

Optimizing Voltage Parameter of Deep Brain Stimulation for Parkinsonian Patients by Modeling

M. Sadeghi, A.H. Jafari, and S.M.P. Firoozabadi

Abstract—Deep Brain Stimulation or DBS is the second solution for Parkinson's Disease. Its three parameters are: frequency, pulse width and voltage. They must be optimized to achieve successful treatment. Nowadays it is done clinically by neurologists and there is not certain numerical method to detect them. The aim of this research is to introduce simulation and modeling of Parkinson's Disease treatment as a computational procedure to select optimum voltage. We recorded finger tremor signals of some Parkinsonian patients under DBS treatment at constant frequency and pulse width but variable voltages; then, we adapted a new model to fit these data. The optimum voltages obtained by data fitting results were the same as neurologists' commented voltages, which means modeling can be used as an engineering method to select optimum stimulation voltages.

Keywords—modeling, Deep Brain Stimulation, Parkinson's disease, tremor.

I. INTRODUCTION

PARKINSON'S Disease (PD) is the second most common neural system disorder that is usually seen in old people [1]. Dopamine neurotransmitter is released in Basal Ganglia (BG) of the brain. It controls the movements and to some extent trains them [2]. So its reduction could cause Parkinson's Disease [3]. Some symptom of this disease are hyperkinesia, bradykinesia, akinesia and tremor [4]-[5]. We can call tremor the most important symptom which results in a rhythmic oscillation with a frequency of 4-6 Hz [6]. The first treatment of PD is drug treatment [7] by prescribing Levodopa, a combination of dopamine [8]. Levodopa releases this neurotransmitter in the brain and causes decrement of symptoms like tremor [9].

Unfortunately brain cells become resistant to this substance by passing the time and treatment fails, subsequently Deep Brain Stimulation (DBS) becomes the next solution to PD treatment [6].

DBS is electrical stimulation with high frequency by implanting electrodes at selected areas of the brain depending

on symptoms. Stimulation pulses are generated by pulse generator which is planted under Clavicle bone [4]. In 1968's, for the first time electrical stimulation of BG was used to treat the tremor. In 1980's, thalamus was a new target to stimulate; also, in 1994's, bilateral stimulation of SubThalamic Nucleus (STN) was done for treatment of tremor.

After a while other disorders were treated by this method; for example, epilepsy, depression and obsession [10].

Stimulation parameters are frequency, pulse width and voltage [11]-[12]. There is no any certain and accurate way to optimize these parameters and to regulate them and it is just done by a process of trial and error, which leads to a high cost, patient's inconvenience and time wasting problems. The characteristics of these parameters are degree of freedom, unknown effects and complicated responses [11].

Although there are some hypotheses to explain it, accurate mechanism of DBS with high frequency is unknown yet. Assuming that Parkinsonian tremor is abnormal oscillation in some regions of the brain, DBS might act to block or interfere with the transmission of oscillatory activity to the motor neurons, or it may act to desynchronize these oscillators. Alternative hypothesis is that DBS might lead to changes in system parameters, and this in turn would lead to a Hopf bifurcation in the dynamics, so the abnormal limit cycle associated with the tremor would be destabilized. This change in system parameters could be related to a gradual change in network properties generating the tremor [13]-[14]-[15].

There are a lot of simulations for PD. Most of them are conceptual and depended on personal comprehension, and a few of them are computational. Some of them are Asai model focusing on patients pedaling, Fokomoto model for parkinsonian tremor, Fernandez model for dyskinesia, and Edward model based on neural network. There are, also, some simulations for PD treatments; for instance, Haciasalihzade's model for drug treatment and Titcombe model for DBS [6].

The aim of this research is to fit parkinsonian patient's tremor under DBS into adapted Titcombe model and to obtain optimum voltage by applying fitting results. In fact, our model is a new method to recognize optimum voltage.

II. MATERIALS AND METHODS

A. Titcombe Model

Titcombe studied DBS mechanisms on parkinsonian tremor by studying its dynamic during the onset and offset of high

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frequency DBS. He recorded rest tremor velocity in four subjects with Parkinson's Disease throughout switching the DBS on(at an effective frequency) and off.

As it is said in Introduction section, there are different hypotheses about DBS mechanism. In Titcombe model it is supposed that DBS leads to a change in system parameters and in turn this leads to a Hopf bifurcation in the dynamics. Consequently, the abnormal limit cycle associated with the tremor becomes unstable.

To illustrate the properties of the Hopf bifurcation, he presented a mathematical model of a three-unit network with negative feedback.

$$\frac{dy}{dt} = f(y; g, \theta) + \zeta \tag{6}$$

Where $\zeta=0.02$ * (normally distributed random noise). Given an initial value, y_0 , and the value of the exponent g , he solved the system of three ordinary differential equation in (1) and (2) for y . Fig. 1 and Fig. 2 shows $\bar{g} = \frac{g}{g_0}$ for two values of the time constant: $t_c=0.16$ (sec) and $t_c=0.08$ (sec) respectively, whereas $f=125$ (Hz) and $\delta=6/30$ when stimulation is on and off.

$$\frac{dy_1}{dt} = f_I(y_3) - y_1, \quad \frac{dy_i}{dt} = f_E(y_i - 1) - y_i, \quad i = 2,3 \tag{1}$$

This network exhibits feedback inhibition in which y_1 excites y_2 , y_2 excites y_3 and y_3 inhibits y_1 . Here $f_I(y)$ and $f_E(y)$ are inhibitory and excitatory response functions respectively. Titcombe used Hill functions to represent the response of the units:

$$f_I(y) = \frac{\theta^g}{y^g + \theta^g}, \quad f_E(y) = \frac{y^g}{y^g + \theta^g}, \quad \theta = 0.5 \tag{2}$$

Where the exponent g controls the slope (gain) of the response θ is units' threshold. Hopf bifurcation would be induced by gain increasing. The network in (1) and (2) exhibits a Hopf bifurcation at $g_c=4$. For $g < g_c=4$ solution has a stable fixed point, which means suppression of tremor whereas for $g > g_c=4$ it has a stable limit cycle which indicates tremor and illness. Titcombe suggested (3) for $g(t)$:

$$g(t) = g_0 - z(t) \tag{3}$$

Where $z(t)$ expresses the deviation due to stimulation of the response, g , from its baseline value, g_0 , without stimulation. He assumed that $g_0=6$ and (4) for $z(t)$ when stimulation is on:

$$z(t) = \frac{\delta(e^{-t/t_c} - 1)}{1 - e^{1/f t_c}} \tag{4}$$

And (5) for $z(t)$ when stimulation is off:

$$\frac{dz}{dt} = \frac{-1}{t_c} z \tag{5}$$

Where δ and f are stimulation parameters, also, t_c and the response, g , are network parameters. He included additive noise to system:

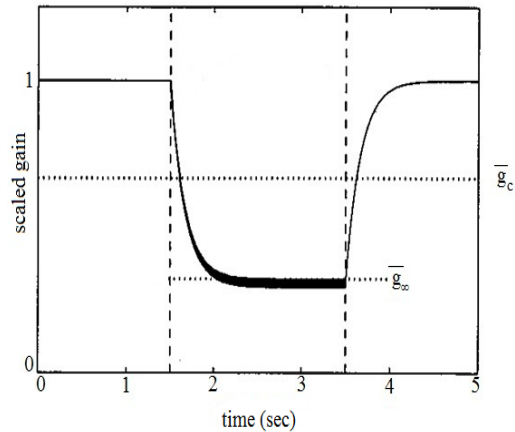


Fig. 1 scaled gain related to $t_c = 0.16$ (sec)

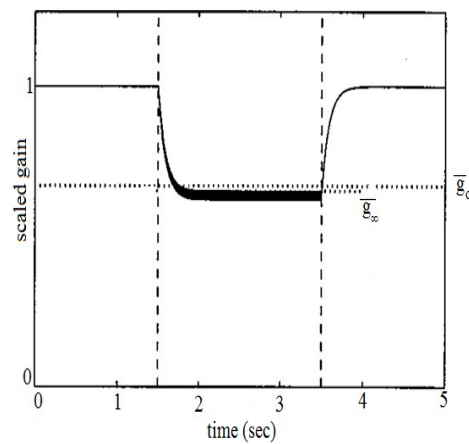


Fig. 2 scaled gain related to $t_c = 0.08$ (sec)

Fig. 3 and Fig. 4 shows the solution of y_1 , in (1) and (2), as the parameter \bar{g} varies.

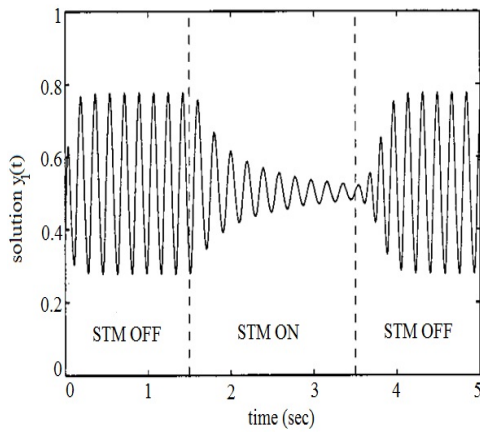


Fig. 3 solution $y_1(t)$ related to $t_c = 0.16$ (sec)

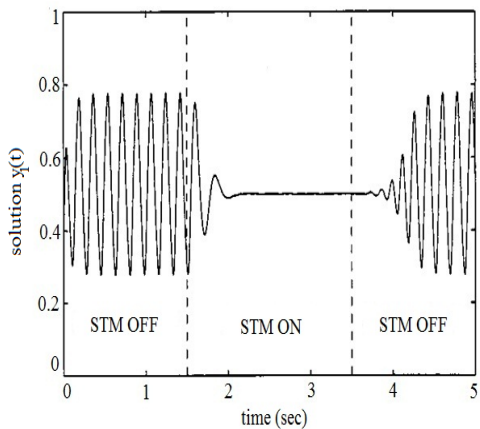


Fig. 4 solution $y_1(t)$ related to $t_c = 0.16$ (sec)

When stimulation is off, \bar{g} is 1 and y_1 is oscillatory, which simulates tremor. During the stimulation scaled gain value, \bar{g} , decrease and after crossing the \bar{g}_c reaches the stable scaled gain, \bar{g}_∞ :

$$\bar{g}_\infty = 1 - \frac{\delta}{1 - e^{1/f t_c}} \quad (7)$$

Therefore oscillation amplitude of y_1 response decreases, which means tremor has suppressed and treatment has happened. The deviation of \bar{g} from \bar{g}_c in $t_c = 0.16$ (sec) is more than the deviation of \bar{g} from \bar{g}_c in $t_c = 0.08$ (sec) and \bar{g}_∞ in $t_c = 0.16$ (sec) is less consequently, so treatment amplitude damps fast and becomes a constant value that shows treatment [13].

B. Adapting Titcombe Model

As it is said Titcombe Model is about DBS mechanisms that occur in high frequency. He recorded tremor data of 4 patients

throughout switching the DBS on and off while the stimulation parameters were fixed on optimum values. In our research tremor signal was recorded 3 or 4 times for every patient. During all recordings of a patient frequency, and pulse width were constant, but we changed the voltage after every recording. Titcombe model is dependent on just frequency, so it was necessary to adapt it in a way that it includes voltage in order to fit our data. He used three-unit network model whose parameters were t_c and g_0 . Stimulation parameters were f and δ where δ was pulse width stimulation amplitude and f was stimulation frequency. In our research, it was assumed that $\delta = k * v$ so (4) in Titcombe model changed to:

$$z(t) = \frac{k * v(e^{-t/t_c} - 1)}{1 - e^{1/f t_c}} \quad (8)$$

So (3) became:

$$g(t) = g_0 - \frac{k * v(e^{-t/t_c} - 1)}{1 - e^{1/f t_c}} \quad (9)$$

In next sections our recording protocol and filtering methods are explained; then, new fitting method and adapted stimulating model parameters are expressed.

C. Data Recording

In this research, nine patients' fingers tremor signals who were under DBS were recorded. The signals were recorded without any medicine consumption. Instruments used for this recording included: two piezoelectric accelerometers model 4375, four-channel Amplifier with filtering, A/D card, and a computer.

In order to obtain the tremor signal along with the finger and perpendicular to the finger, two accelerometers were fixed on two shafts. The shafts were perpendicular to each other. Signals were recorded from that side of body which had started tremor first, also thumb or index fingers were selected depending on which finger had more tremor, and the shafts were fixed on them.

Every patient sat on a chair and his/her hand got fixed on the chair arm in a way that patient's wrist was free. After tremor signal was measured by the accelerometers, it was amplified, and transmitted to an A/D terminal, and saved in a computer by Labview8 software.

Tremor signal was recorded 3 or 4 times for every patient. Frequency and pulse width in all the recordings of one patient were constant and determined by neurologist, whereas voltage was varied after every recording of a patient. One of the voltages was optimal voltage which had been determined by neurologist before that.

D. Data Filtering

After obtaining data, it was filtered in several stages, such as;

1) By using a lowpass filter designed in the amplifier, frequencies higher than 15 (Hz) were filtered while recording.

2) A fourth order Butterworth filter was designed and used while saving data by Labview8 software, and frequencies over 10 (Hz) were filtered.

3) Since the frequencies of parkinsonian patients tremors are between 4 and 6 (Hz), an Elliptic bandpass filter designed by Matlab2007 software was used to filter frequencies lower than 0.5 (Hz) and upper than 8 (Hz).

4) Basic frequency of each data passed through above filters was determined by fft; finally, they were passed through bandpass Elliptic filter around discovered basic frequency. By this procedure we obtained single frequency signals.

E. Fitting Data into Adapted Model

Every recording lasts for 50 seconds with 0.001 sampling frequency. For fitting, (1), (2), (9) were simulated using simulink of Matlab 2007 software. v and f variables in the above equations were assumed stimulation voltage and frequency of every recording of patients. Initial values of t_c and k were assumed 0.16 (sec), - 0.01 respectively to make y_1 response oscillatory.

Output of the adapted model was single frequency. In order to fit data signals into our model, their basic frequencies were obtained by fft and as it is said in filtering section we turned them into single frequency signals. Fitting was done in every 5000 samples of signals by error back propagation method; then, the best values of k and t_c for fitting the signals to our new model were obtained by their training. The main goal of this fitting was determining the value of g at the end of fitting in every boundary. Since every recording of a patient included 10 fitting boundaries with one constant voltage, average value of g (g_{ave}) related to this voltage could be calculated by averaging obtained values of g in all 10 boundaries of a recording.

III. RESULTS

In Fig (5) tremor signal curve of patient number 1 and its model response before fitting are shown with continuous line and dot line respectively. These curves are related to 35-40 seconds of recording at 175 (Hz) frequency, 60 (μ s) pulse width and 2.4 (v) voltage. Related curves after fitting are shown in Fig. (6). Performance index of error which is deviation of signal from model is plotted at Fig. (7).

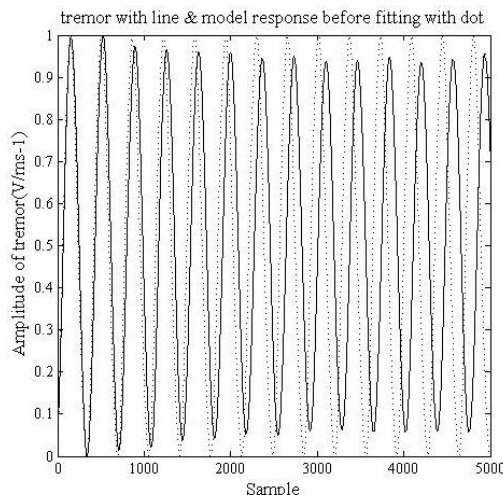


Fig. 5 tremor signal and output of model before fitting

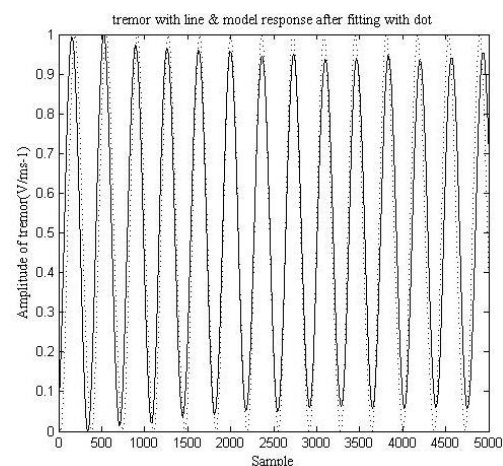


Fig. 6 tremor signal and output of model after fitting

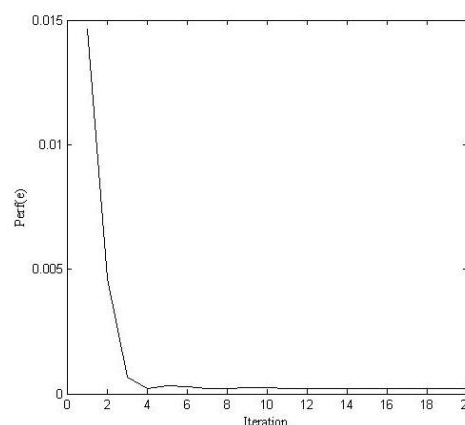


Fig. 7 performance index of error

All figures show brilliant fitting with negligible deviation. Bar diagram of all g values related to fitting boundaries of patient 1 for every recording voltage are plotted at Figs. (8), (9), (10) and bar diagram of g_{ave} of each voltage of that patient is plotted at Fig. (11).

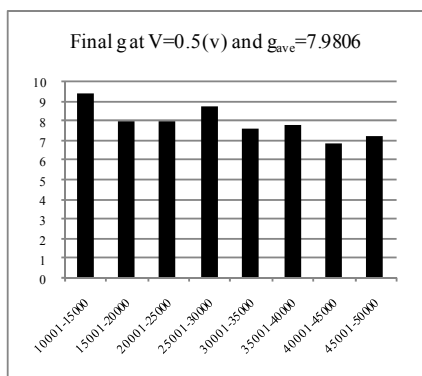


Fig. 8 Bar diagram of all g values of patient (1) at $V=0.5(v)$

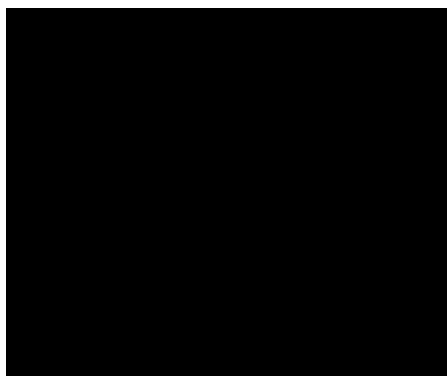


Fig. 9 Bar diagram of all g values of patient (1) at $V=1(v)$

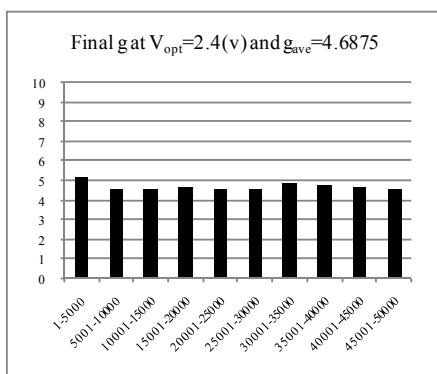


Fig. 10 Bar diagram of all g values of patient (1) at $V_{opt}=2.4(v)$

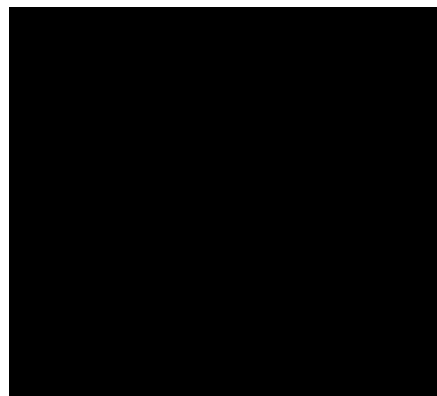


Fig. 11 Bar diagram of g_{ave} values of patient (1) at all Voltages

The best stimulation voltage according to neurologist comment was 2.4(v) for this patient. As it is said if $g < g_c = 4$, model will have a fixed point, which means suppression of tremor and treatment. Fig. (11) indicates the least g is related to 2.4(v) which was neurologist recommended voltage too; therefore, results of modeling and data fitting into that model is equivalent to clinical diagnosis. In other word, selected voltage for fitting data into our model was compatible to selected voltage by neurologist, which shows accuracy of our new adapted model and its possible ability or potential to be used as a new computational method in selecting optimum voltage of stimulation.

IV. CONCLUSION

Parkinson’s Disease is the second most common neural system disorder that is usually seen in old people. Deep Brain Stimulation or DBS is a surgical treatment for Parkinson's Disease with three parameters: frequency, pulse width and voltage. There is no certain way for optimizing these parameters and regulating them, and it is just done by a process of trial and error, which leads to high cost, patient’s inconvenience and time wasting problems. Although there are some hypotheses to explain it, accurate mechanism of DBS with high frequency is unknown yet. The aim of this research is to introduce simulation and modeling as a computational way to select optimum voltage. There are a lot of simulations for PD. Most of them are conceptual and depended on personal comprehension, and a few of them are computational. There are, also, some simulations for PD treatments; for instance Titcombe model for DBS. We adapted Titcombe model to fit our data into it. The recognized optimum voltage obtained by data fitting to our new model was matched to neurologists recommended voltages, which means modeling can be used as an engineering method to select optimum stimulation voltage.

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