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A computational model of GPe prototypic and arkypallidal neurons with automated parameter fitting.

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Parkinson's disease is characterized by pathological oscillations in the basal ganglia. To gain insight on the origin of these oscillations, we developed a computational model of the globus pallidus (GPe). Our model consists of interconnected prototypic (GPeP) and arkypallidal (GPeA) neurons [1, 5]. We modeled GPeP and GPeA neurons as single-compartment neurons using Hodgkin-Huxley formalism. The GPeA and GPeP neurons have similar ionic currents (I_{NaP}, I_{NaF}, I_{HCN}, I_{SK}, I_{Kv3}, $I_{Ca^{2+}}$, I_{leak}) but differ from their conductance values. We tuned the parameters automatically with a multi-objective optimization approach, a variant of the differential evolution [4, 6]. From extensive simulations performed with the **SiReNe** software (Neural networks simulator, in french: **Si**mulateur de **Ré**seaux de **Ne**urones [3]), we show that our model of GPeP and GPeA neurons are in good agreement with the physiological results of [1], i.e. F-I curves (see Fig. 1A), Voltage-Clamp and I-V relation (see Fig. 1B,C), shape of Action Potentials. Moreover, we show that our GPeP/A neurons interconnected with GABAergic synapses exhibit activity patterns similar to those observed in vivo [2]. This work aims at better understanding the influence of these two different types of neurons in Parkinson's disease.

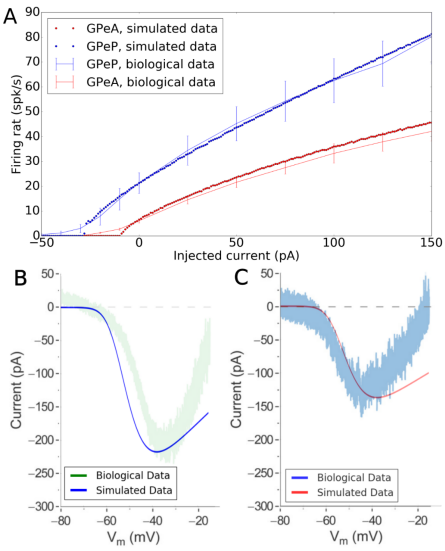

Figure 1. Comparing simulated data with biological data.
A Firing rate vs. injected current (F-I curves).
B,C Persistent sodium channel (NaP) current vs. the membrane voltage V_m in a prototypic neuron (**B**) and an arkypallidal neuron (**C**).

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A computational model of GPe prototypic and arkypallidal neurons with automated parameter fitting.

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Introduction

Parkinson's disease is characterized by pathological oscillations in the basal ganglia. To gain insight into the origin of these oscillations, we developed a computational model of the globus pallidus extern (GPe). Our model consists of interconnected prototypic (GPeP) and arkypallidal (GPeA) neurons that reproduce single cells in vivo recordings **[1,6]**. Our GPeP/A neurons interconnected with GABAergic synapses exhibit network activity patterns similar to those observed in vivo **[2]** (not shown here). This work aims at better understanding the influence of these two different types of neurons in Parkinson's disease both in terms of intrinsic cellular properties and connectivity with other structures of the basal ganglia, in particular the role of the interplay with D1 and D2 dopaminergic neuron populations of the direct and indirect pathways.

Methods

We modeled GPeP and GPeA neurons as point neurons using the Hodgkin-Huxley formalism. The GPeA and GPeP neurons have similar ionic currents (I_{NaP}, I_{NaF}, I_{HCN}, I_{SK}, I_{Kv3}, $I_{Ca^{2+}}$, I_{leak}) but differ from their conductance values g_{ion}.

$$C_m \frac{dV}{dt} = \sum_{ion=\{NaP,NaF,HCN,SK,Kv3,Ca,leak\}} g_{ion} m^a h^b s^c (V - E_{ion}) \quad (1)$$

Our equations are based on the modeling work from **[5]** where we customized some values of the I_{NaP} gating variables to fit experimental data. In contrast to **[5]**, we have made the distinction between GPeA and GPeP in order to take into account their different roles in Parkinson rhythmogenesis. We tuned the parameters automatically with a multi-objective optimization approach gathering different criteria, namely fitting the experimental FI-curve and adding additional weights at some key points, in a single fitness function. To this end, we use a variant of the differential evolution **[4,7]**. Simulations were performed with the **SiReNe** software (Neural networks simulator, in french: **Si**mulateur de **Ré**seaux de **Ne**urones **[3]**, available at `https://sirene.gitlabpages.inria.fr/sirene/index.html`).

Results

The table below summarizes the parameters that best fit the biological FI-curve. Some values of the I_{NaP} gating variables of **[5]** were customized to fit the biological I-V relationship.

	Conductances (mS)							I_{NaP}					
	Leak	NaP	NaF	Kv3	HCN	Ca	SK	Θ_m	k_m	k_h	τ_h^0	τ_h^1	E_K (mV)
GPeP	5.614	18.0	19474.447	9670.274	2.19	49.592	0.802	52.0	7.0	15.0	1.5	2.5	-80.0
GPeA	2.731	6.0	8698.126	9330.831	0.79	1.911	19.968	58.7	5.7	15.0	1.5	2.5	-80.0

From extensive simulations, we show that our model of GPeP and GPeA neurons are in good agreement with the physiological results of **[1]**, i.e. F-I curves (see Figure A), Voltage-Clamp and I-V relation (see Figure B,C) and the shape of Action Potentials (see Figure D,E).

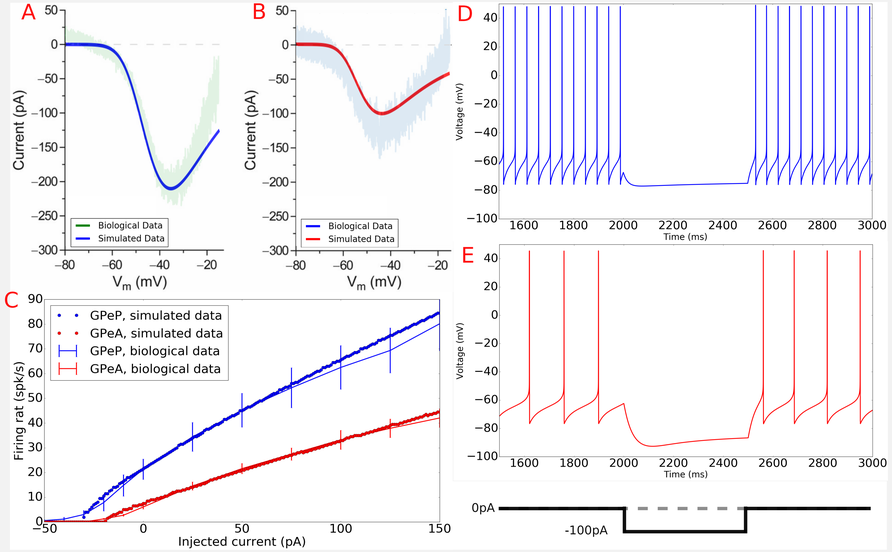

Figure: Comparison between simulated and biological data. **A, B** Persistent sodium channel (NaP) current vs. the membrane voltage V_m in a prototypic neuron (**A**) and an arkypallidal neuron (**B**).**C** Firing-rate vs. injected current (F-I curves). **D, E** The prototypic neuron (**D**) and arkypallidal neuron (**E**) activity are plotted. An hyperpolarized current (-100pA injected) is injected from 2s to 2.5s otherwise it's an autonomous firing (0pA injected).

Discussion - Perspectives

The purpose of this work is to 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]**. We intend to reproduce the experimental results of **[2]** using our basal ganglia model (STN-GPeP-GPeA-MSN) in order to test plausible hypotheses among which: Would the connectivity of GPeA to D1 dopamine neurons be strengthened under pathological conditions? Can the hypoactivity of D1 and the hyperactivity of D2 be explained only by these connectivity properties?

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