gabapentine, increases amount of GABA in the brain. We showed by our model, that increasing GABA can improve the tremor. This model predicts Gabapentine to be a supplementary drug for PD, whenever the side effects of Levodopa limit its use.

For greater matching between model response and clinical data, sources of unpredictable behaviors of nervous system were identified and considered in the

model. The results of this model improvement were observed obviously in power spectra of system responses. The effects of two main treatments were added to the completed model. The results approached to the clinical data.

We have designed a holistic model for better understanding of PD. Our model, not only has considered available physiological information, but also has simulated control of PD by therapeutic methods. It seems that our model have many similarities with actual body system and can be used as a primary choice for studying PD and evaluating theoretical attitudes about it.

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