# Computational model of Deep Brain Stimulation (DBS). Transitions from Healthy to Parkinsonian and DBS treatment.

Konstantinos Spiliotis*, Jens Starke *
*Institute of Mathematics, University of Rostock, D-18057 Rostock, Germany

*Summary*. The basal ganglia network plays an important role in the movement and emotional control. Changes in the structure and dynamics of the network are closely related to pathological disorders (Parkinson, Dystonia, Depression etc). We developed a large scale biophysical neuronal model in order to study the effect of Deep Brain Stimulation (DBS) in Parkinson and Dystonia. The neural network model consists of 4 major areas of basal ganglia, Globus Pallidus External and Internal (GPE)-(GPI), Subthalamic nucleus (STN) and Thalamus. By changing several model parameters related to the synaptic weights, as well as the frequency of external DBS stimulus, the model switches the dynamics from normal to pathological (Parkinson-Dystonia) to DBS treatment behavior. Combining both, numerical bifurcation analysis and Equation Free Methodology (IEFM), we detect systematically in the parametric space, the dynamical regimes of different dynamics.

## Introduction

Deep Brain Stimulation (DBS) consists a revolutionised treatment for movement and mental disorder. After 1997 when the Food and Drug Administration (FDA, USA) approved DBS as a treatment for tremor, the development was rapid including several diseases (Parkinson, Dystonia, Epilepsy) but also mental Disorders (Depression and Obsessive-Compulsive Disorder)[1]. Even in our days then main mechanism behind this treatment remain mysterious. One of the main obstacles is the lack of one coherent framework which joins the different levels-scales of mechanism ranging from microscopic (neurophysiology and genetic variations of the neurons), to macroscopic (i.e. tremor and dyskinesia). An intermediate level, the mesoscopic, is related with dynamics of specific networks of neurons in different nucleus of BG. The dynamics of these networks constitute the bridge of micro and macro behaviour since are affected from the neuron's properties and the emergent patterns which arise define the macroscopic action. In this spirit we propose a computational large-scale biophysical model related to the Parkinson Disease (PD) and DBS treatment. Based on the work presented in [2, 3] we model 4 areas of the Basal Ganglia (BG); the Globus Pallidus External and Internal (GPE-GPI) the Sub-Thalamic Nucleus (STN) and the Thalamus. We show how the variations in the synaptic weights connectivity between the BG areas affects the macroscopic dynamics, switches from normal to PD and how the DBS on the STN acts as a treatment affecting the whole network. In addition, during DBS the model reveals a de-synchronization of the GPI activity which is projected to Thalamus. Combining both, numerical bifurcation analysis and Equation Free Methodology (EFM) [4] and Implicit Equation Free Methodology [5] for multiscale modelling, we detect systematically in the parametric space, the dynamical regimes of different dynamics. Main parameters are the connectivity weights and frequency of DBS.

## Description of the Basal Ganglia Network

All BG regions follow the Hodgkin Huxley current balanced formalism. The STN neurons follow the equation [2]

$$C\frac{dV_i}{dt} = -I_{Ca} - I_{Na} - I_K - I_T - I_L - I_{AHP} - I_{GS} - I_{SS} + I_{DBS} \tag{1}$$

where $C$ is the membrane capacity, $I_{Ca}, I_{Na}, I_K$ are the ionic currents, $I_L$ is the leak current, $I_{AHP}$ and $I_T$ are the after hyperpolarized and $T$ currents which are depended on the calcium concentration. The postsynaptic currents $I_{SS} = g_{SS}(V - V_S)\sum_j s_j$ and $I_{GS} = g_{GS}(V - V_G)\sum_j s_j$ correspond to internal STN excitation and inhibition from GPE respectively. The $s_i$ is the activation variable [2, 3] and the summation is taken over the presynaptic neurons. The GPE-GPI neurons follow similar current balance equation

$$C\frac{dV_i}{dt} = I_{app} - I_{Ca} - I_{Na} - I_K - I_T - I_L - I_{AHP} - I_{SG} - I_{GG} \tag{2}$$

where the currents are defined in the same way as the STN [2]. $I_{app}$ represents the input current from the striatum and has the same constant value for all GPE neurons. Finally the Thalamic neurons follows the equation

$$C\frac{dV_i}{dt} = I_L - I_{Ca} - I_{Na} - I_K - I_T - I_L - I_{GiTh} + I_{SM} \tag{3}$$

where the $I_{SM}$ describes the input from sensory motor cortex. The detailed form of the currents and the values of parameters are described in [2].
The STN and GPE areas include N=500 neurons each while the GPi and Thalamus consist of N=200 neuron. For each area we use a small world of network with $k = 10$ and $p = 0.01$[6]. The interconnections between different layers are 1-1 i.e. one STN neuron is adjacent with one GPE neuron and one GPI neuron communicate with one thalamic neuron. A representative image is depicted in Fig.1.

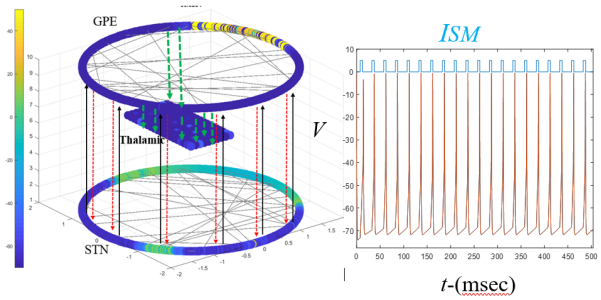


Figure 1: Illustrative image of the whole BG network. Different areas are depicted as small world network. (b) Dynamics of Thalamic neurons under the external input which comes from sensory motor cortex.

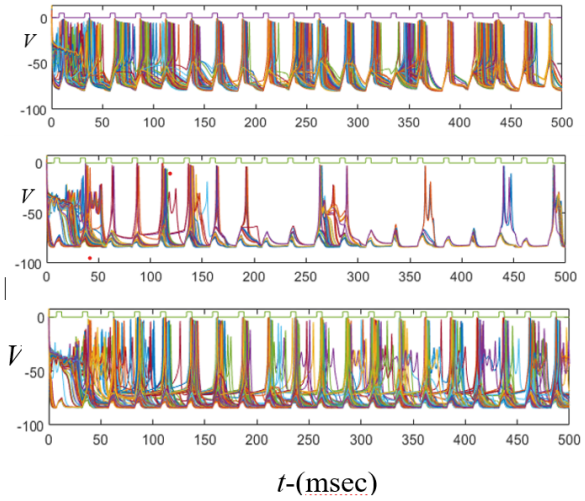


Figure 2: Dynamics of the Thalamics neurons in normal case(first row). During the PD (middle row) and finally under the DBS treatment.

## Results

We investigate the dynamics with respect the connectivity weights between the GPI and thalamus. For small value of inhibition $g_{GiTh}$ the thalamic neurons reacts in rights way to external sensory motors inputs see Fig 2. For higher value of $g_{GiTh}$ i.e. higher inhibition, thalamus produces Parkinsonian behaviour: ineffective response to external sensory motor input, while with DBS on and with same connectivity parameters as the PD behaviour, the model shows dynamics close to normal case: The thalamus after transient period, reacts similar (approximately) to healthy normal case see Fig.2. In order to analyse the emergent dynamics we will perform numerical bifurcation analysis, under the Equation Free Methodology [5]. The macroscopic variables are the mean values of the membrane voltage of the four areas.

## References

[1] Pycroft L, Stein J., Aziz T. (2018) Deep brain stimulation: An overview of history, methods, and future developments. *Brain and Neuros. Advances* **2**:1-6.

[2] Rubin J., Terman D. (2004) High frequency stimulation of the subthalamic nucleus eliminates pathological thalamic rhythmicity in a computational model. *J Comput Neurosci.* **16**(3):211-235.

[3] Ermentrout B., Terman D.(2012) Neural networks as spatio-temporal pattern-forming systems. Mathematical Foundations of Neuroscience, Vol. 35 Spriner, New York.

[4] Kevrekidis et al. (2003) Equation-free, coarse-grained multiscale computation: Enabling mocroscopic simulators to perform system-level analysis. *Communications in Mathematical Sciences* **1**(4): 715-762.

[5] Marschler C, Sieber J., Berkemer R., Kawamoto A., Starke J. (2014 )Implicit Methods for Equation-Free Analysis: Convergence Results and Analysis of Emergent Waves in Microscopic Traffic Models.*SIAM J. Appl. Dyn. Syst.* **13**(3): 1202–1238.

[6] Watts D., Strogatz S. (1998) Collective dynamics of 'small-world' networks. *Nature* **393**: 440.