Basic mechanisms of DBS for Parkinson’s disease: computational and experimental studies on neural dynamics
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Chapter 2

Frequency-selectivity of a thalamocortical relay neuron during Parkinson’s disease and Deep Brain Stimulation: a computational study

Authors

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Abstract

In this computational study, we investigated 1) functional importance of correlated Basal Ganglia (BG) activity associated with Parkinson’s disease (PD) motor symptoms by analyzing effects of globus pallidus internum (GPi) bursting frequency and synchrony on a thalamocortical (TC) relay neuron, which received GABAergic projections from this nucleus; 2) effects of subthalamic nucleus (STN) Deep Brain Stimulation (DBS) on the TC relay neuron's response to synchronized GPi oscillations; and 3) functional basis of the inverse relationship that has been reported between DBS frequency and stimulus amplitude, required to alleviate PD motor symptoms (Benabid et al., *Lancet*, 337, 403-406, 1991). The TC relay neuron selectively responded to and relayed synchronized GPi inputs bursting at a frequency located in the range of 2-25 Hz. Input selectivity of the TC relay neuron is dictated by low threshold calcium current dynamics and passive membrane properties of the neuron. STN-DBS prevented the TC relay neuron from relaying synchronized GPi oscillations to cortex. Our model indicates that DBS alters BG output and input selectivity of the TC relay neuron; providing an explanation for the clinically observed inverse relationship between DBS frequency and stimulus amplitude.
2.1 Introduction

Deep Brain Stimulation (DBS) is a treatment for late stage Parkinson's disease (PD) during which high-frequency electrical stimuli are chronically delivered to targets such as subthalamic nucleus (STN), globus pallidus internum (GPi) or ventral intermediate nucleus of the thalamus (Th). Clinically effective stimulation parameters (120-180 Hz stimulus frequency, 1-5 V stimulus amplitude and 60-200 µs pulse width) have been determined empirically and are accepted as benchmark worldwide (Benabid 2003). Benabid et al. (1991) observed an inverse relationship between stimulation frequency and amplitude, indicating that for lower stimulation frequencies, suppression of PD motor symptoms can only be achieved with increased stimulus amplitude (Benabid et al. 1991; Gao et al. 1999; Moro et al. 2002; Rizzone et al. 2001).

PD motor symptoms (e.g. bradykinesia, rigidity and tremor) are directly correlated with enhanced synchronized activity of the Basal Ganglia (BG) in the theta (3.5-7 Hz) and beta (13-30 Hz) bands (Brown and Williams 2005; Chen et al. 2007; Levy et al. 2002; Levy et al. 2000). It has also been noted that suppression of PD motor symptoms due to treatment (e.g. L-dopa, DBS) is linked to suppression of synchronized BG activity in these frequencies (Brown et al. 2004; Brown et al. 2001; Brown and Williams 2005). Based on these observations, Brown (2003) hypothesized that thalamus relays anti-kinetic BG oscillation frequencies to cortex (CTX), giving rise to PD motor symptoms and that DBS results in alleviation of the motor symptoms by suppressing enhanced activity in the theta and beta bands in the thalamo-cortico-basal ganglia loop (Brown 2003).

Despite high clinical efficacy of DBS, a consensus regarding the underlying mechanism of action is lacking (Dostrovsky and Lozano 2002). Experimental studies have indicated that DBS results in somatic block and subsequent elimination of enhanced synchronized activity in the BG, giving rise to alleviation of PD motor symptoms (Beurrier et al. 2001; Tai et al. 2003). Nevertheless, modelling studies suggested that myelinated axons, within the activation field of the electrode, can exhibit synchronous activity at the DBS frequency, despite block of neuronal activity at the soma (Holsheimer 2002; McIntyre et al. 2004). Activation of axons during DBS could
potentially spread the high-frequency activity to other nuclei, under the assumption that synaptic depression and/or depolarization block do not occur (Brown et al. 2004; Hashimoto et al. 2003; Lozano et al. 2002; Miocinovic et al. 2006). Building on these observations, Rubin and Terman (2004) have demonstrated that thalamocortical (TC) relay capability is restored, due to low threshold calcium current dynamics, when the oscillatory BG input to the neuron is fully overwritten by high-frequency input (Rubin and Terman 2004). However, this study does not specifically address for which conditions BG oscillations are relayed by TC relay neurons to CTX and the mechanism behind the frequency-amplitude dependency of DBS. To address these issues, we investigate TC relay neuron frequency selectivity during PD and STN-DBS and based on cellular dynamics, provide an explanation for the inverse relationship between DBS frequency and stimulus amplitude.
2.2 Materials and Methods

In this paper, we have investigated frequency selective properties of TC relay neurons during PD using two TC relay neuron models; a morphologically realistic multi-compartment model and a single compartment model (Table 1 and Appendix). We have also studied the changes that occur in frequency selective properties of TC relay neurons during STN-DBS by incorporating a BG network model (Rubin and Terman 2004) projecting onto the single compartment TC relay neuron model (Fig. 1).

Figure 1: Nuclei and connections incorporated in the network model, which is used in the simulations investigating effects of STN-DBS on the TC relay neuron functionality: Solid lines indicate inhibitory synaptic connections between nuclei while dash lines indicate excitatory synaptic connections between nuclei. External inputs (e.g. DBS, projection from striatum to GPe, striatum to GPi, projection from CTX to STN or projection from CTX to Th) are indicated by dash – dot lines.

Section A: TC Frequency Selectivity during PD

2.2.1 Multi-compartment and single compartment TC relay neuron model

The multi-compartment TC relay neuron model consisting of 208 compartments (Destexhe et al. 1998; Huguenard and Prince 1992) was downloaded from ModelDB (http://senselab.med.yale.edu/modeldb/) and simulated in the NEURON environment (Hines and Carnevale 1997). The
membrane current equation for compartment $i$ connected to $k$ branches that relate the voltage $V_i$ to the membrane current $I_{ion}$ is:

$$C_m \frac{dV_i}{dt} = -(I_{Na,i} + I_{K,i} + I_{T,i} + I_{h,i} + I_{Ks,i} + I_{Naleak,i} + I_{Kleak,i} + I_{GPI-Th,i} - (V_{i-1} - V_i)g_{i-1,i} - \sum_k(V_{i+k} - V_i)g_{i,i+k})$$

(1)

Detailed analysis was performed on a simplified single compartment model representing the soma of the TC relay neuron which was implemented in MATLAB (Mathworks, Inc). Membrane potential ($V_m$) of the single compartment model is described by:

$$C_m \frac{dV_m}{dt} = -(I_{Na} + I_{K} + I_{T} + I_{h} + I_{Ks} + I_{Naleak} + I_{Kleak} + I_{GPI-Th} + I_{CTX-Th} + I_{app})$$

(2)

Ion current descriptions and maximum ion channel conductance used in the single compartment model and the multi-compartmental model can be found in the Appendix and Table 1.

<table>
<thead>
<tr>
<th>$E_{Na}$</th>
<th>45 mV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_K$</td>
<td>-95 mV</td>
</tr>
<tr>
<td>$E_h$</td>
<td>-43 mV</td>
</tr>
<tr>
<td>$g_{Na}$</td>
<td>0.03 S/cm$^2$</td>
</tr>
<tr>
<td>$g_K$</td>
<td>0.003 S/cm$^2$</td>
</tr>
<tr>
<td>$g_{Ks}$</td>
<td>0.0007 S/cm$^2$</td>
</tr>
<tr>
<td>$g_h$</td>
<td>0.0005 S/cm$^2$</td>
</tr>
<tr>
<td>$g_{Naleak}$</td>
<td>0.000015 S/cm$^2$</td>
</tr>
<tr>
<td>$g_{Kleak}$</td>
<td>0.00005 S/cm$^2$</td>
</tr>
</tbody>
</table>

Table 1: Parameters for the soma and the dendritic tree of the TC relay neuron

2.2.2 GPi projection in the multi-compartment model

Neuronal tracings indicate that a group of GPi neurons converge on a single TC relay neuron (Smith et al. 1998). We modelled the effect of the GABAergic GPi projection by implementing conductance based exponential synapses (Eqs. 1 and 3). At compartment $i$, synaptic density ($\rho$) was
equivalent to 0.025 synapses per $\mu\text{m}^2$ (Smith et al. 1998). Total number of synapses at a given compartment was set to the floor of $A_i\rho$ i.e. rounded down to the nearest integer ($\lfloor A_i\rho \rfloor$), where $A_i$ is the area of compartment $i$.

$$I_{\text{GPI-TH},i}(t) = \frac{1}{A_i} \left( \sum_j g_{GABA,j}(t)(V_i - E_{GABA}) \right) 0 \leq j \leq \lfloor A_i\rho \rfloor$$  \hspace{1cm} (3)

$g_{GABA,j}$ is the conductance of synapse $j$ and $E_{GABA}$ is the synaptic reversal potential (-85 mV) (Kim et al. 1997; McIntyre et al. 2004; Rubin and Terman 2004; Terman et al. 2002).

At synapse $j$, an artificially generated spike train, modelling the firing pattern of a single pre-synaptic GPi neuron, was received. Artificially generated spike train contained bursts of 50 ms duration, which consisted of 8 spikes on average (Raz et al. 2000; Wichmann et al. 2002). The time interval between bursts modelled the bursting frequency ($f_{\text{GPI}}$) of a GPi neuron and the variation between burst arrival times ($\delta t = N(0,\sigma)t_{\text{start}}$) at different synapses was used as a measure of correlation level ($C$) between pre-synaptic GPi neurons (Raz et al. 2000). When the correlation was $0 \leq C \leq 1$, spike arrival times were normally distributed with mean 0 and variance ($\sigma$) of $(1 - C)/C$. When a spike was observed at synapse $j$, $g_{GABA,j}$ was instantaneously incremented by 0.5 nS and decayed exponentially with a time constant of 10 ms (Rudolph and Destexhe 2006).

2.2.3 GPi projection in the single compartment model

In order to reflect the essential properties of the multi compartment synaptic input (Supplementary material), the GABAergic GPi projection was modelled as an oscillatory signal with phase noise:

$$I_{\text{GPI-TH}}(t) = g_{\text{GPI-TH}}(1 + \alpha \sin(\varphi(t)))(V_m - E_{GABA})$$  \hspace{1cm} (4)

where $E_{GABA}$ is the synaptic reversal potential (-85 mV) (Kim et al. 1997; McIntyre et al. 2004; Rubin and Terman 2004; Terman et al. 2002), $g_{\text{GPI-TH}}$ is the mean synaptic conductance, $\alpha$ is the modulation depth (between 0 and 1) and $\varphi(t)$ is the phase of the oscillatory conductance change. The temporal evolution of the phase $\varphi(t)$ of the oscillatory input is modelled by:
\[ \phi(t + dt) = \phi(t) + 2\pi f_{\text{GPi}}dt + N(0, \sigma)\sqrt{dt} \]  

(5)

where \( f_{\text{GPi}} \) defines the average bursting frequency of the GPi input and \( N(0, \sigma) \) defines the phase noise as a random number drawn from a normal distribution with mean 0 and variance \( \sigma \).

2.2.4 Cortical projection in the single compartment model

In addition to the GABAergic GPi input, TC relay neurons receive excitatory projections from the pre-motor and supplementary motor CTX. Connections between TC relay neurons and CTX are predominantly reciprocal but can also contain non-reciprocal components (McFarland and Haber 2002). The relaying capability of the TC relay neuron in the physiological state, during PD and STN-DBS, was tested with excitatory, conductance based, synaptic current \( I_{\text{CTX-}\text{Th}} \), modelling the cortical input (Guo et al. 2008; Pirini et al. 2009; Rubin and Terman 2004)

\[ I_{\text{CTX-}\text{Th}} = g_{\text{CTX-}\text{Th}} H(\sin(2\pi f_{\text{CTX}})) \]

\[ (1 - H(\sin(2\pi (t + \delta_{\text{CTX}})f_{\text{CTX}})))(V_m - E_{\text{Glut}}) \]

(6)

where \( g_{\text{CTX-}\text{Th}} \) is the mean synaptic conductance, \( f_{\text{CTX}} \) is the frequency and \( \delta_{\text{CTX}} \) is the duration of the cortical input. The reversal potential for the cortical synaptic input \( (E_{\text{Glut}}) \) is set at 0 mV. H refers to the Heaviside step function, where \( H(x) \) is zero for \( x < 0 \) and is equivalent to 1 when \( x > 0 \).

Section B: TC Frequency Selectivity during DBS

2.2.5 Network model

The BG network model used in order to investigate frequency selective properties of the TC relay neuron during STN-DBS is an extension of the network model described in Rubin and Terman (2004). STN, globus pallidus externum (GPe) and GPi neurons are modelled using single compartment conductance based equations (Pirini et al. 2009; Rubin and Terman 2004; Terman et al. 2002). We have replaced the TC relay neuron model described in Rubin and Terman (2004) with the single compartment TC relay neuron described in Section A and Appendix (Rubin and Terman 2004). The network model...
includes 16 STN, 16 GPe, 16 GPi neurons and one TC relay neuron. Each STN neuron receives inhibitory input from two GPe neurons and each GPe neuron receives excitatory input from three STN neurons and inhibitory input from two GPe neurons. Each GPi neuron receives excitatory input from three STN neurons and inhibitory input from two GPe neurons. All GPi neurons project onto the same TC relay neuron. Parameters defining the properties of STN, GPe and GPi neurons and properties of the network are the same as the parameters described in Rubin and Terman (2004) and Pirini et al. (2009), unless explicitly mentioned in Appendix. The network has only been simulated in the Parkinsonian state (Pirini et al. 2009; Rubin and Terman 2004).

The model includes the following external inputs: 1) striatum to GPe (indirect pathway); 2) striatum to GPi (direct pathway) 3) CTX to STN (hyper-direct pathway) and 4) CTX to TC relay neuron (Pirini et al. 2009; Rubin and Terman 2004). Recent experimental studies indicate that the hyper-direct pathway plays a crucial role in the generation of sustained oscillations in the BG nuclei in the beta frequency bands during PD (Baufreton et al. 2005; Hammond et al. 2007; Wilson et al. 2006). Therefore, we included the hyper-direct pathway from CTX to STN represented as:

$$ I_{CTX-STN} = g_{CTX-STN}(1 + \sin(2\pi f_{CTX-STN} t))(V_m - E_{Glut}) $$

where $f_{CTX-STN}$ is the frequency of the cortical input and is set at 15 Hz (Levy et al. 2000). $g_{CTX-STN}$ is the mean synaptic conductance and is equivalent to 1 pA/µm².

### 2.2.6 Deep Brain Stimulation

Effect of DBS on STN neurons is modelled as a train of pulses injected into STN neurons (Rubin and Terman 2004).

$$ I_{DBS} = i_D H(\sin(2\pi f_{DBS} t))(1 - H(\sin(2\pi f_{DBS}(t + \delta)))) $$

$i_D$ is the amplitude of the current injection and is set at 400 pA/µm². $\delta$ is the duration of a single pulse and is set to 3 ms. $f_{DBS}$ represents the frequency of the pulse train and is equivalent to the frequency of DBS. As in equation 6, $H$ represents the Heaviside step function. Based on the notion that DBS activation volume is stimulus amplitude dependent (Butson et al. 2007; Butson and McIntyre 2005), we assume a
Thalamic Response to Frequency: DBS and PD

monotonic relationship between stimulus voltage and percentage of neurons activated due to DBS. Percentage of STN neurons activated due to DBS is represented by varying the number of STN neurons receiving $I_{DBS}$. Somatic block due to DBS is not modelled in this study since activated STN neurons receive both $I_{DBS}$ and $I_{CTX-STD}$.

Section C: Quantification of TC relay functionality

Several studies have linked BG activity patterns in the theta and beta frequency bands to PD motor symptoms (Chen et al. 2007; Chen et al. 2006; Fogelson et al. 2005; Hutchison et al. 2004; Levy et al. 2002; Levy et al. 2000; Trottenberg et al. 2007) and suppression of these activities with alleviation of PD motor symptoms (Brown et al. 2004; Brown et al. 2001; Brown and Williams 2005; Hammond et al. 2007).

Building on the notion that pathophysiology and treatment efficacy relate to frequency content in the thalamo-cortico-basal ganglia loop, we used spectral analysis (Fast Fourier Transform) to quantify functionality of a TC relay neuron which received excitatory cortical, inhibitory GPi and under certain conditions DBS induced inputs. TC relay functionality was evaluated by comparing the frequency content of binary spike trains obtained from the TC output to the frequency contents of the various input signals. Influence of DBS induced activity on TC relay functionality was assessed by the level of suppression of GPi burst frequencies in the TC output (Brown et al. 2004; Hammond et al. 2007). Level of suppression of GPi burst frequencies was quantified by measuring the change in the magnitude of GPi burst frequencies during DBS with respect to the magnitude of GPi burst frequencies during PD.
2.3 Results

Section A: TC Frequency Selectivity during PD

2.3.1 Response to GABAergic GPi projection in the multi-compartment TC relay neuron model

First the response of a TC relay neuron to inhibitory GPi projection was studied. The response of the multi-compartment TC relay neuron was investigated as a function of pre-synaptic correlation ($C$) while bursting frequency ($f_{GPi}$) of the pre-synaptic GPi neurons was kept constant. When the pre-synaptic correlation was above a critical value, the neuron fired action potentials due to the inhibitory input from the GPi at the bursting frequency of the pre-synaptic GPi neurons (Fig. 2B). For pre-synaptic correlations below the critical correlation level, the membrane potential at the soma exhibited sub-threshold oscillations at the bursting frequency of the pre-synaptic GPi neurons (Fig. 2A).

![Figure 2](image)

Figure 2: Selective TC response to correlated, bursting GPi inputs: Results, obtained using the multi-compartment model and the single compartment model, are shown in A-C and D-F, respectively. A: the membrane potential oscillates between the resting membrane potential and a relatively hyperpolarized value when GPi burst frequency is equivalent to 8 Hz and the correlation level ($C$) among the GPi neurons is 0.4 ($f_{GPi}$ and $C$ values are indicated with x.)
in Fig. C); B: TC relay neuron fires action potentials at the GPi burst frequency (8 Hz) when the correlation level (C) among the GPi neurons is 0.8 ($f_{\text{GPi}}$ and C values are indicated with + in Fig. C); C: selectivity curve defines the boundary between GPi burst frequencies and correlation levels which induce action potential generation at GPi burst frequency (parameters above the selectivity curve) and GPi burst frequencies and correlation levels that lead to sub-threshold oscillation of the TC relay neuron’s membrane potential (parameters below the selectivity curve) (resting membrane potential = -65mV); D: the membrane potential oscillates between the resting membrane potential and a relatively hyperpolarized value when the GPi burst frequency is 8 Hz and input modulation depth ($\alpha$) is 0.75 ($f_{\text{GPi}}$ and $\alpha$ values are indicated with * in Fig. F); E: TC relay neuron fires action potentials at the GPi burst frequency (8 Hz) when the modulation depth ($\alpha$) is 0.95 ($f_{\text{GPi}}$ and $\alpha$ values are indicated with ¤ in Fig. F); F: selectivity curve when the resting membrane potential is -65 mV, describing GPi burst frequency and modulation depth selectivity of the single-compartment TC relay neuron (for D-F $g_{\text{GPi}-\text{Th}} = 0.2 \text{mS/cm}^2$).

The previous analysis was repeated for various frequencies in order to understand how the response to correlation level changes for different pre-synaptic bursting frequencies. We observed that the TC relay neuron exhibited frequency dependent selectivity to pre-synaptic correlation levels for firing action potentials and as the bursting frequency of the GPi neurons varied, the critical correlation level above which the TC relay neuron fired action potentials shifted. The same analysis was performed for non-bursting GPi inputs leading to similar results (not shown). Figure 2C shows the selectivity curve of a TC relay neuron. It defines the boundary between sub-threshold oscillation (Fig. 2A) and action potential generation (Fig. 2B) in response to inhibitory GPi projection at the GPi bursting frequency. Figure 2C also shows that there exists an optimum frequency (i.e. GPi bursting frequency) at which minimum amount of pre-synaptic correlation is required to drive the TC relay neuron at the GPi bursting frequency.

2.3.2 Response to GABAergic GPi projection in the single compartment TC relay neuron model

The analysis in the multi-compartment model was repeated in the single compartment TC relay neuron model in order to test whether the response to inhibitory GPi projection was
preserved and realistically represented in the reduced model with simplified synaptic input. When the GPi burst frequency was at 8 Hz and modulation depth of the reduced synaptic input was set at 0.75, the membrane potential in the single compartment TC relay neuron model showed sub-threshold oscillations (Fig. 2D). When the synaptic input was set at a higher modulation depth (0.95) at the same GPi burst frequency, the model responded with action potentials (Fig. 2E). Figure 2F shows the selectivity curve of a TC relay neuron obtained using the single compartment model. The selectivity curves of the single and multi compartment model are qualitatively equivalent (Figs. 2C and 2F), given that there exists a monotonic relationship between the correlation level \((C)\) of the multi-compartment synaptic input model and modulation depth \((\alpha)\) of the reduced synaptic input model (Supplementary Material).

2.3.3 Shape of the selectivity curve

The precise shape and position of the selectivity curve is closely linked to sub-threshold resonance of the TC relay neuron (Hutcheon and Yarom 2000). Sub-threshold resonance is conveniently examined by driving the membrane with a chirp signal \(g_{\text{GPI-TH}} = 0.2\, \text{mS/cm}^2, \alpha = 0.5, \text{frequency} (f_{\text{GPI}}) \text{ slowly increasing from 0 to 100 Hz}\) and recording the response of the neuron assessed by the amplitude of the membrane potential of the TC relay neuron \(V_m\) as a function of input frequency (Figs. 3A and 3B). Sub-threshold resonance and input selectivity of the TC relay neuron is predominantly dependent on \(I_T\) inactivation and membrane time constant, while \(I_T\) activation amplifies the response at the resonant frequency (Hutcheon and Yarom 2000). Resonance frequency and optimum frequency range of the selectivity curve are determined by inactivation time constant of \(I_T\) and the membrane time constant (Hutcheon and Yarom 2000). Oscillatory GPi input, where frequency of the input corresponds to average GPi bursting frequency, de-inactivates \(I_T\) providing a driving force for depolarization of the TC relay neuron (Destexhe et al. 1996; Destexhe et al. 1998; Golomb et al. 1996; 1994; Kepecs et al. 2002). GPi burst frequencies and modulation depths (correlation levels); chosen above the selectivity curve, give rise to \(I_{\text{Na}}\) activation and action potential generation at the GPi burst frequency. For oscillatory GPi inputs at frequencies less than the resonance
frequency, release of hyperpolarization is sufficiently slow for $I_T$ to inactivate. This reduces the depolarizing drive by $I_T$ and hence prevents action potential generation. Therefore, at low input frequencies, higher modulation depth (correlation level) is required for TC relay neuron to respond to the oscillatory GPi input (Fig. 3C). This effect subsides as the input frequency approaches $1/(2\pi\tau_h)$ where $\tau_h$ is the inactivation time constant of $I_T$ (Hutcheon and Yarom 2000). For oscillatory GPi inputs at frequencies beyond $1/(2\pi\tau_h)$ passive membrane properties start influencing response of the TC relay neuron. At GPi oscillation frequencies greater than $1/(2\pi\tau)$, where $\tau$ is the membrane time constant, passive membrane properties (i.e. leak conductance and membrane capacitance) attenuate response of the cell to high-frequency input.

![Figure 3: The relationship between sub-threshold resonance and the selectivity curve](image)

As a result, stronger oscillation amplitude i.e. higher modulation depth (correlation level) is required to drive the TC membrane potential beyond the threshold for action potential generation (Fig. 3C) (Hutcheon and Yarom 2000). Active and passive properties of the membrane change with...
the membrane potential which is directly affected by depolarizing or hyperpolarizing current injection. Depolarizing current injection ($I_{app} = -0.6 \mu A/cm^2$) lowers both the inactivation time constant of $I_T$ and the membrane time constant, shifting the resonance frequency and selectivity curve to higher frequencies and lower correlation level or modulation depth values (Figs. 3B and 3D).

2.3.4 Sensitivity analysis for the selectivity curve in the single compartment model

![Figure 4: Sensitivity analysis of the selectivity curve during constant hyperpolarising or depolarising current injection representing background synaptic activity: Shape of the selectivity curve and position of the optimum frequency range are defined by the passive and active properties of the membrane which are in turn dependent on the TC relay neuron’s membrane potential. During constant hyperpolarizing current injection ($I_{app} > 0$), the selectivity curve shifts to lower frequencies and higher modulation depth values. On the other hand, during constant depolarizing current injection ($I_{app} < 0$), the selectivity curve shifts to higher frequencies and lower modulation depth values ($g_{GPI-Th} = 0.2 mS/cm^2$).

We investigated the sensitivity of the selectivity curve to changes in the membrane potential that may result from
excitatory and/or inhibitory synaptic background activity. Figure 4 shows how the selectivity curve changes as $I_{app}$ increases from $-1.2\mu A/cm^2$ to $1.2\mu A/cm^2$ (Eq. 2). With increasingly hyperpolarizing current injection ($I_{app} > 0$), the selectivity curve shifted to higher modulation depth values and covered narrower frequency ranges. Also, the optimum frequency range shifted to lower frequencies. On the other hand, with increasingly depolarizing current ($I_{app} < 0$), the selectivity curve shifted to lower modulation depth values and covered higher frequency ranges. Thus, dependent on the synaptic background activity, TC relay neurons preferentially relay the frequency content of the synchronised drive from GPi neurons exhibiting burst activity at a frequency located in the range of 2-25 Hz. Such oscillations in the GPi have been observed experimentally (Brown 2003).

2.3.5 Effect of Inhibitory input selectivity on TC relay function in the single compartment model

We next investigated TC relay function in the presence of an excitatory cortical input and various states of GPi input (i.e. uncorrelated, correlated, bursting, etc.) by monitoring the frequency content of the TC relay neuron’s output patterns using the single compartment TC relay neuron model. In the absence of correlated GPi bursting ($\alpha = 0$), the TC relay neuron faithfully relayed the excitatory cortical input as evidenced by the presence of a single peak centred at the cortical input frequency in the TC cell’s output spectrum (Figs. 5A (time signal) and 5D (Fourier transform of the signal)). For correlated GPi input parameters chosen below the selectivity curve (Fig. 4), the GPi bursting frequency appears in the output spectrum but the overall signal is still dominated by the frequency components corresponding to the excitatory cortical input (Fig. 5E). On the other hand, for GPi input parameters chosen above the selectivity curve (Fig. 4) primary frequency component of TC neuron’s output shifted from the excitatory cortical input frequency to the inhibitory GPi bursting frequency (Fig. 5F).
Figure 5: Relationship between TC relay neuron’s inhibitory input selectivity and relay function: Spike trains obtained from the TC relay neuron \( s(t) \) are shown in A-C and Fourier Transforms of the spike trains \( S(f) \) are shown in D-F. Magnitude of GPi burst frequency \( f_{GPi} = 13 \text{ Hz} \) (black bar) and cortical frequency in the TC output for various cortical frequencies are shown in G-I \( f_{CTX} = 10 \text{ Hz} \) (white bar), \( f_{CTX} = 20 \text{ Hz} \) (light gray bar) and \( f_{CTX} = 37 \text{ Hz} \) (dark gray bar)). For G-I, differences between cortical frequency magnitudes in the TC output is a direct consequence of Fourier Transform. A, D and G: for uncorrelated GPi input (i.e. \( \alpha = 0 \)) TC neuron only relays cortical input frequency; B, E and H: for GPi input parameters chosen below the selectivity curve (Fig. 3C), TC neuron relays GPi burst frequency together with the cortical input frequency; predominant component being the cortical input frequency; C, F and I: for correlated oscillatory GPi input parameters chosen above the selectivity curve (Fig. 3C), TC neuron relays GPi burst frequency together with the cortical input frequency, predominant component being the GPi burst frequency \( g_{CTX} = 0.2 \text{ mS/cm}^2, \delta_{CTX} = 1.5 \text{ ms}, g_{GPl-Th} = 0.2 \text{ mS/cm}^2, f_{GPl} = 13 \text{ Hz} \).
Section B: TC Frequency Selectivity during DBS

2.3.6 Effect of STN-DBS frequency and stimulus amplitude

Figure 6: A: Activity pattern of a GPi neuron activated during STN-DBS at 40 Hz; B: Activity pattern of a GPi neuron bursting at 15 Hz during STN-DBS at 40 Hz; C: Activity pattern of a GPi neuron activated during STN-DBS at 130 Hz; D: Activity pattern of a GPi neuron bursting at 15 Hz during STN-DBS at 130 Hz. High-frequency DBS is more effective in regularizing GPi activity patterns than low frequency DBS.

We investigated effects of STN-DBS on the TC relay neuron by implementing the BG network model of Rubin and Terman (2004) (Fig. 1) (Rubin and Terman 2004). Rubin and Terman (2004) assume 100% activation of STN neurons and refer to pulse amplitude as the amplitude of current injected into the STN neurons during DBS (i.e. $i_D > 0$ and the same for all STN neurons during DBS) (Rubin and Terman 2004). In order to investigate effects of both DBS frequency and stimulus amplitude on the TC relay neuron, we assume a monotonic relationship between stimulus amplitude and the percentage of STN neurons activated by DBS (Butson et al. 2007; Butson and McIntyre 2005). Percentage of STN neurons activated by
DBS is equivalent to percentage of neurons receiving non-zero current injection due to DBS ($i_D > 0$); for the neurons which are not activated on the other hand, $i_D$ is set at 0.

DBS induces high-frequency tonic activity in STN, GPe and GPi neurons and the percentage of GPe and GPi neurons activated is monotonically related to the percentage of STN neurons activated. The monotonic relationship between percentage of GPe and GPi neurons activated with respect to percentage of STN neurons activated is dependent on the network connectivity. STN, GPe and GPi neurons, which are not relaying high-frequency tonic activity, continue to exhibit synchronized bursting activity driven by the hyper-direct pathway. Figure 6 demonstrates activity patterns exhibited by a GPi neuron when it is activated by STN-DBS (Figs. 6A and 6C) and when it is bursting at 15 Hz due to the influence of the oscillatory hyper-direct pathway ($f_{CTX-STN} = 15$ Hz) (Figs. 6B and 6D).

In order to study effects of DBS stimulus amplitude on the relay properties of the TC relay neuron, we varied percentage of STN neurons activated, for a given DBS frequency. We observed that as the percentage of STN neurons activated increased, magnitude of GPi burst frequencies in the TC output decreased (Figs. 7A-B). We repeated the same analysis in the presence of cortical input to the TC relay neuron, and observed that GPi burst frequencies were suppressed as the percentage of STN neurons activated increased while cortical input frequencies were not affected (Figs. 7C-D).

Next we determined which DBS parameters resulted in significant suppression of GPi burst frequencies in the TC output. Significant suppression is defined as greater than 50% reduction in the magnitude of GPi burst frequencies with respect to magnitude of GPi burst frequencies in the absence of DBS. Figure 8 shows the boundary between relay of GPi burst frequencies and suppression (65% and 100%) of GPi burst frequencies in the TC output. There exists an inverse relationship between DBS frequency and percentage of STN neurons that needs to be activated in order to suppress GPi burst frequencies in the TC output. Figures 7A and 7B are particular examples of figure 8 and qualitatively represent frequency content of the TC output during STN-DBS with parameters chosen below the inverse relationship and above the inverse relationship; respectively.
Figure 7: As the percentage of STN neurons activated by DBS increases from 0 to 100%, magnitude of GPi burst frequency in the TC output decreases. Total number of STN neurons included in the network model is 16 and average GPi burst frequency is 15 Hz. Fourier Transform of the spike train's obtained from the TC relay neuron ($S(f)$) A: during STN-DBS at 110 Hz when 12.5% of STN neurons are activated by DBS and B: when 31.25% of STN neurons are activated by DBS; Fourier Transform of the spike train's obtained from the TC relay neuron ($S(f)$) in the presence of cortical input C: when frequency of DBS is 110 Hz and 12.5% of STN neurons are activated and D: when 31.25% of STN neurons are activated. In the presence of an excitatory cortical input to the TC relay neuron, as the percentage of STN neurons activated by DBS increases, relay of the cortical input is restored due to suppression of GPi burst frequencies, which can be as strong as the magnitude of cortical frequencies in the TC output (For C and D $f_{CTX}= 37$ Hz, $g_{CTX}= 0.2$ mS/cm², $\delta_{CTX} = 5$ ms).

For 100% suppression of GPi burst frequencies, DBS frequency should be greater than or equal to 60 Hz. DBS frequencies less than 60 Hz were not effective in 100 % suppression of GPi burst frequencies since low frequency DBS was not as effective as high-frequency DBS in regularizing oscillatory BG activity patterns (Rubin and Terman 2004). We
repeated the same analysis in the presence of cortical input and observed that the inverse relationship between DBS frequency and percentage of STN neurons activated holds. In the presence of cortical input, it was not possible to fully suppress (i.e. 100%) GPi burst frequencies in the TC output due to aliasing between multiple frequencies inputted into the system.

The inverse relationship between DBS frequency and percentage of STN neurons activated is based on an intricate interaction between network properties and TC relay neuron’s membrane properties.

![Figure 8](image)

**Figure 8:** Inverse relationship between DBS frequency and percentage of STN neurons activated required to suppress relay of GPi burst frequencies: As the frequency of DBS decreases, more STN neurons need to be activated by DBS in order to suppress GPi burst frequencies in the TC output. The data points (indicated by ■ and ●) separate relay of the GPi bursting to CTX from significant suppression of GPi burst frequencies in the TC output. Amount of GPi burst frequency suppression is computed with respect to GPi burst frequency in the TC output in the absence of DBS. 65% and 100% suppression levels are chosen as examples to illustrate the changes which occur in the inverse relationship for different suppression levels.
2.3.7 Network properties contributing to the inverse relationship

Figure 9: Variations in the frequency content of the summed GPi input to the TC relay neuron \( g_{GPI-Th} \) for different DBS frequencies and percentages of STN neurons activated: Frequency spectrum of the summed GPi input to TC relay neuron is obtained using Fourier Transform \( G_{GPI-Th(f)} \) (DC component of the frequency spectrum is removed for visualization concerns). As the percentage of STN neurons activated by DBS increases, GPi bursting frequency decreases while the constant inhibition applied to TC relay neuron increases (DC component of the frequency spectrum). A and B: frequency of DBS is 50 Hz. As the percentage of STN neurons activated increased from 12.5% to 62.5%; DC component of the frequency spectrum increased from \( 5.75 \times 10^4 \) to \( 9 \times 10^4 \) and magnitude of GPi burst frequency decreased from \( 1.7 \times 10^4 \) to \( 5 \times 10^3 \). C and D: frequency of DBS is 110 Hz. As the percentage of STN neurons activated increased from 12.5% to 62.5%; DC component of the frequency spectrum increased from \( 5.9 \times 10^4 \) to \( 9.75 \times 10^4 \) and magnitude of GPi burst frequency decreased from \( 1.56 \times 10^4 \) to \( 2.8 \times 10^3 \).
As the percentage of STN neurons activated by DBS increase, magnitude of GPi burst frequencies decrease in the summed synaptic input from GPi neurons to the TC relay neuron (Fig. 9). Simultaneously, DC component, which corresponds to the mean of the summed synaptic conductance, and DBS induced high-frequency component increase (Fig. 9). Changes in the magnitude of different frequencies expressed in the summed synaptic output are dependent on the percentage of STN neurons activated by DBS and the DBS frequency (Fig. 9).

Modulation depth approximates temporal changes in the summed synaptic input from GPi neurons and this approximation is well-defined when the number of pre-synaptic neurons is large (i.e. greater than 100) (Section A). The network model includes 16 GPi neurons. Therefore, temporal changes in the summed synaptic input cannot be quantified by modulation depth changes. However, changes occurring in the summed synaptic input can be related to changes in the modulation depth through the magnitude at GPi burst frequency.

With respect to magnitude of GPi burst frequency in the absence of DBS ($2 \times 10^4$), reduction in the magnitude of GPi burst frequency during DBS at 50 Hz is analogous to reducing the modulation depth from 0.85 (12.5% STN neurons activated) to 0.25 (62.5% STN neurons activated). On the other hand, during DBS at 110 Hz, reduction in the magnitude of GPi burst frequency is comparable to reducing the modulation depth from 0.75 (when 12.5% STN neurons are activated) to 0.15 (when 62.5% STN neurons are activated).

2.3.8 Cellular properties contributing to the inverse relationship

In addition to the changes in the overall BG output profile, TC relay neuron’s membrane properties also contribute to the inverse relationship. As described in Section A, oscillatory GPi input gives rise to de-inactivation of $I_T$ which provides a depolarizing drive to the TC relay neuron (Destexhe et al. 1996; Destexhe et al. 1998; Golomb et al. 1996; 1994; Kepecs et al. 2002). For GPi inputs within the TC relay neuron’s selectivity window, this depolarizing drive recruits $I_{Na}$ leading to action potential generation at the GPi burst frequency (Fig. 10). Action potential generation at the GPi burst frequency occurs only during a narrow time window
(Fig. 10). During DBS, high-frequency component of the GPi input periodically hyperpolarizes the TC relay neuron. If DBS induced high-frequency component of the GPi input coincides with this time window, action potential generation is disrupted (Fig. 10).

Figure 10: TC cellular properties contributing to the inverse relationship between percentage of STN neurons activated and DBS frequency required to suppress relay of GPi burst frequencies: Grey bars indicate the onset and duration of DBS pulses (Eq. 8). A: membrane potential of the TC relay neuron during DBS 90 Hz when 31.25% of the STN neurons were activated. High-frequency component of the GPi output driven by DBS periodically hyperpolarizes the TC relay neuron; B: dashed line depicts $I_T$ inactivation gating variable while solid line corresponds to $I_{Na}$ activation; C: dashed line corresponds to $I_{Na}$ inactivation gating variable. Periodic hyperpolarization of the membrane disrupts $I_{Na}$ influx and prevents action potential generation if brief hyperpolarization occurs at the right time (e.g. as shown at 150 ms).
2.4 Discussion

A computational model was used to investigate the neuronal basis of DBS as it is used for the treatment of PD. First, the response of a TC relay neuron to correlated GPi input in the theta and beta band was studied in order to determine the changes in thalamic functionality during PD. The effects of STN-DBS on TC information processing were investigated next and we particularly focused on the inverse relationship that has been observed between clinically effective DBS frequency and amplitude (Benabid et al. 1991; Gao et al. 1999; Moro et al. 2002; Rizzone et al. 2001). The main findings are 1) the TC relay neuron selectively responds to highly synchronized GPi inputs bursting at a frequency located in the range of 2-25 Hz. When the TC relay neuron responds to the GPi input, the GPi burst frequencies are introduced in the TC output while simultaneously relay of excitatory cortical input is suppressed. 2) DBS with sufficient frequency and amplitude suppresses relay of pathological GPi induced frequencies to CTX 3) our model provides an explanation for the clinically observed inverse relationship between DBS amplitude and frequency based on the cellular dynamics of TC relay neurons.

To investigate the response of a TC relay neuron to correlated GPi input, we have used two different TC relay neuron models; one computationally intensive multi-compartment model with realistic morphology and multi synaptic input and one single compartment model with collapsed morphology and simplified synaptic input, capable of capturing in its modulation depth the essence of the correlated GPi input. In this way we could validate the single compartment model against the detailed multi-compartment one, which enabled us to utilize the computationally less intensive single compartment model for performing specific analyses in large parameter spaces (e.g. Figs. 4 and 8). To investigate effects of DBS on the TC relay neuron, a BG network model has been utilized (Pirini et al. 2009; Rubin and Terman 2004). The network model consists of 16 STN, 16 GPe and 16 GPi neurons. Use of this model has enabled us to study the interactions within the BG network resulting from STN-DBS and to investigate the effects of altered GPi output on the TC relay neuron. Changes we observe in the BG output during STN-DBS and consequences on TC relay function are
analogous to effects of correlation level and modulation depth changes studied in Section A.

We did not observe mismatch between the multi-compartment and single compartment TC relay neuron models for the properties that we highlight in this study, suggesting that the main mechanism dictating TC input frequency selectivity is not strongly dependent on the dendritic structure but is rather based on more fundamental membrane properties and ion-channel dynamics. Simulations revealed that correlated low frequency GPi input induced action potentials at the GPi burst frequency while high-frequency input patterns did not lead to a response. The GPi input burst frequency range which the TC relay neuron selectively responds to is approximately 2-25 Hz (depending on membrane potential). Such frequencies have been recorded experimentally during PD and associated with PD motor symptoms (Brown et al. 2001; Magnin et al. 2000; Nini et al. 1995; Raz et al. 2000). Our simulations also highlight that GPi burst frequency is not the only key determinant of TC relay neuron response. Input correlation level also dictates how the TC relay neuron responds to the synaptic input. It has been shown that correlation levels among GPi neurons increase during PD (Raz et al. 2000).

In agreement with earlier studies (Gao et al. 1999; Rubin and Terman 2004) we observed that for phasic GPi inputs the relay of excitatory cortical inputs by TC relay neurons becomes impaired. We have studied relay of excitatory cortical inputs using the single compartment model. Therefore, intricate details of the excitatory and inhibitory synaptic interactions in the dendritic tree have not been taken into account. We have chosen to study frequency components of the TC output as a measure for TC functionality instead of the “error – index” analysis, introduced by Rubin and Terman (2004) (Rubin and Terman 2004). “Error – index” analysis provides information regarding how well the TC neuron relays an excitatory input to CTX while spectral analysis provides insight about the temporal content of the TC output, enabling assessment of relative contribution of GPi and cortical frequencies to the TC output. Moreover, use of spectral analysis as a measure for TC functionality provided a clear link to several clinical studies which have highlighted the relationship between emergence and alleviation of PD motor symptoms and frequencies observed in BG (Chen et al.

We observed that the magnitude of GPi burst frequencies increased in the TC output, with increasingly correlated GPi drive. Simultaneously, the magnitude of frequencies related to the relay of cortical information dropped with the appearance of GPi burst frequencies in the TC output. These findings support the hypothesis that thalamus transmits synchronized BG oscillations to CTX during PD (Brown 2003). We have observed that under “PD conditions”, the TC relay neuron switches to a regime where the oscillatory drive from GPi is transmitted into the cortico-thalamic loop. This suggests a mechanism through which low frequency BG oscillations, via thalamus, result in synchronization of the motor CTX at anti-kinetic low frequencies during PD (Brown 2003; Hammond et al. 2007).

Rubin and Terman (2004) pointed out that regularization of BG output through DBS induced high-frequency activity may restore TC relay functionality (Rubin and Terman 2004). In their model, it is assumed that DBS replaces all oscillatory activity in the STN and hence excludes effects of stimulus amplitude from the analysis and provides a possible mechanism for DBS efficacy based on DBS frequency. Under the assumption that DBS replaces all oscillatory activity, DBS restores TC relay functionality by replacing phasic inhibition of TC relay neurons (DBS off) with constant inhibition (DBS on) (Rubin and Terman 2004).

Based on modelling studies demonstrating that there exists a monotonic relationship between DBS stimulus amplitude and the size of the activation field of the electrode, we included a DBS stimulus amplitude dependent activation of the STN (Butson et al. 2007; Butson and McIntyre 2005). The assumption that DBS does not replace all oscillatory synchronous activity in the BG is also supported by clinical observations indicating that for therapeutic stimulation frequencies and sub-therapeutic stimulus amplitudes, PD motor symptoms are still present (Moro et al. 2002; Rizzone et al. 2001).

Brown (2003) categorized frequency bands of oscillation in the BG as anti-kinetic (oscillation frequencies in the theta and beta bands) and pro-kinetic (oscillation frequencies in the
high gamma band) based on their net effect on movement (Brown 2003). Our simulations indicate that DBS stimulus amplitude, which is monotonically related to the percentage of STN neurons activated, predominantly dictates the balance between anti-kinetic low frequency and pro-kinetic high-frequency activity patterns in the BG network (Brown 2003; Hahn et al. 2008). We observe suppression of anti-kinetic frequencies in the TC output for certain DBS frequencies and percentage of STN neurons activated which are inversely related to one another (Fig. 8) (Brown et al. 2004; Brown et al. 2001; Hammond et al. 2007). There exists a minimum activation level of STN neurons below which suppression of anti-kinetic low frequencies in the TC output does not occur independent of DBS frequency, which is in line with clinical observations of a DBS stimulus amplitude threshold for therapeutic efficacy (Moro et al. 2002). On the other hand, DBS frequency affects both the content of the high-frequency activity patterns in the BG network and the cellular dynamics of the TC relay neuron. For instance, for DBS frequencies less than 60 Hz; STN, GPe and GPi neurons carry both the DBS induced high-frequency and anti-kinetic low frequency activity patterns even during 100% activation of STN neurons. At these DBS frequencies, 100% suppression of anti-kinetic frequencies in the TC output is not possible indicating that there exists a minimum DBS frequency below which a given level of anti-kinetic frequency suppression cannot be achieved.

It still remains unknown why relatively high-frequency stimulation (e.g. 130 Hz) is required for clinical efficacy of DBS (Benabid et al. 1991; Moro et al. 2002). The modeling work presented in this study indicates towards three potential mechanisms which could play a role in the efficacy of high-frequency stimulation: (1) high-frequency DBS is more effective in suppressing anti-kinetic low frequencies in the BG output; (2) high-frequency DBS gives rise to increased constant inhibition of the TC relay neuron; reducing the region where TC neuron selectively relays inhibitory oscillatory inputs at anti-kinetic low frequencies; (3) probability that relay of anti-kinetic frequencies is suppressed by DBS induced inhibitory post synaptic potentials in TC relay neuron, is proportional to DBS frequency. In the following paragraph, we explain in more detail these mechanisms.
DBS suppresses anti-kinetic frequencies in the TC output by altering the BG output and affecting TC relay neuron’s cellular dynamics. STN-DBS alters the BG output by introducing high-frequency tonic (regular) activity in the BG output. Changes in the BG output are proportional to the fraction of STN neurons activated and frequency of DBS. During DBS, the BG output consists of two distinct activity patterns: anti-kinetic oscillatory component and high-frequency regular component induced by DBS (Fig. 9). As the percentage of STN neurons activated increases, magnitude of anti-kinetic oscillation frequencies decreases in the BG output while simultaneously the average level of inhibition applied to the TC relay neuron increases (Rubin and Terman 2004). Application of constant hyperpolarization, shifts TC relay neuron’s selectivity curve to lower GPi burst frequencies and higher modulation depths (Fig. 4). As a result, the pre-synaptic frequency-amplitude window to which TC relay neurons selectively respond to, shrink as the number of STN neurons activated by DBS increase. Additionally, DBS induced high-frequency component of the BG output briefly hyperpolarizes the TC relay neuron at regular intervals. Based on the assumption that DBS does not fully replace anti-kinetic frequencies in the BG output, TC relay neuron can still fire action potentials at these frequencies (Fig. 10). Regular inhibitory post synaptic potentials induced by DBS interfere with action potential generation due to oscillatory BG input and further suppress anti-kinetic frequencies in the TC output (Fig. 10). Frequency of DBS directly controls the probability of the inhibitory post synaptic potentials occurring at the right time and is therefore more effective than low-frequency DBS.

It is remarkable that relay of cortical frequencies is much more robust to the presence of DBS than relay of BG oscillation frequencies (Figs. 7C-D). The time window during which action potentials are generated due to the cortical input is an order of magnitude shorter than the time window during which action potentials are generated because of the oscillatory BG input. Action potential generation driven by the cortical input can be temporarily suppressed only in case of perfect alignment of an inhibitory post synaptic potential induced by DBS with the cortical input. As a result, magnitude of cortical frequencies in the TC output remains on average constant while BG oscillation frequencies are effectively suppressed during DBS. In the absence of DBS, anti-kinetic frequencies can be expressed as strong as the cortical
frequencies in the TC output. With increasing percentage of STN neurons activated during DBS, relay of cortical frequencies is restored due to suppression of these anti-kinetic frequencies in the TC output (Fig. 7D).


2.5 Appendix

2.5.1 Thalamocortical relay neuron model

Both multi-compartment and single compartment TC relay neuron models included traditional fast spike generating currents $I_{Na}$ and $I_{K}$, and a low threshold calcium current $I_{T}$, which plays a vital role in generation of action potentials after hyperpolarizing input. In addition, a hyperpolarisation activated cation current $I_{h}$, a slowly activating potassium current $I_{Ks}$, and sodium and potassium leak currents $I_{Na, leak}$ and $I_{K, leak}$, which determine the resting membrane potential of the TC relay neuron were included. $I_{T}$ used the Goldman-Hodgkin-Katz current equation while all other currents $I_{Na, leak}$, $I_{K, leak}$, $I_{Na}$, $I_{K}$, $I_{h}$, and $I_{Ks}$ used the Nernst equation to incorporate the ionic driving force. Ionic concentrations were assumed constant under the conditions present in our study. Voltage dependent currents were modelled using the Hodgkin-Huxley formalism and reflect well-established parameters for the TC relay neuron (Destexhe et al. 1998; Huguenard and McCormick 1992; McCormick and Huguenard 1992; McIntyre et al. 2004).

Ion currents described using the standard Hodgkin-Huxley model can be represented using the following general form:

$$I_{ion} = g_{ion} m^a h^b (V_m - E_{ion})$$

where $g_{ion}$ is the maximum ion channel conductance, $m$ is the activation gating variable, $h$ is the inactivation gating variable and $E_{ion}$ is the reversal potential. Time and voltage dependency of a gating variable ($w$) can be described by a time constant ($\tau_w$) and a steady state ($w_\infty$) value.

$$\tau_w = \frac{1}{\alpha_w + \beta_w}$$

$$w_\infty = \frac{\alpha_w}{\alpha_w + \beta_w}$$

$$\frac{dw}{dt} = \frac{w_\infty - w}{\tau_w}$$

Membrane dynamics and ion current descriptions are based on the modelling and experimental work of Destexhe et al. (1998), McCormick and Huguenard (1992), Huguenard and McCormick (1992) and McIntyre et al. (2004). In the model, time is in ms, voltages are in mV, ion concentrations are in
mM. In the reduced single compartment model, currents are in $\mu$A/cm$^2$ and maximum ion channel conductance is in mS/cm$^2$. The single compartment model is implemented in MATLAB. In the multi-compartment model, currents are in mA/cm$^2$ and maximum ion channel conductance is in S/cm$^2$. The multi-compartment model is implemented in NEURON. Equations describing ion channel activation and inactivation gating variables are temperature corrected for 36°C.

Soma and dendrite sodium current

$$I_{Na} = g_{Na} m^3 h (V_m - E_{Na})$$
$$\alpha_m = 0.32(-V_m + 55)/[e^{-(V_m+55)/4} - 1]$$
$$\beta_m = 0.28(V_m + 28)/[e^{(V_m+28)/5} - 1]$$
$$\alpha_h = 0.128e^{-(V_m+51)/18}$$
$$\beta_h = 4/[e^{-(V_m+28)/5} + 1]$$

Soma and dendrite potassium current

$$I_K = g_K m^4 (V_m - E_K)$$
$$\alpha_m = 0.032(-V_m + 63.8)/[e^{-(V_m+63.8)/5} - 1]$$
$$\beta_m = 0.5e^{-(V_m+68.8)/40}$$

Soma and dendrite hyperpolarisation activated cation current

$$I_h = g_h m^3 (V_m - 43)$$
$$\tau_m = 1/e^{(-15.45-(0.086V_m))} + e^{(-1.17+0.0701V_m)}$$
$$m_\infty = 1/e^{(V_m+85)/5.5} + 1$$

Soma and dendrite slowly activating potassium current

$$I_{Ks} = g_{Ks} m(0.4h1 + 0.6h2) (V_m - E_K)$$
$$\tau_m = 2.5 + 0.253/(e^{((V_m-81)/25.6)} + e^{-(V_m+132)/18})$$
$$m_\infty = [1 + e^{-(V_m+43)/17}]^4$$
$$\tau_{h1} = 30.4 + 0.253/(e^{((V_m-1329)/200)} + e^{-(V_m+130)/7.1})$$
$$h_{1\infty} = 1 + e^{(V_m+58)/10.6}$$
$$if \ V_m \leq -70 \ \tau_{h2} = \tau_{h1}; \ else \ \tau_{h2} = 2260$$
$$h_{2\infty} = h_{1\infty}$$
Soma and dendrite T-type calcium current

\[ I_T = P_{CaT} m^2 h G(V_m, C_{a_i}, C_{a_o}) \]

\[ G(V_m, C_{a_i}, C_{a_o}) = \left( \frac{z^2 F^2 V_m}{RT} \right) \left( \frac{C_{a_i} - C_{a_o} e^{-z F V_m / RT}}{1 - e^{-z F V_m / RT}} \right) \]

\[ \frac{dC_{a_i}}{dt} = \left( \frac{0.00024 - C_{a_i}}{5} \right) - \frac{I_T k}{z F d} \]

\[ \tau_m = 0.204 + 0.333 / (e^{-(V_m+135/16.7)} + e^{(V_m+19.8/18.2)}) \]

\[ m_{\infty} = 1 / 1 + e^{-((V_m+60)/6.2)} \]

\[ \text{if } V_m < -80 \quad \tau_h = 0.333 e^{((V_m+470)/66.6)} \]

\[ \text{else } \tau_h = 9.33 + 0.333 e^{((V_m+25)/10.5)} \]

\[ h_{\infty} = 1 / 1 + e^{-((V_m+84)/4)} \]

T-type calcium current is described by the Goldman-Hodgkin-Katz Ion current equation. \( P_{CaT} \) is the maximum T-type calcium channel permeability in \( \text{cm/s} \) and \( C_{a_o} \) is 2mM. \( z \) is the charge of a calcium ion, \( F \) is the Faraday’s constant in \( \text{J/(V mol)} \), \( R \) is the gas constant in \( \text{J/(K mol)} \) and \( T \) is the absolute temperature in Kelvin. \( k \) is a unit conversion factor and is equivalent to 10 when \( d \) is 1 µm and \( I_T \) is in \( \mu A/cm^2 \). In the multi-compartment model, \( P_{CaT} \) is set at 0.0001 cm/s at the soma, 0.0004 cm/s at the proximal dendrites (defined as dendrites 0-45 µm away from the soma) and 0.00005 cm/s at the medial (45-90 µm away from the soma) and distal dendrites (>90 µm away from the soma) (Destexhe and Sejnowski 2003; McIntyre et al. 2004; Rhodes and Llinas 2005; Williams and Stuart 2000). In the single compartment model, maximum T-type Ca²⁺ permeability is set at 0.0001 cm/s (Huguenard and McCormick 1992; McCormick and Huguenard 1992).

2.5.2 Network model

The membrane potential of the single compartment STN neuron is represented by:

\[ C_m \frac{dV_{STN}}{dt} = -(I_L + I_{Na} + I_K + I_T + I_{Ca} + I_{AHP} + I_{GPe-\text{STN}} + I_{CTX-\text{STN}} + I_{DBS}) \]

The membrane potential of the single compartment GPe neuron is represented by:
\[
C_m \frac{dV_{GPe}}{dt} = -(I_L + I_{Na} + I_K + I_T + I_{Ca} + I_{AHP} + I_{GPe-GPe} + I_{STN-GPe} + I_{striatum-GPe})
\]

The membrane potential of the single compartment GPi neuron is represented by:

\[
C_m \frac{dV_{Gpi}}{dt} = -(I_L + I_{Na} + I_K + I_T + I_{Ca} + I_{AHP} + I_{GPe-GPi} + I_{STN-GPi} )
\]

\(I_L\) is the leak current, \(I_{Na}\) is the fast sodium current, \(I_K\) is the fast potassium current, \(I_T\) is the low-threshold \(Ca^{2+}\) current, \(I_{Ca}\) is the high-threshold \(Ca^{2+}\) current and \(I_{AHP}\) is the \(Ca^{2+}\) activated potassium current. Refer to Rubin and Terman (2004) and Terman et al. (2002) for parameter values and equations describing the ionic currents (Rubin and Terman 2004; Terman et al. 2002).

a) Synaptic input model

Synaptic currents \(I_{GPe-GPe}, I_{GPe-GPi}, I_{GPe-STN}, I_{STN-GPi}\), and \(I_{STN-GPe}\) are modelled as:

\[
I_{\alpha-\beta} = g_{\alpha-\beta}(V_{\beta} - E_{\alpha-\beta}) \sum_j s_{\alpha}^j
\]

\[
\frac{ds_{\alpha}^j}{dt} = A_{\alpha}(1 - s_{\alpha}^j)H(V_{\alpha} - \theta_{\alpha}) - B_{\alpha}s_{\alpha}
\]

\(\alpha\) represents the pre-synaptic nucleus and \(\beta\) represents the post-synaptic nucleus.

For \(I_{GPe-GPe}, I_{GPe-GPi}, I_{GPe-STN}, I_{STN-GPi}\), and \(I_{STN-GPe}\), \(g_{\alpha-\beta}\) and \(E_{\alpha-\beta}\) are equivalent to (0.3, -85), (0.75, -100), (0.3, -100), (0.3, 0), (0.3, 0).

For all synaptic currents (i.e. \(I_{GPe-GPe}, I_{GPe-GPi}, I_{GPe-STN}, I_{STN-GPi}\), and \(I_{STN-GPe}\)) \(A_{\alpha}, B_{\alpha}\) and \(\theta_{\alpha}\) are equivalent to 5, 0.25 and -10 mV respectively. Projection from striatum to GPe \((I_{striatum-GPe})\) is represented as a constant inhibitory current and the value is set at -5 pA/\(\mu m^2\).
2.6 Supplementary Materials

Figure SM1: Derivation of the reduced synaptic input: As the firing patterns of the pre-synaptic GPi neurons vary due to PD from uncorrelated firing to correlated bursting (A-C) (Chen et al. 2007; Chen et al. 2006; Fogelson et al. 2005; Hutchison et al. 2004; Levy et al. 2002; Levy et al. 2000; Raz et al. 2000; Terman et al. 2002; Trottenberg et al. 2007), the temporal characteristics of the synaptic input observed by the post-synaptic TC relay neuron alter (D-F) (Guo et al. 2008; Rubin and Terman 2004). We studied the summed synaptic conductance change applied to the multi-compartment neuron model for different synaptic input correlation levels (C) and firing patterns (i.e. regular firing, bursting, frequency-modulated tonic firing) of individual GPi neurons, in order to reduce the synaptic input to perform quantitative analysis on the single compartment model. D: For uncorrelated pre-synaptic GPi input (C = 0), the summed synaptic conductance induced in the TC relay neuron resembled a fixed conductance with superimposed noise; E: As the correlation level increased; the summed synaptic conductance converged to an oscillatory signal. Enhancing the correlation level in the GPi input increased the ratio between the summed synaptic conductance amplitude and mean conductance in a nonlinear fashion (C = 0.8); F: For very high correlation levels, the synaptic conductance resembled the scaled postsynaptic conductance change induced by a single GPi neuron (C = 1). G: The reduced synaptic input for the single compartment model approximates the multi-compartment synaptic input model using a constant synaptic conductance with noise when the group of pre-synaptic GPi neurons are in the intrinsic uncorrelated state (i.e. α = 0). H: The reduced synaptic input approximates the multi-compartment synaptic input model by using a noisy sinusoidal signal when the group of pre-synaptic GPi neurons are in the correlated state due to PD (i.e. 0 < α ≤ 1). The nonlinear increase in the ratio between the summed synaptic conductance amplitude and mean level due to changes in the correlation level (multi-compartment model) is approximated by varying the modulation depth (α) of the sinusoidal signal (α = 0.75). I: The reduced synaptic input model no longer captures all the temporal characteristics of the summed synaptic input when pre-synaptic correlation level is greater than 0.95 (α = 1). Correlation levels greater than 0.95 correspond to pre-synaptic neurons being synchronized at biologically implausible levels (e.g. Fig. SM1C).
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