RANDOMIZED STIMULATION SIGNAL DESIGN TO CREATE PARTIAL INFORMATIONAL LESIONS IN PARKINSONIAN NEURONAL NETWORKS

Samantha R. Summerson[⋆] *Charlie Grealish* [†] *Behnaam Aazhang* [⋆] *Caleb T. Kemere* [⋆‡]

[⋆] Rice University, Houston, TX
[†] Carnegie Mellon University, Pittsburgh, PA
[‡] Baylor College of Medicine, Houston, TX

ABSTRACT

Deep brain stimulation is a treatment for Parkinson's disease that uses electrical stimulation to modulate neural activity in order to reduce motor symptoms associated with the disease. The design of the electrical stimulation signal used is strongly linked to the efficacy of such a treatment. We present computational models of the brain structures impacted by Parkinson's disease which are modulated by electrical current injections from chronically implanted electrodes as a part of deep brain stimulation. This work demonstrates that a high frequency signal with small random deviations in pulse timing can simultaneously induce regularized activity associated with improved motor symptoms and permit greater variation in neural responses, which are necessary to encode neural information.

I. INTRODUCTION

Neural activity can be artificially modulated by injecting current via implanted electrodes in the neural tissue. This is due to the fact that neurons communicate through electrical and chemical signaling, and is called *neuromodulation*. The concept of neuromodulation is the basis for a treatment of Parkinson's disease called *deep brain stimulation* (DBS). This treatment uses chronically implanted electrodes in deep brain structures to modulate the neural activity, with the goal of ameliorating the pathological neural signaling associated with the disease. DBS can help restore motor function by altering the pathological signaling which is sent to the motor cortex, which ultimately controls motor movement performed by the patient. Naturally, how restorative the treatment is depends on the design of the electrical stimulation signal used.

Typically, two conductive contacts on the implanted electrode are active and an electrical stimulation signal is transmitted between these two contacts [1]. The signal may be defined in terms of voltage or current; for this work we assume that the stimulation signal is designed in terms of the current flow between the two contacts. The standard stimulation signal is a series of constant-current bi-phasic square pulses. The pulses are short in duration, typically 50 - 200 ms per phase, have fixed amplitude, and are administered at a constant frequency [2].

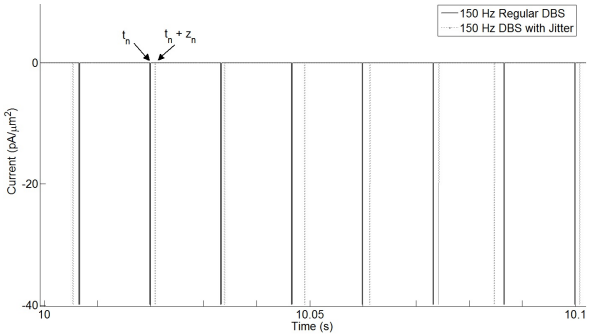

Fig. 1. Example of DBS signals used. Both signals have an average pulse frequency of 150 Hz, but the regular DBS signal has periodic pulses while the timing of pulses for the jittered signal is distorted with a small amount of noise, z. For example, the n^{th} pulse in the regular DBS signal occurs at time t_n while the n^{th} pulse in the jittered DBS signal occurs at time $t_n + z_n$.

From human and animal studies, it has been empirically found that higher frequencies stimulation signals tend to be more effective and that a mixture of changes in firing rates occur in response to therapeutic stimulation [1], [2], [6]. It has been found in computational and animal studies that with increasing frequency there is an increasing incidence of stimulus-locked firing by neurons, meaning neurons fire in response to a current pulse and thus become entrained to fire at the same rate as the stimulation signal. Although this is effective because bad information can no longer be transmitted by these entrained neurons, this "informational lesion" may also be a limiting feature of the treatment since good information cannot be transmitted by the neurons either.

To promote the mixture or variability in firing rate responses seen by the impacted brain structures in response to DBS with regular current pulses, we propose a stimulation signal with irregular timing of pulses. Previous work has found that stimulation signal with pulse times drawn from

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a gamma distribution and instantaneous pulse frequencies drawn from a log-uniform distribution were not therapeutically effective [3], [4] and suggest that regularization of neural activity is the key to the therapeutic benefit. However, recent work by [5] suggests that a partial "informational lesion", corresponding to partial entrainment and regularization of neurons, is necessary to allow low-rate encoding of behaviorally relevant information while still blocking pathological signals.

In this work, we consider adding a small amount of jitter to the timing of pulses from a DBS signal with stimulation frequency f. This design ensures that the average rate of current pulses is preserved, but timing is irregular; see Fig. 1. We hypothesis that a high stimulation rate may be required to hold the state of the neurons away from the attractor state of parkinsonian activity and that random timing of pulses will ensure that high variability of some responses is preserved, thus creating a partial lesioning effect.

II. BACKGROUND

The basal ganglia is a group of deep brain structures that are involved in regulating motor movement, among other things. This area of the brain is affected by Parkinson's disease and is the focus of this computational study. The striatum is the main input component to the basal ganglia. Its strongest output connection is to the globus pallidus externus (GPe); with Parkinson's disease, the striatal input to the GPe inhibits the neural activity more than in the healthy brain. The GPe connects to the subthalamic nucleus (STN) and the globus pallidus internus (GPi). The STN connects back to the GPe, forming a loop of activity, and is considered to be the "clock" in this system. It is for this reason that DBS electrodes are implanted in the STN. Additionally, the STN also connects to the GPi, which is the main output structure of the basal ganglia. The GPi forwards information from the basal ganglia to the thalamus. The neurons that transmit information from the thalamus to the motor cortex, where motor movements are encoded, are called thalamocortical (TC) neurons.

Connections between neurons in each brain structure are made via synapses, which are small junctions between the output end of one neuron (i.e. the presynaptic neuron) and the input end of another neuron. These connections can either be excitatory or inhibitory, which means that they promote or impede activity at the receiving neuron, respectively. Activity at a neuron is characterized by voltage spikes, which are brief, sharp increases in voltage that occur when sufficient excitation by other neurons and certain chemicals has been received. The timing and rate of these spikes carry the message the neuron wants to communicate with other neurons downstream.

III. MODEL

Conductance based biophysical models, which consist of a set of ordinary differential equations, are used to characterize the voltage potential across the membrane of the neurons over time. Four cell types are models here, one type per nucleus that is incorporated in the system model. Below the four models are described. Note that it is understood that current vary with time and a current x is denoted as I_x, which is shorthand for $I_x(t)$. All neuron models are based on previous work [7], [8], though parameter adjustments have been made so that the spiking activity of the neurons in the full network match experimental data [1], [6]. We also add noise to the model by incorporating noise currents, I_z, into the differential equations, where z is zero-mean Gaussian variable.

III-A. STN Neurons

The voltage equation for the membrane potential, v_{STN}, is

$$C_m \frac{\partial}{\partial t} V_{STN} = -I_l - I_K - I_{Na} - I_{Ca} - I_{GPe,STN} + I_{DBS} + I_z. \tag{1}$$

The leak current is denoted by I_l, while the potassium, sodium, and calcium ionic currents are denoted by I_K, I_{Na}, and I_{Ca}, respectively. Inhibitory synaptic current from GPe neurons, $I_{GPe,STN}$, is also included in the model and is a weighted sum of the inputs from all presynaptic GPe neurons. Since the STN neurons are the target of the DBS, the stimulation current, I_{DBS}, is incorporated into the voltage equation above.

III-B. GPe Neurons

The voltage equation for the membrane potential, v_{GPe}, is

$$\begin{aligned} C_m \tfrac{\partial}{\partial t} V_{GPe} = \quad & -I_l - I_K - I_{Na} - I_T - I_{Ca} \\ & -I_{STN,GPe} - I_{GPe,GPe} + I_{str,GPe} + I_z. \end{aligned} \tag{2}$$

The same nomenclature for I_l, I_K, I_{Na}, and I_{Ca} as with the STN neurons is used. The GPe neurons have an additional ionic current which is a T-type calcium current, denoted as I_T. It is assumed that there is excitatory input from STN neurons and inhibitory input from other GPe neurons, represented by $I_{STN,GPe}$ and $I_{GPe,GPe}$, respectively. Additionally, the input to the GPe neurons from the striatum is modeled as a constant current, $I_{str,GPe}$.

III-C. GPi Neurons

The GPi neurons are very similar to the GPe neurons and have the membrane potential equation

$$\begin{aligned} C_m \tfrac{\partial}{\partial t} V_{GPi} = -I_l - I_K \quad & -I_{Na} - I_T - I_{Ca} \\ & -I_{STN,GPi} + I_{app} + I_z. \end{aligned} \tag{3}$$

The same types of ionic currents are present as with the model GPe neurons. However, there is no assumed inhibitory inputs between individual neurons within the brain structure. It is also important to note that I_{app}, a constant current input, is applied in order to ensure that the intrinsic firing rate of

the GPi neurons is higher than GPe neurons, in agreement with experimental data [1].

III-D. TC Neurons

The voltage equation for the membrane potential, V_{TC}, is

$$C_m \frac{\partial}{\partial t} V_{TC} = -I_l - I_K - I_{Na} - I_T - I_e - I_{GPi,TC} + I_{app} + I_z. \quad (4)$$

The current denoted I_e represents time-varying excitatory synaptic inputs from cells not explicitly included in the simulation. These cells also receive excitatory inputs from GPi cells, as represented by $I_{GPi,TC}$. A constant excitatory current, I_{app}, is also applied since in the absence of inputs this cell model will not fire.

III-E. DBS Pulse Timing

In practice, DBS pulses are bi-phasic, so current alternates directions between electrical contacts on the electrode. This is done so that charge does not accumulate due to the capacitive nature of neural tissue. Here we model the electrode as a point source, so we assume that the DBS current signal, I_{stim}, consists of a pulse train with uni-phase pulses of width ω microseconds and amplitude α pA/μm^2. A single pulse, $p_\alpha(t)$, can be described as

$$p_\alpha(t) = \begin{cases} -\alpha & 0 \le t \le \omega \\ 0 & \text{otherwise} \end{cases}. \quad (5)$$

Assuming for simplicity of notation that stimulation begins at $t = -\infty$, we have

$$I_{stim} = \sum_{n=-\infty}^{\infty} p_\alpha\Big(t - \frac{n}{f}\Big), \quad (6)$$

where f is the stimulation frequency. The above signal has regularly spaced pulses at intervals of $1/f$. With jitter, noise is added to the timing of these pulses. In this case,

$$I_{stim}(z) = \sum_{n=-\infty}^{\infty} p_\alpha\Big(t - z_n - \frac{n}{f}\Big), \quad (7)$$

where z_n are i.i.d. zero-mean Gaussian random variables with variance σ^2 for all n. The average inter-pulse period between pulses is still $1/f$, but the period is no longer deterministic.

III-F. Network Model

Each structure is represented by 16 model neurons, totaling 64 model neurons for the entire network. The links between these neurons, i.e. the synaptic connections, are randomly determined at the beginning of the simulation and the strength of these connections evolves over time according to the synaptic conductivity differential equations. We determine this random synaptic connectivity map by assuming that each cell i receives a fixed number n_x of inputs from a presynaptic cell type x. Thus n_x indices are selected by sampling uniformly without replacement

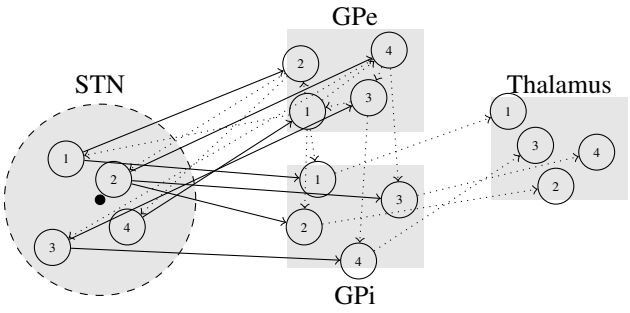

Fig. 2. Cartoon showing synaptic connectivity for a small network with four model neurons per structure. Excitatory connections are depicted with solid lines and inhibitory connections are depicted with dotted lines. The dark circle in the middle of the STN neurons represents the DBS electrode

from the index set of presynaptic cell type x. This is done independently for each cell i. For example, STN cell 1 may receive inputs from GPe cells 2 and 4, while STN cell 2 could simultaneously be connected to GPe cells 2 and 3 since the random assignments are done independently. We chose the numbers of links per cell type, n_x, to match empirical data and previous reports of approximate density of connections between nuclei [2], [7]. The connectivity assignments were selected to be made according to a uniform distribution because it provide maximal randomness in the model of connectivity, which is most appropriate when using a small number of model neurons to globally represent activity in a brain structure which in practice has many orders of magnitude more cells. To illustrate the connectivity model assumed, a smaller example network is depicted in Fig. 2.

For the STN neurons, a notion of distance is also introduced into the model. It has been shown that voltage potential change induced by a current pulse decays as a function of the distance between the neuron and the current source [9], [10]. Thus, we uniformly distributed the STN neurons inside a sphere of radius r, where the DBS electrode is defined to be located at the center of the sphere. Since the STN can be approximated as an ellipsoid with the smallest axis of length around 4 mm [11], we assume that $r = 4$ mm. Hence, for a DBS current signal I_{stim}, the current at the i^{th} STN neuron is

$$I_{DBS} = I_{stim} \exp\{-(d_i/\sigma_d)^2\}, \quad (8)$$

where d_i is the Euclidean distance from the sphere center and σ_d is selected such that there is a large range in current amplitudes seen throughout the sphere.

IV. RESULTS

For a particular realization of synaptic connectivity and STN neuron topology, parkinsonian neural activity is simu-

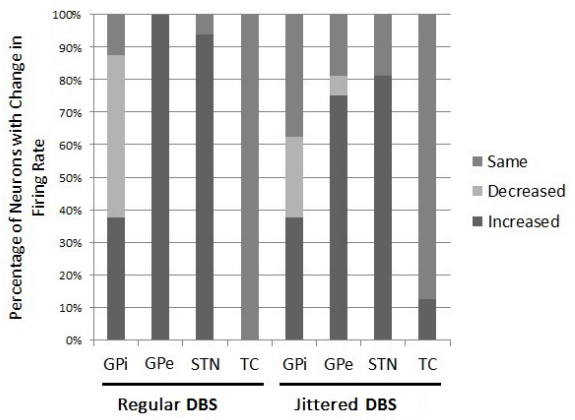

Fig. 3. Distribution of changes in firing rates experienced by neurons while stimulation is administered, relative to the firing rates from the preceding time period without stimulation.

lated in response to (1) a regular, 150 Hz sequence of square current pulses and to (2) the same sequence of pulses with Gaussian jitter added to the timing of the current pulses. The jitter had variance $\sigma^2 = 1$ ms, which is 15% of the regular pulse period. In each scenario, neural activity in response to stimulation is simulated for 10 seconds, with 10 second epochs without stimulation included preceding and following the stimulation period. The final 10 second interval was used to verify that the network activity returned to the parkinsonian state after stimulation ended. The step size in the time domain was 0.01 ms, which was small enough to capture the dynamics of the system. The parameters $\omega = 60$ and $\alpha = 40$ were selected based on what values are used in practice and how consistently the resultant neural activity matched previous reports [2], [7], [8].

Changes in firing rate, with and without jitter, were characterized in order to determine how the stimulation influenced the average spiking activity of all of the neurons. Additionally, the coefficient of variation of the inter-spike intervals (ISI), defined as

$$C_v = \frac{\sigma}{\mu}, \tag{9}$$

was used as a measure of regularity. Spike trains with a low C_v are considered highly regular, or near periodic, while spike trains with high C_v are considered to be more irregular and have more variability in firing time.

Stimulus-locked firing was observed for a subset of STN and GPi neurons in response to both regular and jittered DBS, meaning these neurons had an average firing rate of 150 Hz computed over the 10 second interval. The lack of entrainment of GPe neurons is likely due to the inhibitory connections between GPe neurons. This matches neural activity that has been correlated with improvement in motor symptoms [2], [6]. For non-stimulus-locked neurons, changes in both firing rate and ISI C_v occurred. A mixture of responses was observed with stimulation: some neurons had increased firing rates, some had decreased firing rates, and some neurons remained unchanged. This mixture of responses is also consistent with previous computational and *in vivo* studies [2], [6], [12]. However, we find that there is greater variability in the distribution of firing rate changes induced by DBS with jitter. In Fig. 3, the percentage of neurons that display the three types of changes in firing rate is depicted for each brain structure simulated; the bars on the right half of the graph for the jittered case display a more diverse range of responses.

	r (Pearson)	p	95 % C.I.
STN	0.921	1.21e-15	(0.783, 0.973)
GPi	0.995	6.35e-3	(0.986, 0.998)
GPe	-0.651	4.14e-7	(-0.867, -0.229)

Table I. Correlations between change in C_v for regular and jittered DBS.

In comparing the change in the C_v in response to regular DBS and DBS with jittered pulse timing, there is an interesting correlation between the two for neural activity in the GPe. While the changes in C_v for both STN neurons and GPi neurons are positively correlated, the change in C_v experienced by GPe neurons in the case of regular DBS is negatively correlated with the case of jitter DBS. Exact values are shown in Table I. The neurons with a decreased C_v in response to regular DBS tended to have an increased C_v with jittered DBS.

V. CONCLUSIONS

The goal of DBS is to regularize activity in the basal ganglia structures so that information related to the disease cannot be propagated through this area. However, some variability in response must be allowed to ensure that the basal ganglia can transmit partial information to other brain regions. We presented a jittered design for a DBS signal. Adding this randomness on top of a high-frequency DBS signal enforced partial regularization in the STN and GPi, while still maintaining a mixture of neural firings from all structures and enabling the GPe in particular to function with a wider range of activity, which may be key to creating a partial informational lesion.

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