Deep Brain Stimulation for Parkinson's Disease

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***Abstract*— Deep brain stimulation (DBS) has been applied to address symptoms associated with various brain disorders, particularly movement disorders like Parkinson's disease (PD). Although DBS results in symptom improvement for many patients, the precise mechanisms behind this improvement remain unclear. Computational modeling has played a crucial role in advancing our understanding in this area. The loop between two major nuclei, the Subthalamic Nucleus (STN) and Globus Pallidus Pars Externa (GPe), emerges as a significant coupled excitatory-inhibitory (E-I) system within the basal ganglia (BG) network. In the context of PD, heightened neural synchronization and coherence have been observed in both STN and GPe. Moreover, Parkinsonian symptoms have been alleviated through deep brain stimulation at both these sites.**

Keywords— DBS, PD, STN, GPe, closed loop system.

I. INTRODUCTION

Recently, there has been an increasing focus on the potential advantages of "closed-loop" deep brain stimulation (DBS). In this closed loop system, the patient's clinical condition is measured and employed to adjust stimulation parameters as needed. This approach ensures the delivery of the necessary stimulation to minimize disease symptoms, thereby minimizing potential side effects induced by stimulation while effectively managing symptoms. Currently, the key target for DBS in PD is the STN.

Utilizing an existing study, we will propose a new model that will focus on the STN and GPe pathway, which will demonstrate oscillations and dynamics of our closed loop network. This model will allow us to understand the alterations in brain activity triggered by DBS, and optimize this for clinical therapy use, especially in terms of selecting targets and setting parameters.

II. PARKINSON'S

Parkinson's disease is a neurological condition characterized by involuntary or uncontrolled movements, including tremors, rigidity, and challenges in maintaining balance and coordination.

The main cause of Parkinson's disease is when neurons in the basal ganglia (the part of the brain that controls movement) suffer from impairment or death. These neurons generate dopamine, a crucial neurotransmitter. So, when the neurons die, dopamine production is reduced, which leads to movement problems.[1]

Although there is no cure for Parkinson's disease, medicines, surgical treatment, and other therapies can often relieve some symptoms. And the one we will be discussing today is called Deep Brain Stimulation (DBS).

A. DBS Device Stimulator

DBS is a neurosurgical procedure where high-frequency pulse trains are supplied via an implanted pulse generator and injected into widely used portions of the BG network.

In the surgical procedure, electrodes are inserted into the brain and are connected to an electrical device that is implanted in the chest. This system stimulates designated areas in the brain responsible for movement, potentially alleviating numerous Parkinson's-related symptoms like tremors, slowed movement, and stiffness.

In this approach, four major nuclei (STN, GPe, GPi, and TH) that receive information are linked together by excitatory and inhibitory synaptic connections to create the BG network. [2] We will be modeling the STN and GPe

pathway in our stimulation.

B. Physiological Control Loop System

The main network loop in focus is the closed interaction loop between the subthalamic nucleus (STN) and the globus pallidus pars externa (GPe), highlighted below in Figure 1 [2]. The overall thalamocortical basal ganglia network is responsible for many functions, but primarily the integration of information from cortical areas into outputs that are projected back to the cerebral cortex, which are then represented in motor function [3].

The pathway linking the cortex to the STN, serving as the input to the STN-GPe loop in focus, is characterized in Parkinson's patients through burst activity and high firing rates of beta-band oscillations, which are the cause for hyperactivity in cerebellar cortex output movements [3]. This is why DBS stimulation at this point is thought to be able to improve motor learning on Parkinson's patients, where stimulation is able to suppress large spikes in unwanted motor activity, which are usually associated with severe disabling tremors [4]. More specifically, the repeated stimulation of the neurons of GPe result in decreased excitation of other components of the thalamocortical basal ganglia network and decreased movement overall, which would denote improved symptoms of parkinsonian motor function [4].

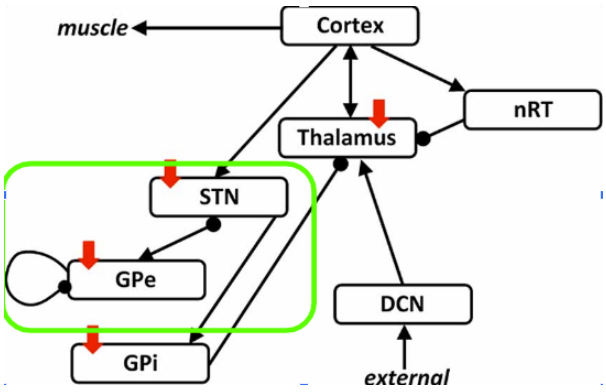

Figure 1. Fleming, John E., et al. *The thalamocortical basal ganglia network* [Online image]. Frontiers. https://www.frontiersin.org/articles/10.3389/fnhum.2020.00055/full.

The STN serves as the main target nucleus for DBS because all parkinsonian symptoms that are typically associated with lack of dopamine can be improved by DBS specifically at the STN, as the STN is the sole excitatory nucleus of the basal ganglia [4]. The STN contains glutamatergic neurons, which increase the activity of the globus pallidus, which in turn, decrease the activity of the thalamus and inhibit movement; this means that the STN helps in preventing unwanted movements by increasing its glutaminergic output to the GPe [6].

This subsection of the overall DBS network shown in the figure is the major coupled excitatory-inhibitory (E-I) loop inside the basal ganglia, thought to be responsible for Parkinsonian motor activity [7]. These excitatory-inhibitory properties of the STN-GPe network generate aberrant beta-band oscillations responsible for Parkinson's disease, and they range between about ~13-30 Hz, where suppression of these oscillations through DBS are shown suppress akinesia, tremors, and similar symptoms of Parkinson's 2]. Evidence shows that low-frequency activity in the subthalamic nucleus is correlated to parkinsonian motor deficit, where more severe symptoms arise from STN beta band oscillations with strong and sustained activity in β-frequencies [2]. These can be modeled and numerically represented to show activity amongst various levels of interaction within both the overall thalamocortical basal ganglia network as well as the specific STN-GPe loop.

III. SIMULATION

A. Derivation

Based on the study conducted by Wilson and Cowan, t equations are under the assumption that neurons within a population are in close spatial proximity, and therefore represent temporal dynamics.This also assumes that all nervous processes are dependent upon the interaction of excitatory and inhibitory cells, thus: E(t) = proportion of excitatory cells firing per unit time at the instant t; I(t)= proportion of inhibitory cells firing per unit time at the instant t [8].

For the rest of the derivation, it will show the equations of excitatory cells which can be substituted for the other. By assumption that the value of these functions at time (t + τ), will be equal to the proportion of cells which are sensitive an equation can be found. This then gives the independent expressions for the proportion of sensitive cells and for the proportion of cells receiving at least threshold excitation [8]. If the absolute refractory period has a duration of τ msec, then the proportion of sensitive cells in the subpopulation will equal;

$$1 - \int_{t-\tau}^{\tau} E(t')\, dt' \quad (1)$$

Within this subpopulation is another subpopulation of an impulse response which gives the expected proportion of cells in a subpopulation which would respond to a given level of excitation if none of them were initially in the absolute refractory state. Thus is derived based on the assumption that there is a distribution of individual neural thresholds within the subpopulation, denoted by the distribution function D(θ) [8]. If all cells in the subpopulation receive the same numbers of excitatory and

inhibitory afferents, then the average excitation level experienced by all cells in the subpopulation is denoted as x(t). The impulse response of this subpopulation is then given as

$$\delta(x) = \int_0^{x(t)} D(\Theta)\, d\theta \quad (2)$$

Using this equation, to determine the average level of excitation within a cell of each subpopulation, an expression needs to be derived. Assuming that individual cells sum their inputs and that the effect of stimulation decays with a time course α(t), the average level of excitation generated in an excitatory cell at time t can be expressed as

$$\int_{-\infty}^{t} \alpha(t - t')\,[c1E(t') - c2I(t') + P(t')]\, dt \quad (3)$$

In this $\alpha(t - t')$ represents decay of the simulation over time, c1 and c2 are the average number of excitatory and inhibitory synapses per cell, and P(t) is the external input to the excitatory population. With these three equations, we are then able to put together the final equation considering that the likelihood of a cell being sensitive is unrelated to its probability of being currently excited above its threshold. The equation being:

$$E(t - \tau) = [1 - \int_{t-\tau}^{\tau} E(t')\, dt'\,] * [\,\delta($$

$$(\int_{-\infty}^{t} \alpha(t - t')\,[c1E(t') - c2I(t') + P(t')]\, dt\,))] \quad (4)$$

To then obtain the coarse-grained forms of these equations, the integrals are replaced with coarse-grained variables, r and k respectively. Using Taylor expansions, to replace the left side $E(t - \tau)$, the final equations for the dynamics of the excitatory subpopulation is shown where the inhibitory population can be written as the same:

$$\tau \frac{dE}{dt} = -E + (k - rE)\delta(c1E - c2I + P) \quad (5)$$

B. Mathematical Representation

As we are only dealing with a certain aspect of this model, we used equations only related to our region of interest, the STN and the GPe. Using the derivations, the following equations represent the change of population in respect to time for the GPe and STN [5].

$$\tau_{GPE} \frac{dI_{GPE}}{dt} = -I_{GPE} + (k_i - I_{GPE}) * Z_i(w_7 E_{STN} - w_8 I_{GPE}) \quad (6)$$

$$DBS(t) = A \sum_{n=1,3,5}^{1,001} \frac{1}{n}(2\pi n f t) \quad (7)$$

$$\tau_{STN} \frac{dI_{STN}}{dt} = -E_{STN} + (k_i - E_{STN}) * Z_e(w_{10} E_{STN} - w_{11} I_{GPE} + DBS) \quad (8)$$

$$Z_p(x) = \frac{1}{1+e^{(-b_p(x-\theta_p))}} - \frac{1}{1+e^{(b_p \theta_p)}} \quad (9)$$

Equation 6 represents the inhibitory population of the GPE, displaying the rate of change or neuron populations being activated here or Tau. This equation describes the rate of change of GPE activity over time, which is influenced by the current GPE activity or I_{GPE}, and excitatory input from the STN as shown in the variable E_{STN}.

In these equations, w_i represents the strength of connection between the 2 populations using information from the previous assumption.

Zi represents the proportion of cells firing in a population for a given level of average membrane potentials. The value of Z, shown in equation 9, is derived under the assumption that the population has a distribution of neural thresholds that are equal, where b and theta are constants, found at steady state [5]

Equation 7 then represents the DBS input, assuming high frequency where A is the amplitude. This creates a square wave as the input and with this to take into account, equation 8 then has this additional term as this region is the one chosen to be stimulated by the DBS [5]. This equation describes the rate of change of STN activity over time, influenced by the current STN activity, and the excitatory input from the GPE or I_{GPE} as well as the DBS input . Additional parameters are shown below, to test out healthy vs unhealthy components.

TABLE I

Table of weights of connection between closed loop system components [5].

Connection	Weight	Tremor Band Parameters	Healthy Band Parameters
STN to GPE	w7	5	19
GPE to GPE	w8	5	5
Cx to STN	w10	20	20
GPE to STN	w11	20	20

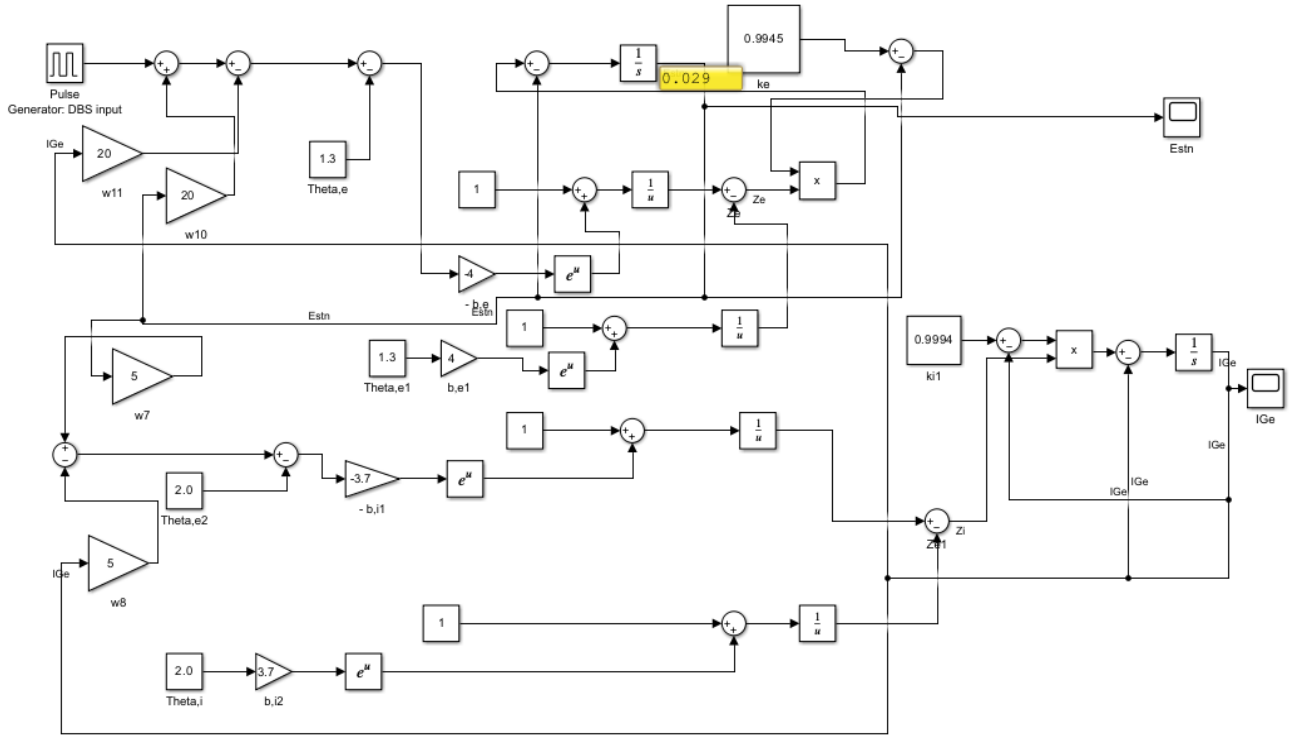

Figure 2. Simulink of IGPE & ESTN closed loop system

B. Simulink System

Using the equations derived previously, the DBS device serves as the input to the system. It is modeled as a square wave, and was added to the ESTN equation. The square wave is a good example to use as it sends periodic pulses just as a real DBS device does [5]. Additionally, one can adjust the amplitude and frequency of the square wave input just as one can with the implantable DBS device. Doctors often spend many sessions with their patients fine tuning the settings of the patients' device. The constraints for these results include that we are not modeling the entire closed loop system, which means we lose a level of complexity. However, with the DBS input being added to the STN we can still effectively observe the initial results of DBS input

C. Limitations and Constraints

By focusing on the STN and GPE, and not including the cortex or thalamus, we modeled a simplified version of the closed loop system. In reality the system is more complex. However, our model is still useful in showing the initial response of the STN after it receives input from the DBS device.

IV. RESULTS

Using the weights and frequency of 4Hz to model the tremor
band activity shown in Parkinson's patients we modeled the IGe output, representing the population of inhibitory neurons at a time and the ESTN representing the population of excitatory neurons [5].

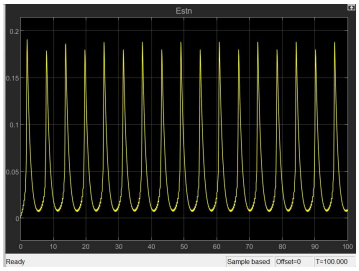

Figure 3. Simulated ESTN with DBS amp =1

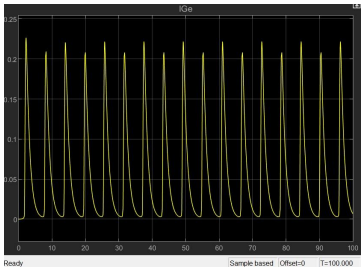

Figure 4. Simulated IGPE with DBS amp =1

At amplitude 1 ,We found an oscillatory, repeating pattern, the ESTN peaks first at 0.5 sec, next the IGPE peaks at about 1.3 seconds. This makes sense because as the previous slides showed, the initial input is the DBS to the ESTN which then feeds to the IGPE . Thus it makes sense for the ESTN to peak first, its activation causes the activation of the IGPE. Furthermore, we wanted to see how changing the DBS amplitude changes the IGPE and ESTN outputs.

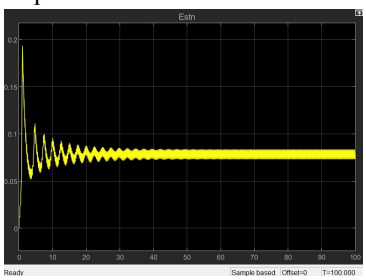

Figure 5. Simulated ESTN with DBS amp =5

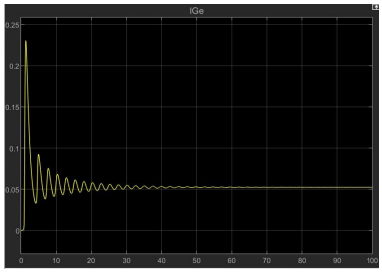

Figure 6. Simulated IGPE with DBS amp =5

As one can see, increasing the amplitude resulted in suppression of oscillations for the IGE and a suppression of amplitude but an increased frequency of oscillations for the STN, both the STN and GE had their amplitudes reduced due to the DBS input. This is similar to past studies demonstrating that DBS input serves to regulate neuronal activity.

V. DISCUSSION

A. Clinical Applications

In the past two decades, deep brain stimulation (DBS) has emerged as an effective treatment for various disorders. Due to advancements in technology and surgical techniques, ablative procedures in many cases have been replaced. In particular, stimulating the ventralis intermedius nucleus of the thalamus has proven to significantly enhance tremor control in tremors relating to Parkinson's disease [9]. Through DBS, it is observed that patients experience notable improvements in bradykinesia, tremor, gait disturbance, and rigidity. Furthermore, DBS enables a reduction in medication for patients, mitigating the disabling effects of dyskinesias, and primary dystonia responds favorably to DBS of the globus pallidus internus [10]. The success of DBS has provoked an extension of its application to various other debilitating conditions, such as neuropsychiatric disorders, intractable pain, epilepsy, camptocormia, headache, restless legs syndrome, and Alzheimer's disease.

In regards to clinical application, deep brain stimulation is commonly used as a therapeutic option of Parkinson's disease. However, it is important to state that DBS is generally considered an option specifically for patients with advanced Parkinson's disease who have not responded well to medications or who experience severe medication-related side effects. The following list includes several clinical applications of deep brain stimulation for Parkinson's disease [9]:

- Reduce motor symptoms
- Smooth out fluctuations of symptoms, providing a more consistent level of symptom control
- Manage medication-induced dyskinesias
- Reduce medication dosages
- Improve the overall quality of life
- Reduce complications with speech and swallowing
- Potentially improve cognitive function
- Long-term sustained benefits

B. Future Uses

Despite the successes and widespread adoption of deep brain stimulation, critical questions persist and new ones arise. The field of DBS for Parkinson's disease is dynamic, and ongoing research continues to explore new avenues for its use. While it's challenging to predict the future with certainty, several potential developments and future uses of DBS for Parkinson's disease are being explored.

One such area being explored is the possibility of a closed-loop system. Current DBS systems operate in an open-loop fashion, delivering stimulation continuously based on pre-programmed settings. Future developments may involve closed-loop or adaptive DBS systems that adjust stimulation parameters in real-time based on the patient's needs and fluctuations in symptoms. This could potentially optimize treatment efficacy and minimize side effects [9]. Additionally, advances in imaging technology and better understanding of the brain's circuitry may lead to more precise targeting of specific brain regions involved in Parkinson's disease. This targeted stimulation could enhance the effectiveness of DBS while minimizing the risk of adverse side effects. In regards to the improvement in telemedicine and remote monitoring technologies, it

may be possible for healthcare providers to monitor and adjust DBS settings remotely, thus improving accessibility to care, especially for patients who live in remote areas or have difficulty traveling to medical facilities. Thus, enhancing patient monitoring. Another area of active research is personalized medicine by tailoring DBS treatment to the individual characteristics of each patient, such as their specific symptoms, disease progression, and response to stimulation [9]. Finally, current DBS devices require periodic battery replacement, which involves surgery. Future development in battery technology may lead to longer-lasting, rechargeable, or potentially wireless systems that do not require an invasive procedure.

While deep brain stimulation is primarily used to treat the motor symptoms of Parkinson's disease, future application may extend to non-motor symptoms, such as cognitive impairment and psychiatric symptoms. This treatment can also be integrated with other therapeutic approaches, such as gene therapy or neuroprotective drugs. The research in these areas is ongoing, and the translation of these potential advancements into clinical applications will require rigorous testing and validation. The future of deep brain stimulation for Parkinson's disease holds great promise for further improving treatment outcomes, expanding its applications, and enhancing the overall care of patients.

VI. CONCLUSION

DBS is a very useful device with many potential applications. By breaking down the excitatory and inhibitory neuron activation in the GPE and STN one can make the system into a simplified model. Then using differential equations and simulink simulation of different frequencies and amplitudes is possible. This simulation provides useful information because DBS devices are programmed by doctor's after their implantation. By simulating the effect of different amplitudes and frequencies with simulink doctors can start off from a more accurate starting point. This means that the doctor can help a patient reach their final tuned DBS settings faster than before.

VII. REFERENCES

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