Imperial College London

Literature review and thesis proposal
MRes. Neurotechonlogy

Investigating plasticity in Cortico-Basal Ganglia-Thalamus models to improve stimulation-based treatments

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Contents

Acronyms: PD Parkinson's disease, CBGT Cortico-Basal Ganglia-Thalamic, SNc Substantia Nigra pars Compacta, DBS Deep brain stimulation, aDBS adaptive DBS, STN Subthalamic nucleus, BG Basal ganglia, STDP spike-timing-dependent plasticity, GPe Globus pallidus pars externa, CRS Coordinated reset stimulation, AP action potential, IF Integrate-And-Fire, HH Hodgkin-Huxley, LFP local field potential.

1 Introduction

Parkinson's disease (PD) is characterised by pathological hypersynchrony in Cortico-Basal Ganglia-Thalamic (CBGT) circuit, driven by dopaminergic degeneration in the Substantia Nigra pars Compacta (SNc). Deep brain stimulation of the Subthalamic nucleus (STN) alleviates tremor by disrupting hypersynchrony in the Basal ganglia (BG). However, the mechanism through which this happens remains not well understood, and therapeutic effects are transient, requiring continuous stimulation. The goal of this study is to propose a computational framework to investigate multi-site phase-locked stimulation in a spiking CBGT network model with spike-timing-dependent plasticity (STDP) rules, aiming to induce lasting desynchronisation through activity-dependent synaptic reorganisation.

Pathological and healthy network regimes will be established through data-driven tuning of spiking neuron models. Systematic simulations then evaluate multi-site phase-locked stimulation across three experimental axes: (1) STDP enabled/disabled in various CBGT nuclei, (2) stimulation applied to different pairs of basal ganglia populations and cortical afferents, and (3) closed-loop adaptation to thalamic oscillatory activity. The network will then be analysed in terms of the inter-populational coupling and the stability of potential stimulation-driven non-pathological states.

This work advances the field in two key directions: (1) integrates phase-locked stimulation with plasticity-targeted protocols, and (2) evaluates stimulation targets across the CBGT circuit focusing on regions with experimentally validated STDP. Results will inform clinical adaptive stimulation protocols that exploit neuroplasticity for lasting symptom relief, while the methodology provides a generalisable computational framework for closed-loop neuromodulation design.

2 Background and literature review

2.1 Parkinson's Disease

PD is characterised by the loss of dopaminergic neurons and the presence of Lewy Bodies in the SNc [Del Rey et al., 2018]. This dopaminergic depletion in the SNc leads to striatal dopamine deficiency, which in turn leads to excessive synchronisation in the basal ganglia. Hypersynchrony is a hallmark of the PD [Hammond et al., 2007, Helmich et al., 2012], and thus, can be a promising therapeutic target.

2.2 Deep brain stimulation: theory and practice

It is believed tremor originates from excessive coupling in the CBGT network. Thus, DBS in this region emerged as an effective tool in treating advanced PD and Essential tremor patients [Del Rey et al., 2018]. DBS works by delivering high-frequency stimulation in regions of the CBGT through implanted electrodes. A prominent theory for this method's success is that it enables stimulation-driven decorrelation of the different BG nuclei, shifting it to a non-pathological state. There is significant evidence that performing DBS in the STN or the GPi can have significant improvements in quality of life in patients, reducing tremor and restoring motor control [Rodriguez-Oroz et al., 2005, Rubin and Terman, 2004].

However, DBS does have significant limitations. Firstly, like any highly invasive procedure, the implantation procedure has many risks. Advances in electrode technology and surgical techniques have reduced some of these risks *cite*. Secondly, patient symptoms are only ameliorated while the stimulation is on. This means that the device needs to be on continuously, which can induce numerous side effects in patients **citeee** and also creates the need for a

continuous power supply. Finally, the mechanism through which DBS reduces tremors is not fully understood yet. For instance, there is a discrepancy in tremor frequency ($\sim$ 20 Hz on average) and the effective frequency range of traditional DBS of 130-180 Hz.

Therefore, several areas of research emerge in improving stimulation-based treatments of PD: finding non-invasive alternatives [Saturnino et al., 2017, Schwab et al., 2020], eliciting lasting, plastic changes in the CBGT circuit, closing the loop and coupling stimulation to the presence of patient symptoms (adaptive DBS (aDBS), [Beudel et al., 2018]), and phase-locking stimulation to rythmic activity in the CBGT [Cagnan et al., 2017, West et al., 2022].

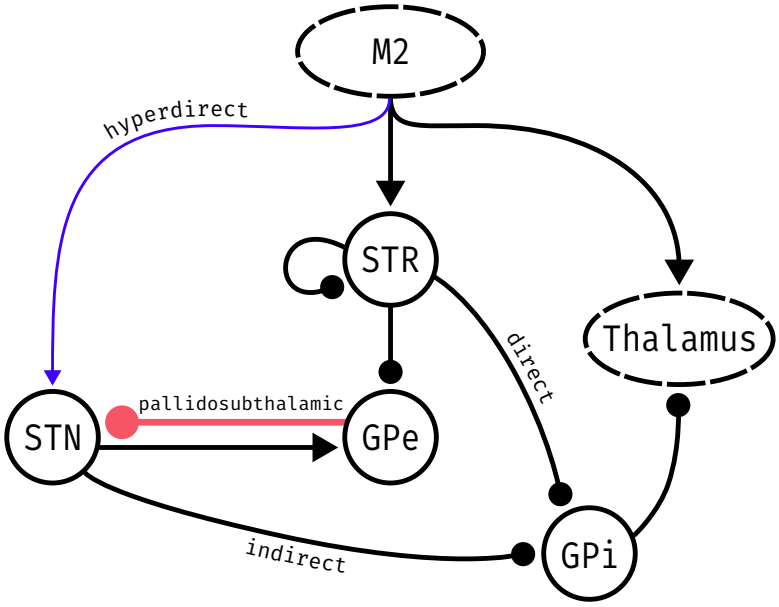

Figure 1: CBGT circuit in PD pathology. Arrow connections represent majority excitatory (glutamate) connections, ball arrows represent inhibitory (GABA) connections.

2.3 Stimulating at the right time

The parkinsonian state results from the complex interplay between four pathways in the CBGT the **hyperdirect** excitatory cortico-subthalamic pathway, the **direct** inhibitory striatopallidal pathway, the **indirect** inhibitory subthalamopallidal pathway and the inhibitory **pallidosubthalamic** (PS) pathway. In pathology the hyperdirect pathway is downregulated, while the PS pathway is upregulated, leading to a shift in beta-band oscillatory activity from sub-band β_1 to sub-band β_2, which correlates to hypersynchrony in the basal ganglia [West et al., 2022].

[Cagnan et al., 2017] demonstrated that phase-specific neuromodulation can disrupt pathological synchrony in essential tremor by delivering stimulation pulses locked to thalamic oscillatory phases. Strategies like this and others (e.g., aDBS [Beudel et al., 2018]) show the potential for closed-loop, adaptive therapies to address hypersynchrony in the BG.

2.4 Plasticity to recover network states

Neuroplasticity can be defined as "the ability of the nervous system to change its activity in response to intrinsic or extrinsic stimuli by reorganising its structure, functions, or connections" [Mateos-Aparicio and Rodríguez-Moreno, 2019]. Plasticity occurs at different scales in the brain, ranging from molecular to neural networks. The focus of this project is synaptic plasticity, which occurs between a pre-synaptic and a post-synaptic neuron. The mechanisms of plasticity

have been thoroughly studied **cite**, and are starting to find their way into clinical applications in neurorehabilitation (e.g., stroke, trauma, spinal cord injury [Cramer et al., 2011]) and neuroprostheses [Lebedev and Nicolelis, 2017].

The potential of plasticity-based treatments in PD depends on the existence of spike-timing-dependent plasticity (STDP) in the synapses of the different BG nuclei, particularly in the STN [Rubin et al., 2012]. Long and short-term plasticity has been found in corticostriatal synapses [Kreitzer and Malenka, 2008, Di Filippo et al., 2009] as well as cell-specific STDP in striatal interneurons [Fino and Venance, 2010]. [Thieu and Melnik, 2024] modelled STDP and random inputs in STN neuronal population and found combining the two can increase coupling between neurons.

To exploit STDP in the CBGT, Coordinated reset stimulation (CRS) has been proposed by Hauptmann and Tass. CRS delivers brief, phase-targeted electrical stimuli to specific neuronal subpopulations within interconnected neural circuits. CRS has been computationally modelled in a Globus pallidus pars externa (GPe)-STN network to successfully disrupt pathological synchronisation in the BG [Hauptmann and Tass, 2009, Hauptmann and Tass, 2010].

2.5 Modeling neural networks

Most neuronal dynamics models are defined by rules of how voltage in a unit changes over time in response to voltage in the network and external current (e.g., noise, stimulation current). This raises the question: what is a unit? From this two broad categories emerge: A unit can be an individual neuron or a cluster of neurons. This section introduces some common types of models, justifying the direction chosen for this project.

Spiking neuron models work by combining networks of units that individually simulate neuronal action potentials (APs). These networks can then be organised into different nuclei (e.g., STN) and coerced to respect excitatory or inhibitory connections between nuclei. Within this class of models, different schemes for modelling neuronal dynamics exist, such as Integrate-And-Fire (IF) [Gerstner et al., 2014a] and Hodgkin-Huxley [Hodgkin et al., 1952, Gerstner et al., 2014b].

Mean-field models simulate the local field potentials (LFPs) of clusters of neurons and connect these clusters with population-level connectivity rules. (e.g., [Jansen and Rit, 1995, West et al., 2022])

2.5.1 Integrate-And-Fire

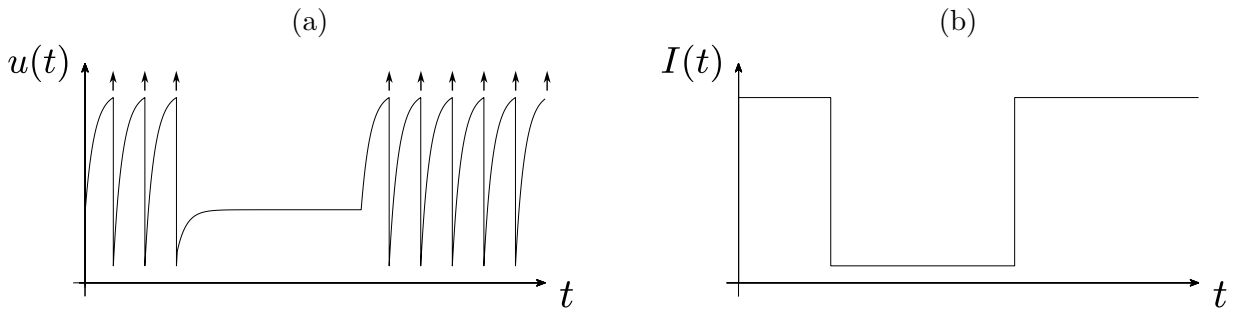

Figure 2: (a) Voltage trace of IF unit overtime in response to external current in (b). When the potential crosses the AP threshold it is reset and the spike is recorded.

IF models treat action potentials as events. This reduction is justified by the fact that the shape of APs is always *approximately* the same, meaning they *cannot* convey information. [Gerstner et al., 2014a] describe a leaky IF model is represented by an electrical circuit with a resistor(R) and a capacitor(C) in parallel ($I(t) = I_R + I_C$), combined with a reset condition when the potential exceeds a threshold θ (fig. 2a). This can be modelled by,

$$\tau_m \dot{u} = -[u(t) - u_{rest}] + RI(t), \tag{1}$$

Together with the reset condition,

$$\lim_{\delta \to 0; \delta > 0} u(t^f + \delta) = u_r, \tag{2}$$

$$t^f = \{t | u(t) = \theta\}. \tag{3}$$

Where u is the membrane voltage, u_{rest} is the resting potential, u_r is the reset potential, $\tau_m = RC$ is the time constant, and I is external current.

These equations describe the update rules in a single unit. Connectivity rules between units can be added to form neural networks. These connections can then be strengthened or weakened depending on spike timings between units, modelling STDP. [Shupe and Fetz, 2021] simulate plasticity in cortical columns; [Kromer et al., 2023] model plasticity between basal ganglia nuclei both using an IF model.

2.5.2 Hodgkin-Huxley

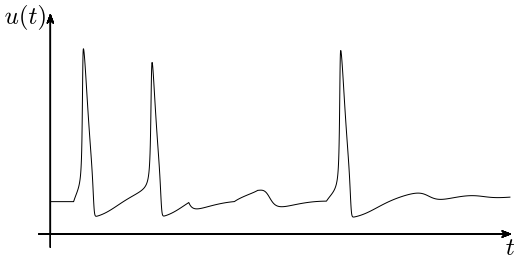

Figure 3: Voltage trace of HH unit in response to external current pulses.

The Hodgkin-Huxley (HH) model [Hodgkin et al., 1952] simulates membrane potential by considering the dynamics of different ion conductances. Each ion has a reversal potential at which the force of the electrical and chemical gradients across the membrane even out. These can be modeled in an electrical circuit as a battery and the total channels of a particular ion can be modeled as a resistor. Each modelled ion has a parallel branch in the corresponding electrical circuit. The following equations adapted from [Gerstner et al., 2014b] describe the HH model:

$$I(t) = I_C(t) + \sum_k I_k(t), \tag{4}$$

Where the current of each ion k can be described in terms of the open probability of a k channel, p_k and the maximum conductance when all k channels are open, g_k:

$$I_k = g_k p_k (u - E_k). \tag{5}$$

In particular Hodgkin and Huxley modeled Na^+, K^+ and a leak L currents:

$$C\dot{u} = g_{Na} m^3 h (E_{Na} - u) + g_K n^4 (E_K - u) + g_L (E_L - u), \tag{6}$$

Where m, h and n are open probabilities for subunints of Na or K channels governed by:

$$\dot{x} = -\frac{1}{\tau_m(u)}[x - x_0(u)], \qquad x \in \{m, h, n\}. \tag{7}$$

As in the IF model, these rules describe the dynamics of a single unit, which can subsequently be connected to model a network of neurons (e.g., [Terman et al., 2002]) and augmented to include plasticity rules [Borges et al., 2016].

2.5.3 Rubin-Terman

[Terman et al., 2002] augmented the HH model to create a subthalamopallido network of the basal ganglia (RT model), where GPe and STN neurons are modelled according to the following equation,

$$C\dot{u} = -I_L - I_K - I_{Na} - I_T - I_{Ca} - I_{AHP} - I_{s\to d} - I_{s\to s} + I_{app} \tag{8}$$

Where leak (L), K^+, Na^+ and high-threshold Ca^{2+} currents [Song et al., 2000], are described in HH-like equations, and low threshold calcium current I_T is different for GPe and STN neurons. I_{AHP} represents Ca^{2+}-activated, voltage-independent *afterhyperpolarisation* (AHP) K^+ current. $I_{s\to d}$ represents the inter-populational influence and is defined by $I_{s\to d} = \sum_j I_{ij}^{ds}$ where $s, d \in \{\text{GPe}, \text{STN}\}$. I_{ij}^{ds} is the current from the presynaptic neuron j in s to the postsynaptic neuron i in d, and is defined by $I_{ij}^{ds} = w_{ij}^{ds} s_{ij}^{ds}(t - \tau_{ds})(u_i - E_{ds})$ where w_{ij} is the synaptic strength, s_{ij}^{ds} is a synaptic variable and τ_{ds} is the transmission delay between d and s. [Madadi Asl et al., 2022] expand on this model by adding inhibitory spike-timing-dependent plasticity to this network with $\Delta w = \eta(\exp(-|\Delta t|/\tau_w) - \alpha)$, where η is the *learning rate*, τ_w is the time constant of the plasticity rule exponential decay and α is the depression factor.

2.5.4 Other modeling approaches

Neuronal populations can also be modelled with networks of coupled phase-oscillators as in [Tass and Majtanik, 2006]. [Duchet et al., 2023] modelled STDP as mean-field phase-locked plasticity in a network of Kuramoto oscillators [Kuramoto, 1984]. In the context of this project studying phase-locked stimulation to exploit phase-dependent plasticity rules would bias the experiments to non-null results.

[Jansen and Rit, 1995] model cortical columns of neurons by considering the PSPs of excitatory and inhibitory populations in a column to replicate EEG-recorded alpha and beta activity. [West et al., 2022] used these building blocks in a full CBGT model to study the effects of phase-dependent stimulation on coupling. Since these approaches work with LFPs, plasticity rules would have to be phase-dependent, so they would introduce the same issue as phase-oscillator networks.

3 Project Plan

The primary objective of this project is to investigate multi-site phase-locked stimulation in a spiking CBGT network model, with the goal of inducing plastic changes that transition pathological network dynamics of the BG toward a healthy desynchronised state. This work will address two important gaps in the current literature:

1. Integrating phase-locked stimulation with plasticity-targeted protocols, closing the loop in coordinated reset paradigms.

2. Systematically evaluating stimulation targets across the wider CBGT network, with emphasis on regions with experimentally validated synaptic plasticity (e.g., corticostriatal connections) while accounting for uncertainties in plasticity mechanisms at other nodes like the STN.

The selection of a spiking network with STDP rules over phase-oscillator models with phase-dependent plasticity is motivated by the following methodological consideration: Simulating phase-locked stimulation within systems governed by *a priori* phase-triggered plasticity introduces inherent circularity. Such coupling risks conflating stimulation mechanisms with network adaptation rules, effectively predetermining intervention outcomes without much dependence on physiological constraints. In contrast, spiking networks with STDP decouple the synchronisation mechanism from the phase-locked stimulation preserving the causal distinction between stimulation protocols and plasticity-driven reorganisation.

3.1 Methodology

To achieve these objectives, the following steps are outlined:

1. Implement STDP mechanisms within a spiking CBGT network model.
2. Tune pathological and healthy dynamical modes through data-driven parameter tuning, initially with plasticity disabled.
3. Conduct systematic simulations of multi-site phase-locked stimulation under different experimental conditions:
   a. STDP enabled or disabled in specific network nodes
   b. Multi-site phase-locked stimulation applied to distinct BG nuclei and cortical afferents

   Quantify network responses by analysing inter-nuclei coupling, and transitions between dynamical states.
4. Derive stimulation protocols optimised for plasticity-driven network desynchronisation.

3.2 Timeline

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Appendices

A Research gap diagram

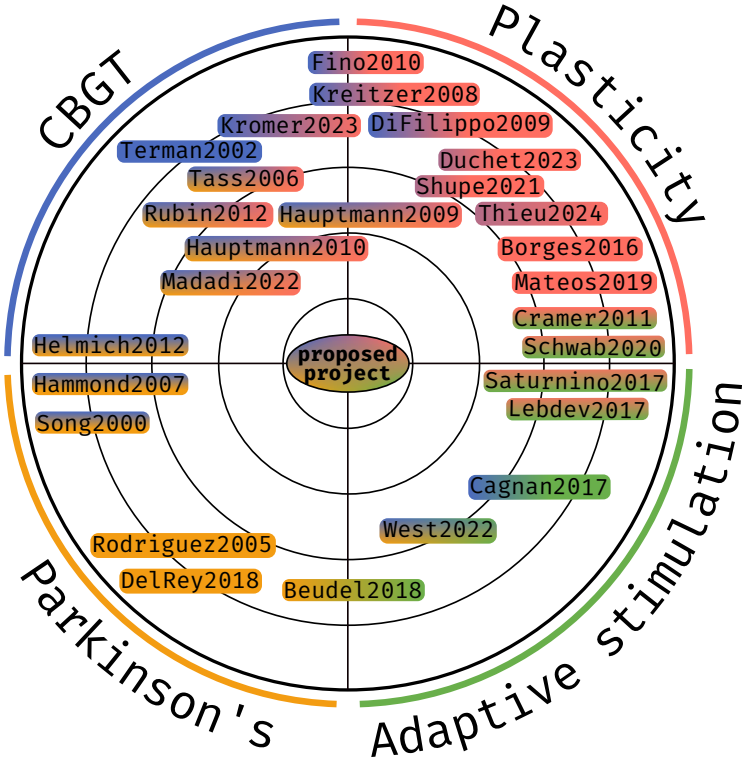

Figure 4: Visulaisation of the targeted research gap.

B Second appendix