A Model of the Cortico-Basal Ganglia Network and Local Field Potential during Deep Brain Stimulation

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Abstract—Oscillatory neural activity in the beta frequency band (12-30 Hz) is elevated in Parkinson’s disease and is correlated with the associated motor symptoms. These oscillations, which can be monitored through the local field potential (LFP) recorded by a deep brain stimulation (DBS) electrode, can give insight into the mechanisms of action, as well as treatment efficacy, of DBS. A detailed physiological model of the cortico-basal ganglia network during DBS of the subthalamic nucleus (STN) is presented. The model incorporates extracellular stimulation of STN afferent fibers, with both orthodromic and antidromic activation, and the LFP detected at the electrode. Pathological beta-band oscillations within the cortico-basal ganglia network were simulated and found to be attenuated following the application of DBS. The effects of varying DBS parameters, including pulse amplitude, duration and frequency, on the LFP at the DBS electrode were then assessed. The model presented here can be further used to understand the interaction of DBS with the complex dynamics of the cortico-basal ganglia network and subsequent changes observed in the LFP.

I. INTRODUCTION

Recent clinical studies have shown that patients with Parkinson’s disease (PD) exhibit increased oscillatory neural activity in the beta frequency band (12-30 Hz) throughout the cortico-basal ganglia network [1]. This activity, which is correlated with motor symptoms of bradykinesia and rigidity, has been shown to be reduced alongside symptoms during and following the application of high frequency deep brain stimulation (DBS) [2]. Given this association, the level of oscillatory activity in the beta-band has been proposed as a biomarker for the treatment efficacy of DBS therapy. Realization of a biomarker that can be measured in real time, through the local field potential (LFP) at the implanted electrode, further allows for the possibility of closed-loop DBS therapy [3].

Despite its clinical success, the mechanisms of action of DBS remain a topic of discussion. The hypothesis that stimulation of the subthalamic nucleus (STN) exerts its effects through activation of afferent fibers descending from the cortex to the STN, through the hyperdirect pathway, has been supported by computational and experimental studies [4]. In accordance with this idea, there is evidence that in addition to orthodromic activation, this stimulation pathway allows for antidromic activation in the direction of the cortical axon to the soma [5]. While the cortex may influence the STN through direct projections, there are indications that other nuclei and circuits within the network are important to consider in understanding the pathological basal ganglia and its treatment with DBS [6].

Computational studies provide a valuable means to gain insight into the complex dynamics of the neural circuits which govern motor control in PD. The aim of this study was to investigate the effects of extracellular DBS on simulated STN LFPs using a detailed computational model of the parkinsonian thalamo-cortico-basal ganglia network. The model captured extracellular activation of corticofugal afferent fibers projecting from the cortex to the STN, modeled here as cortical collaterals, firing patterns of individual neurons within the cortico-basal ganglia network, and the resulting LFP during STN DBS.

II. METHODS

A physiologically based model of the thalamo-cortico-basal ganglia network, incorporating a point source electrode for DBS application and LFP approximation, was developed to investigate the dynamics of the system during DBS. The structure of the network model is presented in Fig. 1 and includes the closed cortico-basal ganglia-thalamo-cortical loop [7], as well as the direct, indirect and hyperdirect pathways through the basal ganglia. The major model components include single compartment, conductance-based biophysical models of the STN, globus pallidus external (GPe), globus pallidus internal (GPI), thalamus, and striatum, each of which have been validated and employed in previous modeling studies [8-11]. The cortex is represented by a network of interneurons and multi-compartment cortical neurons [12]. Each component is described in greater detail below.

Seven hundred cells consisting of one hundred STN, GPe, GPI, thalamic, striatal, interneuron, and cortical neurons were connected through excitatory and inhibitory synapses, glutamergic and GABA, respectively, as described below [15, 16]. The STN neurons received direct excitatory input from the cortex via the hyperdirect pathway and inhibitory input from the GPe. Each STN neuron received excitatory input from two cortical neurons and inhibitory input from one GPe neuron. Each GPe neuron received inhibitory input from two other GPe neurons and one striatal neuron in addition to excitatory input from a single STN neuron. Each GPI neuron received excitatory input from a single STN neuron and inhibitory input from a single GPe and striatal neuron. Each thalamic neuron received inhibitory input from a single GPe neuron and excitatory input from a single cortical neuron. Cortical neurons received excitatory input from a single thalamic neuron and inhibitory input from

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three interneurons. Interneurons received excitatory input from a single cortical soma and cortical collateral. All connections within the network were randomly assigned. To simulate dopamine depletion under parkinsonian conditions, synaptic gains within the network were increased to incorporate the finding that dopamine has an overall damping effect and depletion results in excitability and synchronization within the network [17]. The increased cortical drive to the STN through the hyperdirect pathway allowed for the emergence of beta oscillations.

The effect of DBS was added to the network by calculating the extracellular potential of a point electrode delivering current through a homogeneous, isotropic medium of conductivity \( \sigma \) [18]. The extracellular potential at time \( t \), \( V_E(t) \), at each point on the cortical collateral, \( i \), located a distance \( (x_i, y_i, z_i) \) from the source was calculated as

\[
V_E(t) = \frac{4 \pi \sigma}{4 \pi \sigma} I_{DBS}(t)
\]

where the DBS current, \( I_{DBS}(t) \) was simulated as a series of periodic rectangular current pulses of variable amplitude, frequency, and duration. The cortical collaterals were randomly located around the point source in a square two by two millimeter space. The collaterals were assumed to be orientated parallel to one another, and collateral axons were not lie within a radius of 0.635 mm around the point source, representing the volume of the DBS electrode.

**A. Cortex**

The model used to simulate the cortex consisted of cortical neurons and interneurons. The cortical neuron model included a soma, axon initial segment (AIS), main axon, and axon collateral. The cortical neuron soma is based on the regular spiking neuron model developed by Pospischil et al. in [12]. The membrane potential of the soma is described by

\[
c_m \frac{dV_m}{dt} = -\left( I_l - I_{Na} - I_{Kd} - I_M - \sum_k I_{syn}^k \right)
\]

where \( c_m \) is the membrane capacitance, \( I_l \) is the leak current, \( I_{Na} \) is the sodium current, \( I_{Kd} \) is the potassium current, \( I_M \) is a slow, voltage-dependent potassium current, and \( I_{syn} \) are synaptic currents. Further details regarding the parameters used can be found in [12].

The model used to simulate the AIS, main axon, and axon collateral is based on results from previous experimental and modeling studies [13]. The membrane potentials of the AIS, axon, and collateral are described by

\[
c_m \frac{dV_m}{dt} = -\left( I_l - I_{Na} - I_{Kd} - \sum_k I_{syn}^k \right)
\]

Figure 1. Schematic diagram of the cortico-basal ganglia network, DBS application, and LFP model.

where \( c_m \) is the membrane capacitance, \( I_l \) is the leak current, \( I_{Na} \) is the sodium current, \( I_{Kd} \) is the potassium current, \( I_M \) is the D-current, and \( I_{syn} \) are synaptic currents. Further details regarding the parameters used can be found in [13].

Interneurons were modeled using a threshold crossing, spiking model developed by Izhikevich in [14]. The membrane potential of an interneuron is given by a series of ordinary differential equations of the form

\[
du/dt = a(b(V_m) - u)
\]

with the auxiliary after-spike resetting

\[
\text{if } V_m \geq 30 \text{ mV, then } \begin{cases} \frac{dV_m}{dt} = c & \text{if } u < d \\ \frac{dV_m}{dt} = -\frac{V_m}{\tau} & \text{if } V_m < 30 \text{ mV} \end{cases}
\]

where \( V_m \) is the membrane potential and \( u \) denotes a membrane recovery variable representing the activation of potassium ionic currents and inactivation of sodium currents as well as a negative feedback mechanism to \( V_m \). Further details regarding the parameters used can be found in [14].

Individual synaptic currents, \( I_{syn}^k \), were described by

\[
I_{syn}^k = R_k \cdot (V_m - E_{rev})
\]

where \( I_{syn}^k \) is the \( k \)-th synaptic current, \( R_k \) represents the kinetics of the onset and decay of current following a presynaptic spike for synapse \( k \), and \( E_{rev} \) is the reversal potential for the appropriate type of synapse. Further details regarding the parameter values used in the synaptic models can be found in [15] and [16].

**B. Subthalamic nucleus**

The STN model incorporates a physiological representation of STN neurons developed by Otsuka et al. [8]. The membrane potential of an STN neuron is described by

\[
c_m \frac{dV_m}{dt} = -I_{Na} - I_K - I_A - I_L - I_{Ca-K} - I_{Ca} - \sum_k I_{syn}^k
\]

where \( c_m \) is the membrane capacitance, \( I_{Na} \) is a sodium current, \( I_K \) is a Kv3-type potassium current, \( I_A \) is a voltage dependent A-type potassium current, \( I_L \) is a low threshold calcium current, \( I_{Ca-K} \) is a calcium activated potassium current, \( I_{Ca} \) is the leak current, and \( I_{syn} \) are synaptic currents. Further details regarding the parameter values used can be found in [8]. Synaptic potentials were modeled as expressed by (6).

**C. Globus pallidus and thalamus**

The models used to simulate GPe, GPi, and thalamic neurons are based on those presented by Rubin and Terman in [9] and [10]. The membrane potential of a GPe neuron is described by

\[
c_m \frac{dV_m}{dt} = -I_l - I_K - I_{Na} - I_A - I_H - I_{Ca} - I_{Ca-K} - I_{HP} - \sum_k I_{syn}^k
\]

where \( c_m \) is the membrane capacitance, \( I_l \) is the leak current, \( I_K \) is a potassium current, \( I_{Na} \) is a sodium current, \( I_A \) is a low-threshold T-type calcium current, \( I_{Ca-K} \) is a high-threshold calcium current, \( I_{Ca} \) is a voltage-dependent “afterhyperpolarization” potassium current, and \( I_{syn} \) are synaptic currents. GPi and thalamic neurons were modeled similarly, with the exception of excluding \( I_{Ca} \) and \( I_{HP} \) in the thalamic model. Further details regarding the parameters used for the GPe, GPi, and thalamus can be found in [9] and [10]. Synaptic potentials were modeled as expressed by (6).
E. Striatum

The model used to simulate striatal neurons is based on the model presented by McCarthy in [11]. The membrane potential of a striatal neuron is described by

\[
E_m \frac{dV_m}{dt} = -I_{Na} - I_k - I_M - I_l - \sum I_{syn}
\]

where \(E_m\) is the membrane capacitance, \(I_{Na}\) is a sodium current, \(I_k\) is a fast potassium current, \(I_M\) is an M-current, \(I_l\) is the leak current, and \(I_{syn}\) are synaptic currents. Further details regarding the parameter values used can be found in [11]. Synaptic potentials were modeled as expressed by (6).

F. Simulation of local field potential

The LFP was modeled by summing the contribution of all postsynaptic currents across the entire STN population of \(M\) neurons, each with \(N\) synapses, to the extracellular potential detected at the DBS electrode. Assuming conduction within a purely resistive homogeneous medium of infinite extent, the LFP was described by

\[
V_{LFP}(t) = \frac{1}{4\pi\sigma} \sum_{i=1}^{N} \sum_{k=1}^{M} \frac{I_{syn}^{k}(t)}{(\xi_i^k)^2 + (\eta_i^k)^2 + (\zeta_i^k)^2}
\]

where \(V_{LFP}(t)\) is the extracellular potential at a position in extracellular space and \(I_{syn}^{k}(t)\) is \(k\)-th the synaptic current at point, \(i\), located a distance \((\xi_i^k, \eta_i^k, \zeta_i^k)\) from the point source. It was assumed this distance was sufficiently large that the contribution to the LFP of spiking events, due to propagating action potentials, would be negligible.

F. Simulation details

The model was implemented with a time step of 0.01 ms using NEURON v7.3 with Python as an alternative interpreter [19]. Post-processing was done using custom scripts in MATLAB (The MathWorks, Inc., Natick, MA). To examine activity within the beta-frequency range, the raw LFP signals were down-sampled and band-pass filtered between 12 and 35 Hz. The filtered signal was further full wave rectified and averaged by low-pass filtering at 2 Hz to obtain a biomarker reflecting the magnitude of oscillations.

III. RESULTS

Prior to investigating the effects of DBS on the network, the behavior of individual nuclei as well as the LFP was verified against clinical and experimental data in the literature. The firing pattern of STN neurons exhibited burst firing similar to experimental results under parkinsonian conditions [8]. An example of the filtered LFP and corresponding power spectrum are presented in Fig 2. The power spectrum shows a peak within the beta-band at 27 Hz prior to the application of DBS. Applying extracellular DBS with amplitude, pulse duration, and frequency of 5 mA, 60 µs, and 130 Hz respectively, to cortical neuron collaterals resulted in a visible reduction of amplitude in the filtered LFP signal and reduced beta-band power, Fig 2. The magnitude of the beta oscillations normalized with respect to the amplitude without DBS for various stimulation parameters are presented in Fig. 3.

A. Amplitude modulation

The effect of varying stimulation amplitude on the magnitude of oscillations in the beta-band was investigated using a fixed frequency and pulse duration of 130 Hz and 60 µs, respectively, Fig. 3(a). A progressive reduction in beta activity was observed as the stimulation amplitude increased.

B. Pulse duration modulation

The effect of varying stimulation pulse duration on the magnitude of oscillations in the beta-band was then investigated using a fixed frequency of 130 Hz and multiple stimulation amplitudes, Fig. 3(b). The magnitude of oscillations was initially reduced as the pulse duration increased then leveled off once reaching 100 µs.

C. Frequency modulation

Finally, the effect of varying stimulation frequency on the magnitude of oscillations in the beta-band was investigated using a fixed pulse duration of 60 µs and multiple stimulation amplitudes, Fig. 3(c). The beta-band activity increased with 20 Hz stimulation, exhibiting a resonant effect, and was then reduced as the frequency was increased from 80 to 200 Hz.

IV. DISCUSSION

A computational model of extracellular DBS of the closed thalamo-cortico-basal ganglia network in PD has been presented. The model includes extracellular stimulation of cortical afferent fibers projecting to the STN and a simulation of the resulting LFP. These two features allow for a clearer comparison to clinical and experimental results than models using intracerebral stimulation and membrane potential as an indication of oscillation suppression. The multi-compartment
cortical neuron model also allows for an exploration of antidromic and orthodromic activation of cortico-STN afferent fibers during DBS. These effects have been shown experimentally to result in activation of cortical neurons and subsequent suppression of oscillatory activity [5]. Furthermore, the closed-loop connections within the model allow for greater examination of the mechanisms by which these activations propagate throughout the complex circuitry and DBS exerts its therapeutic effects on the dynamics of the network.

Incorporation of both the extracellular field and the network dynamics allows the effect of varying the DBS parameters of pulse amplitude, duration, and frequency on the LFP to be simulated for the first time within a physiologically based model. As the stimulation pulse duration and amplitude were increased, the magnitude of beta-band oscillations within the network were decreased, consistent with the improvement in motor symptoms that has been seen clinically [20]. Similarly, at a given stimulation frequency oscillations were more effectively reduced as amplitude increased. Improved understanding of this complex relationship provides the potential for development of closed-loop stimulation strategies as well as diversified stimulation paradigms.

Although the simulated LFP presented is in agreement with clinically and experimentally generated signals before and after the application of DBS, and displays temporal and frequency domain characteristics in-line with LFP data recorded from patients, the model has some noteworthy limitations which should be considered. The LFP was assumed to be a point source electrode within an ideal homogeneous resistive volume conducting medium of infinite extent. In reality, the electrode geometry, its encapsulation tissue, and the capacitive and dispersive properties of the tissue can have a substantial effect on the electric field distribution as well as the activation thresholds of target neurons during DBS [21],[22]. The capacitive effect on the simulated LFP, however, is likely to be negligible due to its relatively low frequency content. It was also assumed that the DBS signal was only stimulating the cortical collaterals, though it’s possible that the stimulus is additionally activating other areas. Finally although the model is able to show the effect of various stimulation parameters on the suppression of oscillations, beta frequency and power are not uniform across patients [23].

The computational model presented here can be used to gain further understanding of the interaction between DBS and the complex dynamics of the cortico-basal ganglia network. It provides a manner in which to test and develop hypotheses that may be limited in a clinical and experimental setting. Further it provides a framework for the development and testing of closed-loop therapy to advance the treatment of PD with DBS.

REFERENCES


