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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Aaron Panaitescu
(*CID:* 02054726)

Supervisor:
Dr. Hayriye Cagnan

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Contents

1 Introduction / Abstract?

Stylistically, I would prefere to do an abstract here and breakdown the concepts in the following section

2 Background and literature review

start this off nicely with a diagram of the research gap

2.1 Parkinson's Disease

Parkinson's Disease (PD) is characterized by the loss of dopaminergic neurons and the presence of *Lewy Bodies* (LB) in the *Substantia Nigra pars Compacta* (SNc) [Del Rey et al., 2018]. This dopaminergic depletion in the SNc leads to striatal dopamine deficiency, which in turn leads to excessive synchronization in the basal ganglia. Hyper-synchrony 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

Tremor is primarly generated in the Cortical-Basal Ganglia-Thalamic (CBGT) network. Thus, deep brain stimulation (DBS) in this region emerged as an effective tool in the treatment of advanced PD patients [Del Rey et al., 2018]. DBS works through the implantation of electrodes in particular regions of the brain. The intuition behind this method is that it enables stimulation driven decorelatation of the different basal ganglia nuclei, pushing it to a non-pathological state. There is significant evidence that performing DBS in the STN or the GPi, can have major quality of life improvements in PD patients, reducing tremor and restoring motor control [Rodriguez-Oroz et al., 2005]. DBS does, however have significant limitations.

Firstly, like any highly-invasive procedure, the implatation procedure has many risks. Advances in electrode technology and surgical techniques have reduced some of these risks. *cite*

Secondly, patient symptoms are only ameloriated while the stimulation is on. This means that the device needs to be on continously, which can induce numerous side effects in patients **citeee** and also creates the need for a continous power supply.

Finally, the mechanism through which DBS reduces tremors is not fully understood yet, there are many questions left to answer. For instance, why does DBS in PD get effective results around 130 Hz, when tremor frequency is on average around 20 Hz **check this**.

Therfore, several areas of research emerge in improving stimulation-based treatments of PD: finding non-invasive alternatives [Saturnino et al., 2017, Schwab et al., 2020], eleciting lasting, plastic changes in CBGT circuit, closing the loop and coupling stimulation to the presence of patient symptoms [Beudel et al., 2018], and improving stimulation patterns to harness the exploit the rythmic patterns activity in the basal ganglia [Cagnan et al., 2017, West et al., 2022].

2.3 Stimulating at the right time

The Parkinsonian state is modulated by the interplay between four pathways in the CBGT the **hyperdirect** excitatory cortico-subthalamic pathway, the **direct** inhibitory striato-pallidal pathway, the **indirect** inhibitory subthalamic-pallido pathway and the inhibitory **pallido-subthalamic** (PS) pathway. In the Parkinsonian state the hyperdirect pathway is down-regulated, while pallido-subthalamic pathway is upregulated, leading to a shift in beta band oscillatory activity from sub-band β_1 to sub-band β_2, which corellates to hyper-synchrony in the basal ganglia [West et al., 2022]. ** **add diagram** **

important [Cagnan et al., 2017] [Beudel et al., 2018] [West et al., 2022]

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 reorganizing 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 pos-synaptic neuron. While, the mechanisms of plasticity have been throughly studied **cite**, this understanding is just starting to find its way into clinical applications in neurorehabilitation (e.g. stroke, trauma, spinal cord injury [Cramer et al., 2011]) and neuroprostheses [Lebedev and Nicolelis, 2017].
should mention STDP above
OMG I'm cooked how tf did I miss [Hauptmann and Tass, 2009, Hauptmann and Tass, 2010]?!
****coordinated reset (CR) stimulation****
this should be relevant as well [Schwab et al., 2020]

2.5 Neuron-level vs. Mean-field models

Neuronal dynamics models are defined by defined by rules (ODEs) of how voltage in an unit changes over time in response to voltage in the network and external current (e.g. noise, stimulation current). The question then becomes what is an unit? There are two broad categories branching out of this question: An 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.

Neuron models (or spiking models) work by combining networks of units that individually simulate neuronal action potentials (APs). These networks can then be organized into different nuclei (e.g. STN) and coherced to respect excitatory or inhibitory connections between nuclei. Within this class of models, different schemes for modeling 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])

2.5.1 Integrate-And-Fire

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 threshold θ. This can be modeled 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 strengthend or weakend depending on spike timings between units, modeling STDP. [Shupe and Fetz, 2021] simulate plasticity in cortical columns; [Kromer et al., 2023] model plasticity between basal ganglia nuclei both using a IF model.

2.5.2 Hodgkin-Huxley

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 networks of neurons (e.g. [Terman et al., 2002]) and augumented to include plasticity rules [Borges et al., 2016].

2.5.3 Rubin-Terman

[Terman et al., 2002] augumented the HH model to create a subthalamopallido network of the basal ganglia (RT model), where GPe and STN neurons are modeled according 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 *afterhyperpolarization* (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 transimission 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. [Rubin et al., 2012] expand the RT model into a CBGT model and analyze ...
[Hauptmann and Tass, 2009, Hauptmann and Tass, 2010] → GPe-STN + plasticity + CR stimulation
[Rubin et al., 2012] (on multi-site CR stimulation) *"in its current formulation, does depend critically on spike timing dependent plasticity inconnections among excitatory neurons within the STN, the presence of which currently lacks experimental confirmation. It is possible that the general theory is correct but that the site of plasticity is elsewherein the BG, an idea that remains to be explored"*

2.5.4 Jansen

this should be brief [Jansen and Rit, 1995] [West et al., 2022]
phase-dependent plasticity [Duchet et al., 2023]

2.6 **Other ways of improving stimulation-based treatments**

stimulation parameter optimizations, closing the loop (e.g. aDBS [Beudel et al., 2018]) *Maybe this can be folded into the stimulating at the right time part since they are pretty closely related. Also should mention the idea that these methods are not mutually exclusive, meaning that in principle they could be combined, adaptive stim closing the loop, with inducing plastic changes as target*

3 Project Plan

3.1 Aims

1. Model neuroplasticity in a Parkinsonian CGBT network
2. Investigate the viabillity of harnessing plasticity to remove the system from the pathological state and analyze the dynamics that follow

   here i care about things like for how long and how does the network change. To what degree can we induce changes etc.

   should look into viable timescales + noise analyze how long does it take to rebound to pathological state
3. Try to link potential results to potential stimulation protocols?

3.2 Methodolgy

How indeed? HH/IF Pakrkinsoni model + plasticity rules, trying different stimulation-based protocols (link with experimental data?)
look into how to tune IF model parameters from experimental data

3.3 Timeline

Gant chart thingy

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Appendices

A First appendix

B Second appendix