Imperial College London

Literature review and thesis proposal
MRes. Neurotechonlogy

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

Aaron Panaitescu
(*CID:* 02054726)

Supervisor:
Hayriye Cagnan

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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. This hyper-synchrony is a hallmark of the Parkinsonian state [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) emerged as an effective tool in the treatment of advanced PD patients [Del Rey et al., 2018]. DBS work through the implantation of electrodes in particular regions of the brain. The idea is that this sort of stimulation can be used to decorelate regios of the basal ganglia and to push the network 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]. While effective, DBS has its limitations.

Firstly, it is an highly-invasive procedure, and so it has many risks, though advances in electrode technology and surgical techniques have reduced some of these risks.

Secondly, the stimulation needs to be on at all times; if it is turned off, patient simptoms return.

Additionaly, the mechanism through which DBS removes tremors is not fully understood yet, there are many wuestions left to answer. For example, why does DBS in PD get effective results around 130 Hz, when tremor frequency is on average around 20 Hz.

Finally, stimulating regions of the brain continously and at such high frequencies leads to numerous side effects **citation desperatly needed**.

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** pathway. In the Parkinsonian state the hyperdirect pathway is downregulated, 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

mention [Lebedev and Nicolelis, 2017] [Cramer et al., 2011]

2.5 Neuron-level vs. Mean-field models

briefly, in general and expand in the context of plasticity

cover [Jansen and Rit, 1995] ([Hodgkin et al., 1952] does this really need to be cited?)

important [Terman et al., 2002] [Rubin and Terman, 2004] [Rubin et al., 2012] [Duchet et al., 2023] [Shupe and Fetz, 2021] [Schwab et al., 2020]

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