PARKINSON'S DISEASE: MODELING THE TREMOR AND OPTIMIZING THE TREATMENT

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Abstract: Parkinson's disease is a common neurological disorder, the main symptom of which is tremor. In this study, tremor is modelled using physiological information and clinical recordings. All blocks of the basal ganglia are considered exactly in this model and mathematical relations of each block are designed. Two main therapeutic approaches are implemented on the model. Finally, optimal dose and optimal time of prescribing the drug, Levodopa, is offered. Our results indicate that this model can be used as a primary choice for research on Parkinson's disease. *Copyright © 2005 IFAC*

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1. INTRODUCTION

Parkinson's Disease (PD) is caused by destruction or malfunctioning of substantia nigra, a part of the Basal Ganglia (BG). The main function of BG, which contains several parts, is movement control. The PD as the most common disease of the BG is caused by depletion of a neurotransmitter called Dopamine. The main sign of the PD is tremor, an involuntary oscillating movement with $4-6\ Hz$ frequency and high amplitude. The tremor is seen especially in hands during both on voluntary movements and on the rest.

Although several researchers have tried to model Parkinsonian tremor and analysed the recorded signals, none of them have included the precise physiological information and neural structures in their models (Titcombe, *et al.*, 2001; Edwards, *et al.*, 1999; Asai, *et al.*, 2003). In addition, tremor has been supposed to be a simple sinusoidal signal in the previous researches and the nonlinear behaviours of recorded tremors are not considered (Titcombe *et al.*, 2001).

In this study, we try to present a mathematical model containing physiological information and clinical data, as much as possible. This model considers different parts of the brain involved in PD. Thus, tremor behaviour can be represented in a fairly complete manner. On the other hand, nonlinear and noisy behaviours of recorded tremors are included, as well.

In Section 2 we modelled the PD tremor in the BG structure with considering all available information about this part of brain. In Section 3 two main treatments of the PD have been analysed. In Section 4, problem of drug usage optimization is presented. Finally paper is concluded in Section 5.

2. MODELING THE TREMOR

Fig. 1 illustrates a schematic diagram showing the different parts of the BG (Guyton, *et al.*, 2001).The main criteria for separating different blocks of the BG in physiology are apparent configuration, neuronal structures, and input and output neurotransmitters. There is no precise information on internal functioning of the blocks. Each block, consisting a huge number of neurons, is assumed (at least in our study) to behave like a single neuron, having three passive electrical elements: a membrane resistance, a membrane capacitance and a

longitudinal axonal resistance. Fig. 2 shows the electrical circuit equivalent representation of a single neuron (Guyton, et al., 2001).

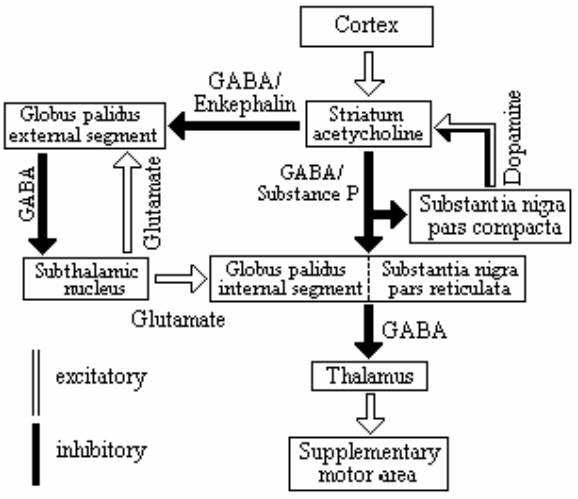

Fig. 1. Different parts of the BG.

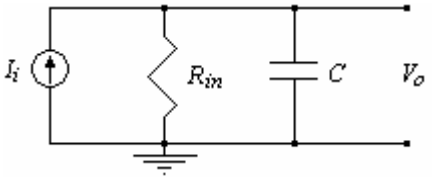

Fig. 2. Electrical circuit equivalent of a neuron.

The relation between V_o (membrane voltage) and I_i (input current of membrane) is therefore given by a first order system. The behaviour of substantia nigra, the most important part involved in tremor, is supposed to be nonlinear. The model relations are as follow.

$G_1(s)$ 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.

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

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

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.

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 an excitatory input and an 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.

$$G_1(s): SNco(t) = \mathrm{sgn}(A(t)),\quad A(s) = \frac{-10}{s+40} g \times So_2(s) \tag{1}$$

$$G_2(s): So_1(s) = \frac{1}{s+30} SNco(s),\quad So_2(s) = \frac{10}{s(s+30)} SNco(s) \tag{2}$$

$$G_3(s): GPo(s) = \frac{-1}{g} \times \frac{10}{s+10} So_1(s) + \frac{1}{g} \times \frac{50}{s+10} STNo_1(s) \tag{3}$$

$$G_4(s): STNo_1(s) = g \times \frac{-.1}{s+40} GPo(s),\quad STNo_2(s) = g \times \frac{-1}{s+40} GPo(s) \tag{4}$$

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

The systemic block diagram of the model is presented in Fig. 3. Parameter g of the model simulates Dopamine level. $g = 10$ represents the disease state and the resulted tremor is depicted in Fig. 4. Setting $g = 1$, suppresses the tremor completely and therefore represents the healthy state.

In transmission of signals between two neurons, several noise sources can be considered: 1) Voltage gated channels (pathways for movement of ions between inside and outside of the neurons), 2) Amount of calcium ion in the neurons (which is a necessary stage for release of neurotransmitter), 3) Diffusion of neurotransmitter between two neurons and 4) Opening of ion channels in response to released neurotransmitter in the destination neuron. Additional noise sources in the PD are: decreased uptake of Dopamine in synapses of striatum and a phenomenon called up-regulation which is the increment of Dopamine receptors in striatum, following a decrease in Dopamine release level. Furthermore, because of substantia nigra destruction, the Dopamine diffusion is higher in the PD.

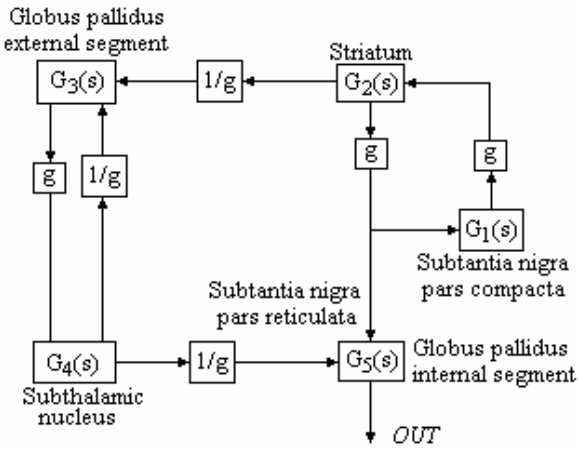

Fig. 3. Block diagram of the model.

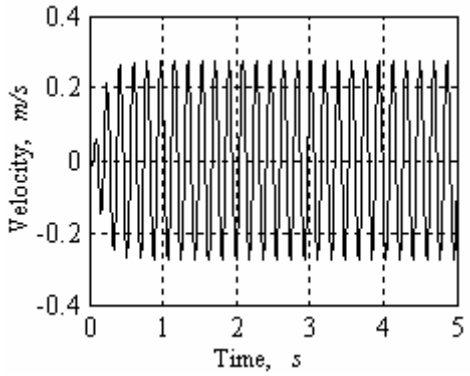

Fig. 4. Response of the model for $g = 10$.

Considering the above mentioned sources of noise in the model, modifies the primary model and makes it more realistic. Because of the nature of noise sources, they are considered in the related sites, i.e. connections. Since the noises show up with higher effects in the PD, we have considered the dependence of noise to parameter g and replaced it in the primary model by $g(1+an(t))$. $n(t)$ is a white noise having mean of 0 and variance of 1. a is a free parameter to model the differences among patients.

Power spectra are used to compare clinical and simulated data. Power spectra of non-noisy response are depicted in Fig. 5. Noisy response is shown in Fig. 6. As it is apparent, the width of the spectra in noisy state is wider than the non-noisy state, just like the clinical data. The power spectra of such a clinical data are depicted in Fig. 7.

Some clinical recordings show frequency contents besides the peak frequency. So, another noise source must be considered just near the output of the model, which simulates noises from sources other than the BG (as muscles dynamics and the transmission pathway). A white noise is passed through a low pass filter which corresponds to muscles dynamics. The final response of the model is as follows.

$$OUTo(s) = OUT(s) + b \times g \times G_{lp}(s) \times n(s) \qquad (6)$$

$$G_{lp}(s) = \frac{50}{s+50} \qquad (7)$$

3. MODELING THE TREATMENT

3.1 Drug modeling

According to clinical findings, drug affects *10 - 15* minutes after the prescription (Hacisalihzade, *et al.*, 1989). Then the PD disorders start to decrease and reach to its minimum state. Nearly after $2-2.5$ hours, the drug effects begin to reduce. Finally after 4 hours, all drug effects are disappeared. We consider behavior of the drug as a system with two parts: For the first part, dose of the drug is the input and plasma level of Levodopa is the output. This part can be modelled as a second order system with the following transfer function (Hacisalihzade, et al., 1989).

$$G(s) = \frac{ke^{-Ts}}{(1+sT_1)(1+sT_2)} \qquad (8)$$

Where k denotes amplification factor, T_1 and T_2 are time constants in hours, s denotes the complex frequency and T is the delay time. Fig. 8 indicates plasma level of the drug and simulated results of the model (Eq. 8).

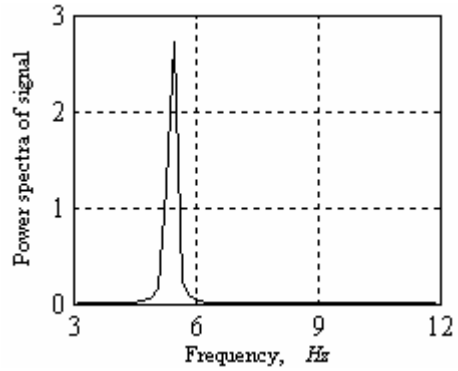

Fig. 5. Power spectra of the non-noisy response.

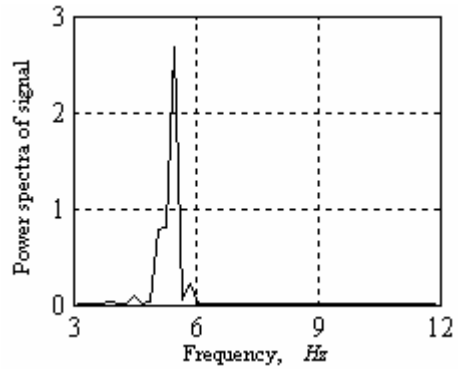

Fig. 6. Power spectra of the noisy response $a = 0.2$.

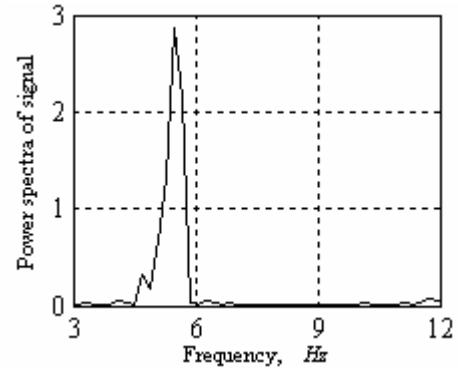

Fig. 7. Power spectra of the clinical data.

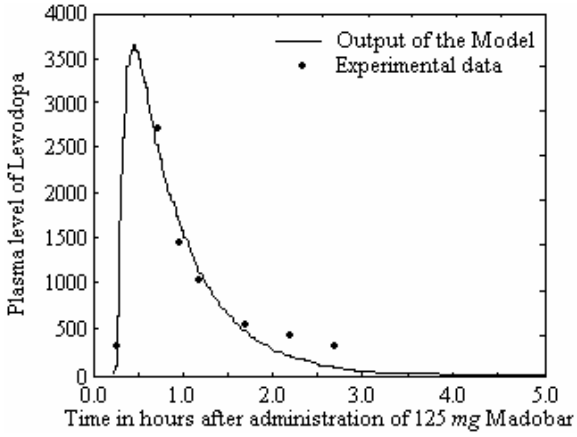

Fig. 8. Drug concentration.

The parameters of the model are estimated using the least square approach and are given as (Hacisalihzade, *et al.*, 1989).

$$k = 1418 \quad T_1 = 0.05473 \quad T_2 = 0.6073 \quad T = 0.2461$$

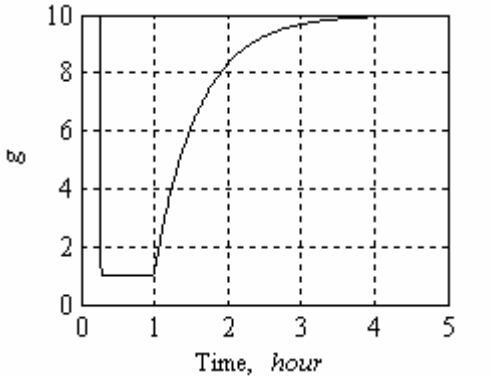

Fig. 9. Variation of g due to the drug prescription.

For the second part, input is the drug concentration in the blood and output is the gain that represents Dopamine changes (g). We divide the second part into two segments: A linear dynamic and a nonlinear relation. We assume that for drug concentration over 1500 , regardless of its exact value, the tremor is suppressed completely. So, the nonlinear part is a saturation element acts on 1500 . The linear part represents relation between the plasma level and the parameter g and is given as follow.

$$G(s) = \frac{0.1}{s + 0.1} \tag{9}$$

Fig. 9 shows the impulse response of the medication on the tremor. As it is stated before there is a reverse relation between the gain parameter g and the level of Dopamine in the BG. We now exert the equivalent g (that represents the drug prescription) on the main model of the tremor in Fig. 3. The tremor behaviour after drug prescription is depicted in Fig. 10.

3.2 Modeling of deep brain stimulation

In general, the amplitude of stimulation voltage is nearly $3v$, pulse width is almost $90\,\mu s$ and the exerted frequency is greater than $100\,Hz$. It seems that DBS causes change in Dopamine content of brain, which in turn affects the tremor amplitude directly. We assume that the parameter g is controlled by DBS. It is supposed that each DBS pulse releases a quantal amount δ of substance z which is died with a time constant t_c . τ is DBS period and we have $f = 1/\tau$.

Let's assume g_0 as the initial value of parameter g . For $g_0 = 10$, our model produces an oscillating response like the tremor of PD. We relate the parameter g to amount of the substance *z* as follows.

$$g(t) = g_0 - z(t) \tag{10}$$

After some mathematical manipulation (Haeri, et al., 2004), the following relation is obtained for *g*.

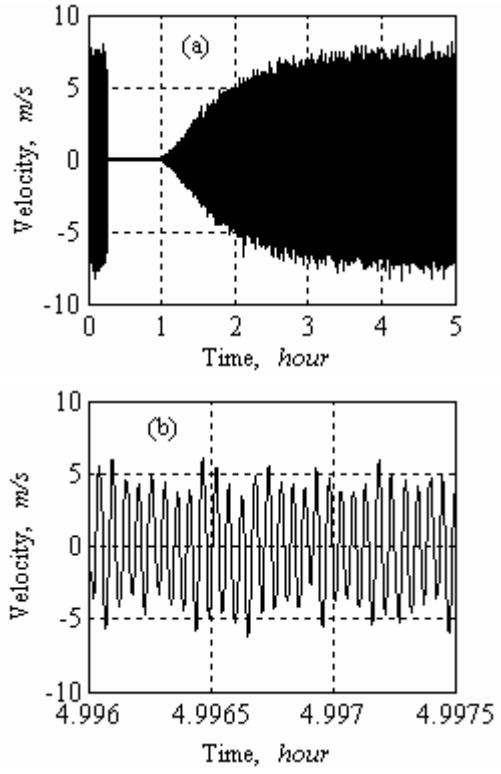

Fig. 10. The tremor behaviour under drug medication. a) Whole time scale, b) Short time scale.

$$g(t) = g_0 - \frac{\delta(e^{-1/t_c} - 1)}{1 - e^{-1/t_c}} \tag{11}$$

It should be noted that frequency of DBS, as well as its amplitude, can be changed for regulation. We suppose that the amplitude changes are represented by increase or decrease in δ (Limousin, *et al.*, 1998).

Now we consider effect of DBS on the main model of Fig. 3. δ is supposed to be 1. Frequency of DBS is considered $125\,Hz$. In order to model different behaviors of patients, t_c is adjust in accordance. Considering the acceptable range of g (1 to 10), in order to obtain g equal to 1, t_c is chosen 0.076. Larger t_c results in smaller steady state g . Since the non-positive values of g are not defined in the model (and have no physical interpretation either) the final value of g should not be 0 or negative.

In Fig. 11, 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 rapidly and reaches 1 in steady state. After stoppage of stimuli, g increases again and approaches to its initial value of 10. Changes on g are applied to the PD model and the given response is depicted in Fig. 12.

As it is stated before t_c represents different patient behaviour, therefore effectiveness of DBS can be modelled by this parameter. For example, if $t_c = 0.05$, the patient will not benefit from this particular DBS. In this case, the tremor amplitude is

decreased, but not suppressed enough. Variation of g and the corresponding model response for $t_c = 0.05$ are given in Figs. 13 and 14 respectively.

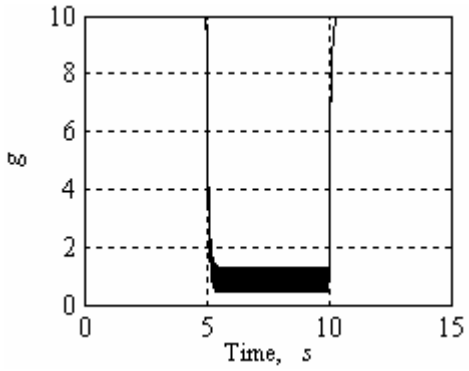

Fig. 11. Variations of g due to DBS exertion, $t_c = 0.076$.

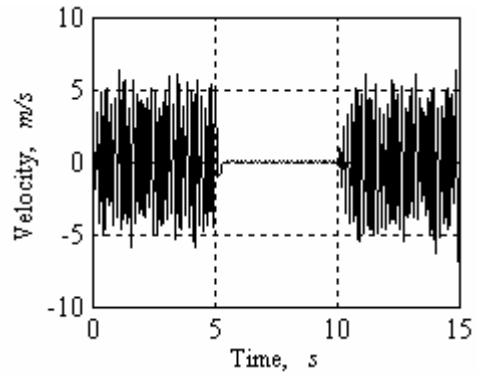

Fig. 12. Response of the model to DBS exertion, $t_c = 0.076$.

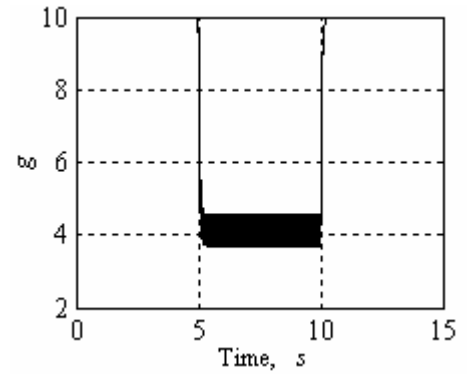

Fig. 13. Variations of g due to DBS exertion, $t_c = 0.05$

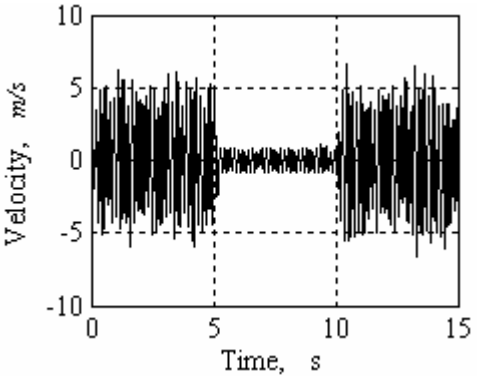

Fig. 14. Response of the model to DBS exertion, $t_c = 0.05$.

4. OPTIMIZATION OF LEVODOPA USAGE

Use of Levodopa causes side effects in patients. Furthermore, chronic prescription of drug reduces its therapeutic advantages as time goes on and therefore requires increasing amounts of the drug prescription. Decrease in amounts of the drug usage in the primary stages of the disease postpones onset of side effects.

Usually the drug dose and usage time are determined by trial and error, which obviously is not necessarily the optimal choice. In next lines we explain how the drug dose and prescription time can be optimized based on the mathematical model which was developed in the pervious sections.

4.1 Defining a cost function for optimal drug usage

Drug usage has two parameters: dose and time of prescription. These two are considered as parameters of the cost function. Decrement in the dose and increment in the time interval between successive prescriptions are desired. The cost function is considered as:

$$F(\delta, T) = b \times \delta + \frac{c}{T} \qquad (12)$$

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

4.2 Relation between drug dose and time of prescription

The relation between the drug prescription dose and the plasma level of the drug is given by a second order system with time delay (Eq. 8). As we know, the plasma level 1500 or higher can effectively suppress the signs of the disease including the tremor. So, we have regulated the time of prescriptions in a manner that just before reaching the concentration of 1500 causes by the pervious prescription, the effect of the next dose is initiated. If an impulse with amplitude of δ is implemented, the time response of the system will be:

$$y(t) = 40.89 \times \delta(e^{-1.6466(t-0.2461)} - e^{-18.2715(t-0.2461)}) \qquad (13)$$

The main constraint will be obtained by considering the critical concentration of 1500:

$$1500 = 40.89 \times \delta(e^{-1.6466(T-0.2461)} - e^{-18.2715(T-0.2461)}) \qquad (14)$$

Where T is the time between consecutive drug prescriptions and δ is the drug dose in each prescription. Another relation between these two parameters is imposed by the maximum daily allowable dose which is 2500 *mg*, so:

$$\frac{24}{T} \times \delta \le 2500 \qquad (15)$$

4.3 Optimization

We have simplified the formulas by determining following two variables:

$$x_1 = \delta,\ x_2 = \frac{1}{T - 0.2461} \tag{16}$$

The cost function is rewritten as:

$$F(x_1, x_2) = a \times x_1 + b \times x_2 \tag{17}$$

And the constraints are:

$$1500 - 40.89 \times x_1 (e^{(-1.6466/x_2)} - e^{(-18.2715/x_2)}) = 0 \tag{18}$$

$$2500 - 24 \times x_1 \times x_2 + 615.25 \times x_2 \geq 0 \tag{19}$$

Since the prescription time and dose of the drug are both of similar important, we considered equal weights ($a = b$) for two parameters x_1 and x_2. The optimization problem was solved using Lagrange method in MATLAB software. The solution is given as follows:

$$x_1 = 58.613,\ x_2 = 2.7977$$

Returning to the main parameters, we have:

$$\delta = 58.613,\ T = 0.6035$$

These amounts will suppress the tremor completely.

5. DISCUSSION

In this study, a complete model was presented to emulate the tremor behaviour of the PD. In addition to a fairly accurate modelling of the effect of Dopamine as the main cause of the disease, the proposed model has simulated the behaviour of different parts in BG well enough. For each part of the BG, the number of inputs and outputs are included exactly and in addition, the inhibitory and excitatory effects are considered and modelled as it is. Finally the differences of strength of connection at health and illness states were considered as well. We also tried to include the noisy and nonlinear behaviour of the tremor observed in clinical recordings. Comparing power spectra, we concluded that the model response and clinical data are fairly similar.

The effects of two main therapeutic approaches of the PD were also considered precisely. Finally, an optimization method was offered in order to decrease side effects of the drug. 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.

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