A physiologically realistic computational model of the basal ganglia network

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The basal ganglia (BG) are a set of nuclei that process movement information: they refine and adjust simple movement actions. The BG has two major pathways: the striatum (STR)-indirect neuron pathway and the subthalamic (STN)-hyperdirect nucleus pathway. The GPe is the connecting nucleus between the two pathways. The STR inhibits the GPe and the STN excites the GPe which is divided into two types of neurons [1, 4], the prototypical and the arkypallidal. This discovery allows for a better understanding of the functioning of this neural network. We model the STN-GPeA-GPeP-STR(D2) network and study the influence of the nucleus on each other like in [2] (see Figure 1**A**). The neurons have been modeled as point neurons using the Hodgkin-Huxley formalism and the synapses as exponential functions. From extensive simulations performed with the **SiReNe** software (Neural network simulator, in french: **Si**mulateur de **Ré**seaux de **Ne**urones [3]), we show that our network is in good agreement with the physiological results of [2]. This simulator is based on a hybrid method combining time-step and event-driven computations with a Runge-Kutta numerical method at inner level. GPe is mainly inhibited by GABAergic inputs of the STR and we study the impact of STR connectivity on GPe. We observe that the GPeP and GPeA react in opposite ways when the STR is activated, i.e. GPeP is entirely inhibited whereas the GPeA and STN are completely excited, as observed in [2] (see Figure 1**B,C**). This work aims at better understanding the synaptic connectivity scheme. This model will allow us to test hypotheses regarding the pathological rhythmogenesis in Parkinson disease, both at the cellular and connectivity levels.
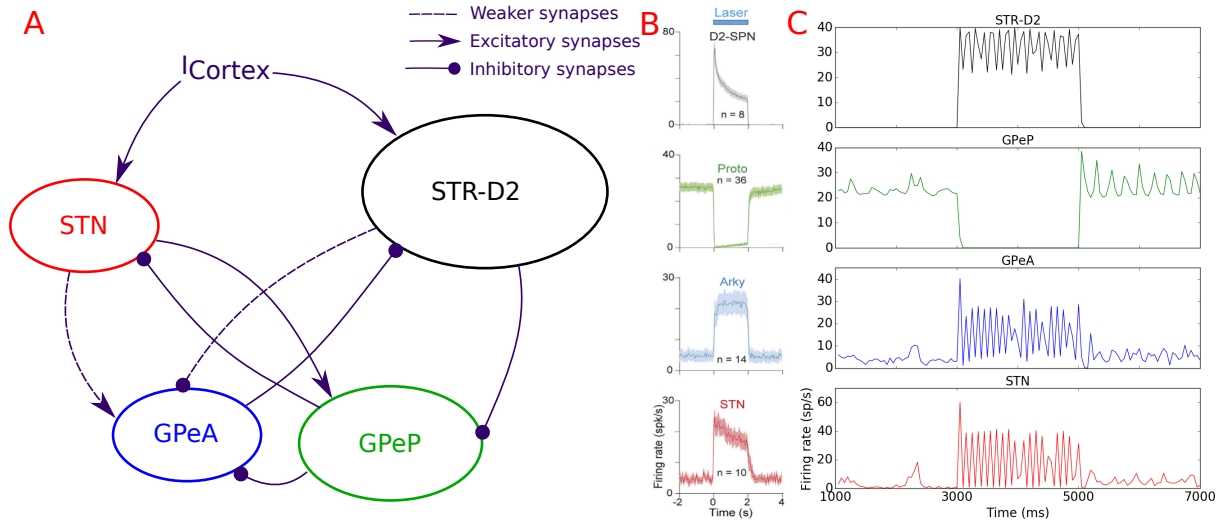

Figure 1: **A** Basal ganglia model STN-GPeA-GPeP-STR(D2) with the connectivity. **B, C** Comparing biological data with simulated data. STN-GPeA-GPeP-STR(D2) firing rate between 1-7s. STR-D2 activated with a stimulation between 3-5s. GPeP and GPeA react oppositely. **B** Biological data reproduced from Aristieta et al. with the courtesy of the authors. **C** Simulated data. Firing rate during stimulation for STN: 20.0 +/- 3.8 Hz, $GPeA$: 15.9 +/- 3.2 Hz, $GPeP$: 0.1 +/- 0.4 Hz, STR-$D2$: 32.3 +/- 0.8Hz.

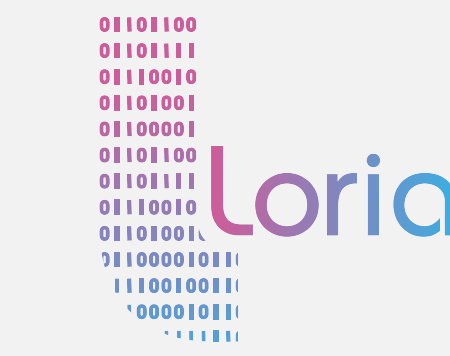# References

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Introduction

Parkinson's disease is characterized by pathological oscillations in the basal ganglia (BG). The BG are a set of nuclei that process movement information: they refine and adjust simple movement actions. This nuclei group has two major pathways: the striatum (STR)-indirect neuron pathway and the subthalamic (STN)-hyperdirect nucleus pathway. The GPe is the connecting nucleus between the two pathways. The STR inhibits the GPe and the STN excites the GPe which is divided into two types of neurons [1,6], the prototypical (GPeP) and the arkypallidal (GPeA). This discovery allows for a better understanding of the functioning of this neural network. We model the STN-GPeA-GPeP-STR(D2) network and study the influence of the nucleus on each other like in [2] (see Figure 1**A**). This work aims at better understanding the influence of GPeP and GPeA neurons in Parkinson's disease and the role of the interplay with STR(D2) neurons.

Methods

The neurons have been modeled as point neurons using the Hodgkin-Huxley formalism and the synaptic current with an exponential function. The synaptic current is the sum over all the spikes that neuron k receives form neuron j and the global synaptic current of neuron k is the sum over all synaptic currents of all the presynaptic neurons.

$$I_{syn,k}(t) = \sum_j \overline{g}_{syn,jk}(V_k - E_{syn,jk}) \sum_{i=1}^{n_j} exp\left(-\frac{t - t_{sp_i}}{\tau_{syn,jk}}\right) \qquad (1)$$

where $\tau_{syn,jk}$ and $\overline{g}_{syn,jk}$ are the time constant and the synaptic conductance of the synapse from neuron j to neuron k and n_j is the number of spikes the neuron k receives from neuron j at time t_{sp_i}. The reversal potential E_{syn} is used to define different types of synapses; inhibitory synapse is defined at $-85mV$ and excitatory synapse at $0mV$. The differential equation of the membrane potential of one neuron looks like:

$$C_m\frac{dV}{dt} = \sum_{ion} -g_{ion}m^a h^b s^c(V - E_{ion}) + I_{Cortex} - I_{syn} \qquad (2)$$

where I_{Cortex} is only applied for the STN and STR(D2) neurons.

Connected with	STN	GPeA	GPeP	STR(D2)
STN	/	30|7.0|2.5	30|5.0|5.5	/
GPeA	/	/	/	10|25.0|0.08
GPeP	30|8.0|1.5	25|5.0|2.5	/	/
STR(D2)	/	/	500|6.0|24.5	/

Neuron type	Currents I_{ion} (pA)
STN [8]	$Na, K, T, Ca^{2+}, AHP, Leak$
GPeP/A [4,5]	$NaP, NaF, HCN, SK, Kv3, Ca^{2+}, Leak$
STR(D2) [7]	$Na, K, M, Leak$

Table: BG synaptic connection. Three different variables to define the synaptic connection; 1. the # of connections, 2. the synaptic time constant (ms) and 3. the synaptic conductance (nS) divided by the number of connections.

Results

From extensive simulations performed with the **SiReNe** software (Neural network simulator, in french: **Si**mulateur de **Ré**seaux de **Ne**urones [3]), we show (Figure 1**B**) that our network is in good agreement with the physiological results of [2] at least for the first results of [2]. Our simulator is based on a hybrid method combining time-step and event-driven computations with a Runge-Kutta numerical method [3]. GPe is mainly inhibited by GABAergic inputs of the STR and we study the impact of STR connectivity on GPe. We observe that the GPeP and GPeA neurons react in opposite ways when the STR is activated, i.e. GPeP is entirely inhibited whereas the GPeA and STN are completely excited, in agreement with experimental results [2] (see Figure 1**B,C**).
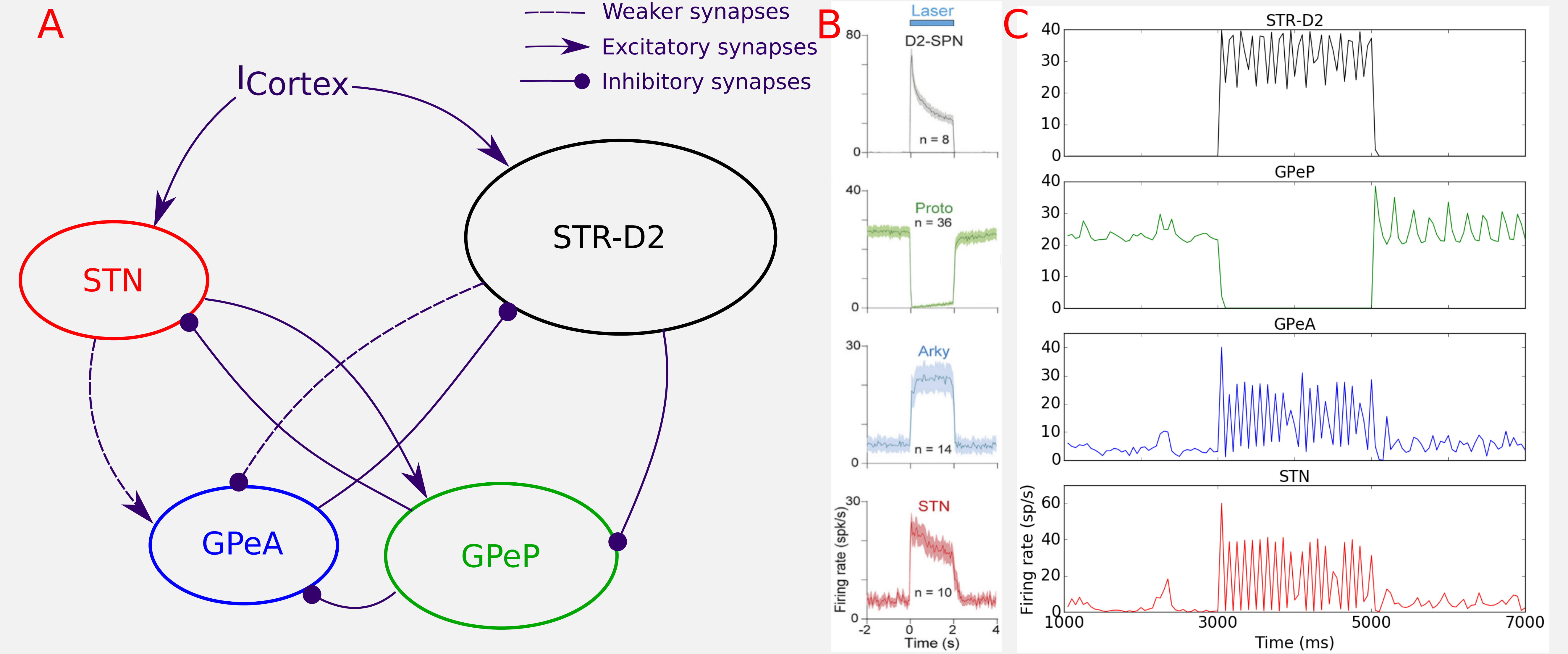

Figure: **A** Basal ganglia model STN-GPeA-GPeP-STR(D2) with the connectivity. **B, C** Comparing biological data with simulated data. STN-GPeA-GPeP-STR(D2) firing rate between 1-7s (simulated data) and between (-2)-4s (biological data). STR-D2 activated with a stimulation between 3-5s (simulated data) and between 0-2s (biological data). GPeP and GPeA react oppositely. **B** Biological data reproduced from [2] with the courtesy of the authors. **C** Simulated data. Firing rate during stimulation for *STN*: 20.0 +/- 3.8 Hz, *GPeA*: 15.9 +/- 3.2 Hz, *GPeP*: 0.1 +/- 0.4 Hz, *STR-D2*: 32.3 +/- 0.8Hz.

Discussion - Perspectives

This work aims at better understanding the synaptic connectivity scheme of the BG. Moreover we show that it is necessary to differentiate GPeA and GPeP neurons because   (1) they are connected to different structures of the basal ganglia; (2) their intrinsic cellular properties influence the network in different ways [2]. This model will allow us to test hypotheses regarding the pathological rhythmogenesis in Parkinson disease, both at the cellular and connectivity levels and we also intend to test plausible hypotheses among which: Would the connectivity of GPeA to STR(D1) dopamine neurons be strengthened under pathological conditions? Can the hypoactivity of STR(D1) and the hyperactivity of D2 be explained only by these connectivity properties?

References

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