Data-driven modelling and topological analysis of the striatal microcircuitry in health and Parkinson's disease

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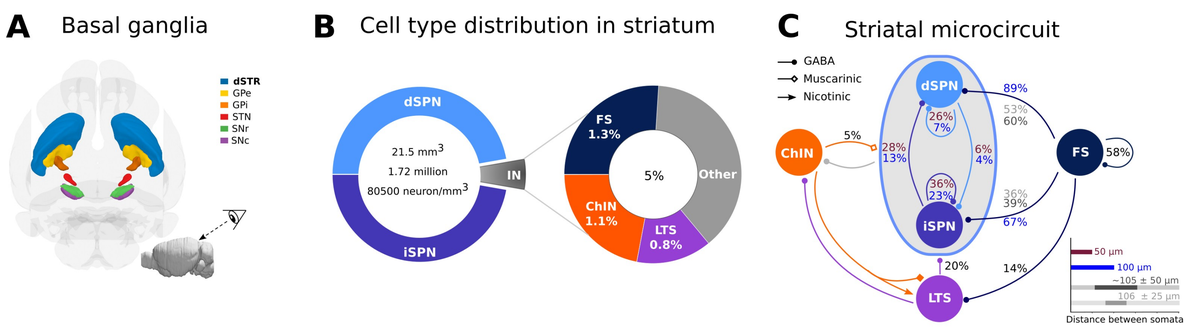
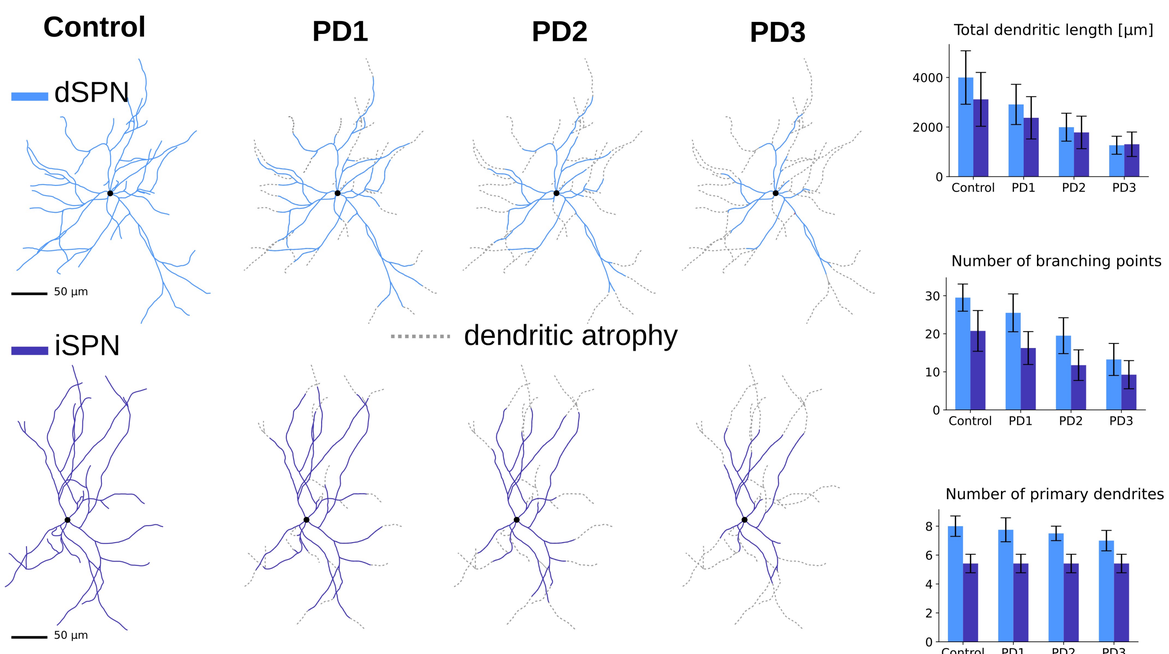
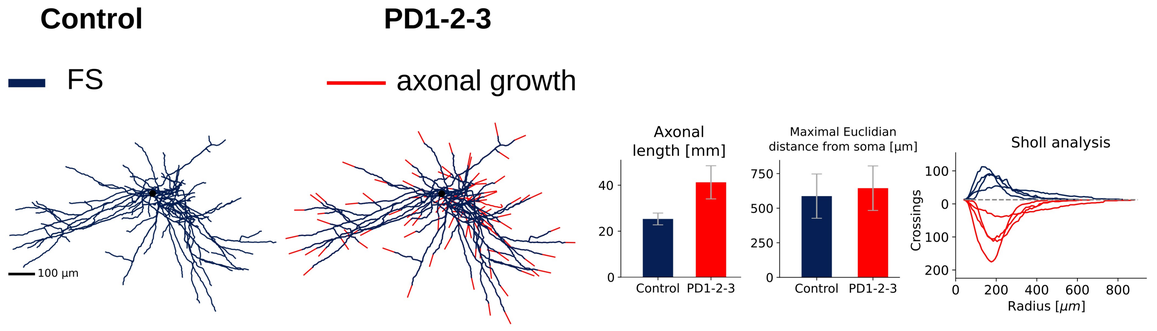
Simulating l**arge-scale networks** of detailed neurons is an important approach when synthesising and interpreting different types of experimental data from the healthy and diseased brain.
In silico approaches furthermore allow us to make quantitative predictions of scenarios that are difficult to measure experimentally today. Here we focus on the **striatum**.
We apply **topological methods** to study the organization of the **healthy** and **parkinsonian** networks and to compare them.

Our starting point is a nearly full-scale data driven model of the mouse striatum we presented in Hjorth *et al.,* 2020. We used available data on cellular morphology, electrophysiological properties, cell density and synaptic connectivity.

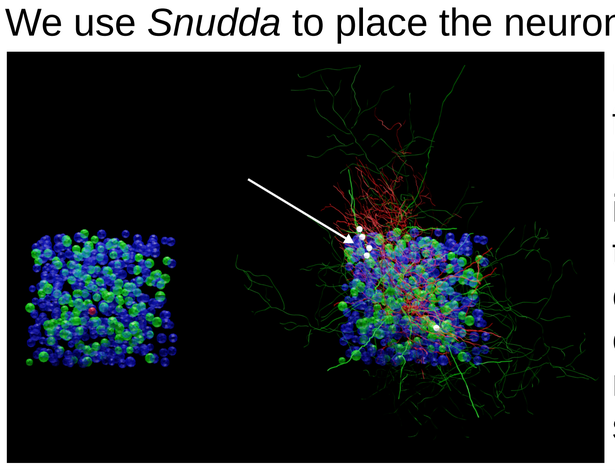


To model the progression of **Parkinson's disease** we iteratively degenerate the morphologies and estimate the change in connectivity. In particular, neurodegeneration is modelled as a progressive loss (P0, PD1, PD2, PD3) of the most distal fragments of the dendritic arbours of striatal projection neurons (SPN).
We also include the compensatory growth of fast spiking (FS) interneuron axons that takes place during early stages of PD degeneration. These processes lead to substantial reduction in the number of distal synapses on SPNs, and the addition of some GABAergic FS synapses, mimicking the disease progression.





We use *Snudda* to place the neurons and detect the synapses.



In order to avoid edge effects we focus on the core of the network. In this image, only 500 soma are illustrated. The core is formed by the green neurons which are either pre or postsynaptic to the central red one. Only two full morphologies are shown and the synapses between them are white.

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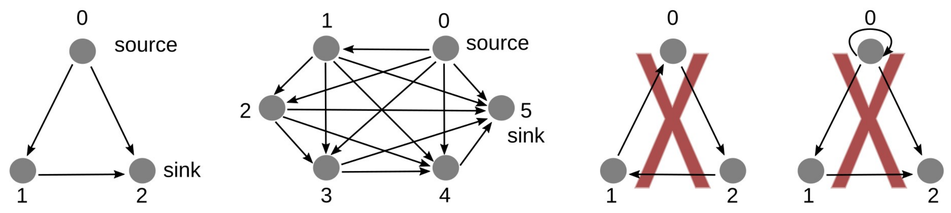
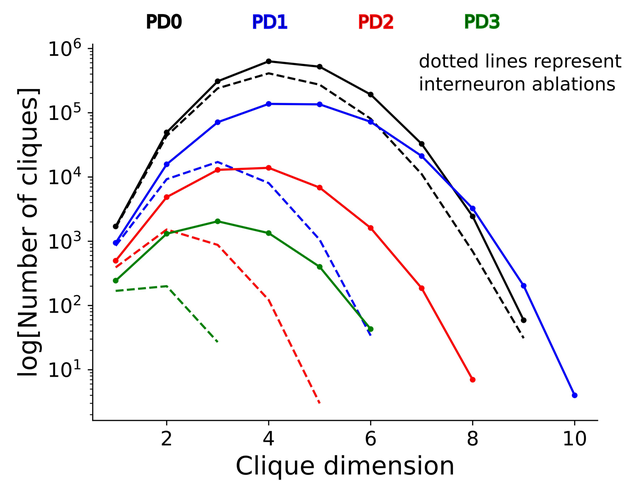
We apply algebraic topology, in particular directed cliques (simplices), to investigate the local structural connectivity in the striatum.

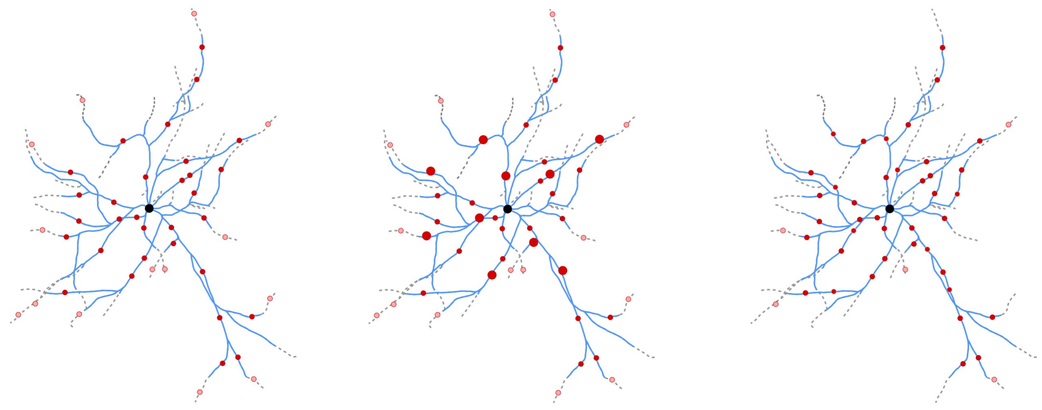


We show that progressive dendritic degeneration not only alters the global connection probabilities but affects also statistics of simplices.

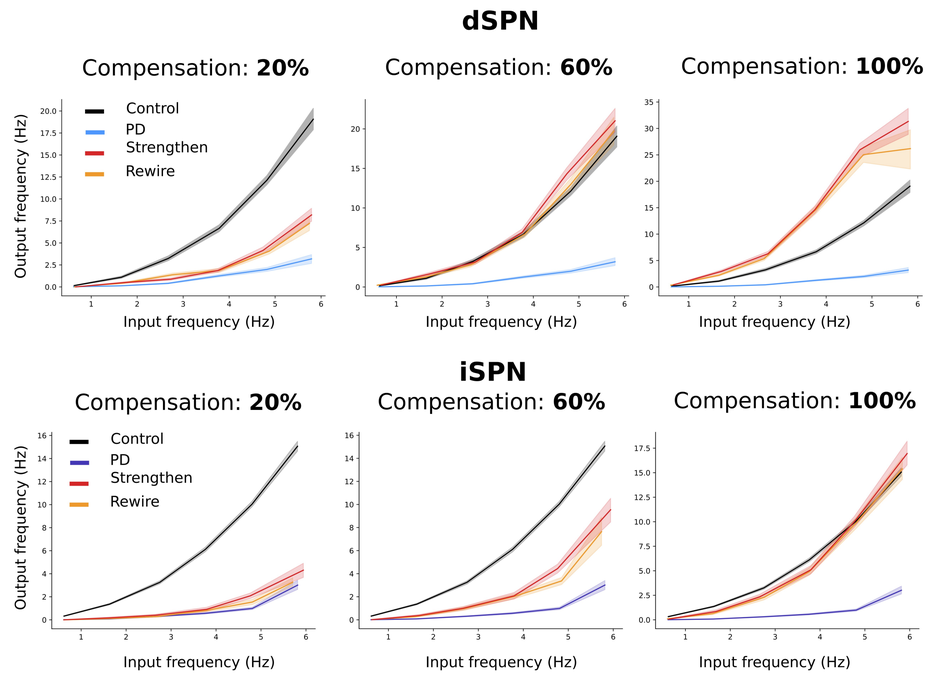
We found that interneurons, despite being the minority, can have a surprisingly large effect on the distribution of simplices, particularly at PD stages.

We have also implemented corticostiatal synapses on the SPNs and investigated two compensatory mechanisms to drive the PD cells toward the healthy firing frequency.





SPNs respond differenty to these mechanisms, in particular while dSPNs need around 60% of compensation iSPNs require 100%.



- We found that interneurons, despite being the minority, can have a surprisingly large effect on the distribution of simplices. These results suggest that interneurons may play a crucial role in shaping the striatal network structure during PD progression.
- Future studies will investigate the dynamical changes during PD progression to understand how the interneurons affect the network dynamics.

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