

Literature review and thesis proposal
MRes. Neurotechnology

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

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1 Introduction / Abstract?

Stylistically, I would prefer 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 primarily 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 decorrelate regions 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 symptoms return.

Additionally, the mechanism through which DBS removes tremors is not fully understood yet, there are many questions 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 continuously and at such high frequencies leads to numerous side effects **citation desperately needed**.

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 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 rhythmic 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****

References

- [Beudel et al., 2018] Beudel, M., Cagnan, H., and Little, S. (2018). Adaptive brain stimulation for movement disorders. *Current Concepts in Movement Disorder Management*, 33:230–242.
- [Cagnan et al., 2017] Cagnan, H., Pedrosa, D., Little, S., Pogosyan, A., Cheeran, B., Aziz, T., Green, A., Fitzgerald, J., Foltynie, T., Limousin, P., et al. (2017). Stimulating at the right time: phase-specific deep brain stimulation. *Brain*, 140(1):132–145.
- [Cramer et al., 2011] Cramer, S. C., Sur, M., Dobkin, B. H., O’Brien, C., Sanger, T. D., Trojanowski, J. Q., Rumsey, J. M., Hicks, R., Cameron, J., Chen, D., et al. (2011). Harnessing neuroplasticity for clinical applications. *Brain*, 134(6):1591–1609.
- [Del Rey et al., 2018] Del Rey, N. L.-G., Quiroga-Varela, A., Garbayo, E., Carballo-Carbajal, I., Fernández-Santiago, R., Monje, M. H., Trigo-Damas, I., Blanco-Prieto, M. J., and Blesa, J. (2018). Advances in parkinson’s disease: 200 years later. *Frontiers in neuroanatomy*, 12:113.
- [Duchet et al., 2023] Duchet, B., Bick, C., and Byrne, Æ. (2023). Mean-field approximations with adaptive coupling for networks with spike-timing-dependent plasticity. *Neural Computation*, 35(9):1481–1528.
- [Hammond et al., 2007] Hammond, C., Bergman, H., and Brown, P. (2007). Pathological synchronization in parkinson’s disease: networks, models and treatments. *Trends in neurosciences*, 30(7):357–364.
- [Helmich et al., 2012] Helmich, R. C., Hallett, M., Deuschl, G., Toni, I., and Bloem, B. R. (2012). Cerebral causes and consequences of parkinsonian resting tremor: a tale of two circuits? *Brain*, 135(11):3206–3226.
- [Hodgkin et al., 1952] Hodgkin, A. L., Huxley, A. F., and Katz, B. (1952). Measurement of current-voltage relations in the membrane of the giant axon of loligo. *The Journal of physiology*, 116(4):424.
- [Jansen and Rit, 1995] Jansen, B. H. and Rit, V. G. (1995). Electroencephalogram and visual evoked potential generation in a mathematical model of coupled cortical columns. *Biological cybernetics*, 73(4):357–366.
- [Lebedev and Nicolelis, 2017] Lebedev, M. A. and Nicolelis, M. A. (2017). Brain-machine interfaces: from basic science to neuroprostheses and neurorehabilitation. *Physiological reviews*, 97(2):767–837.
- [Rodriguez-Oroz et al., 2005] Rodriguez-Oroz, M. C., Obeso, J., Lang, A., Houeto, J.-L., Pollak, P., Rehncrona, S., Kulisevsky, J., Albanese, A., Volkmann, J., Hariz, M., et al. (2005). Bilateral deep brain stimulation in parkinson’s disease: a multicentre study with 4 years follow-up. *Brain*, 128(10):2240–2249.
- [Rubin et al., 2012] Rubin, J. E., McIntyre, C. C., Turner, R. S., and Wichmann, T. (2012). Basal ganglia activity patterns in parkinsonism and computational modeling of their downstream effects. *European Journal of Neuroscience*, 36(2):2213–2228.
- [Rubin and Terman, 2004] Rubin, J. E. and Terman, D. (2004). High frequency stimulation of the subthalamic nucleus eliminates pathological thalamic rhythmicity in a computational model. *Journal of computational neuroscience*, 16:211–235.

- [Saturnino et al., 2017] Saturnino, G. B., Madsen, K. H., Siebner, H. R., and Thielscher, A. (2017). How to target inter-regional phase synchronization with dual-site transcranial alternating current stimulation. *Neuroimage*, 163:68–80.
- [Schwab et al., 2020] Schwab, B. C., König, P., and Engel, A. K. (2020). Spike-timing-dependent plasticity can account for aftereffects of dual-site transcranial alternating current stimulation. *bioRxiv*.
- [Shupe and Fetz, 2021] Shupe, L. and Fetz, E. (2021). An integrate-and-fire spiking neural network model simulating artificially induced cortical plasticity. *Eneuro*, 8(2).
- [Terman et al., 2002] Terman, D., Rubin, J. E., Yew, A., and Wilson, C. (2002). Activity patterns in a model for the subthalamopallidal network of the basal ganglia. *Journal of Neuroscience*, 22(7):2963–2976.
- [West et al., 2022] West, T. O., Magill, P. J., Sharott, A., Litvak, V., Farmer, S. F., and Cagnan, H. (2022). Stimulating at the right time to recover network states in a model of the cortico-basal ganglia-thalamic circuit. *PLOS Computational Biology*, 18(3):1–32.

Appendices

A First appendix

B Second appendix