Brain Modelling Project - 23.02.2025

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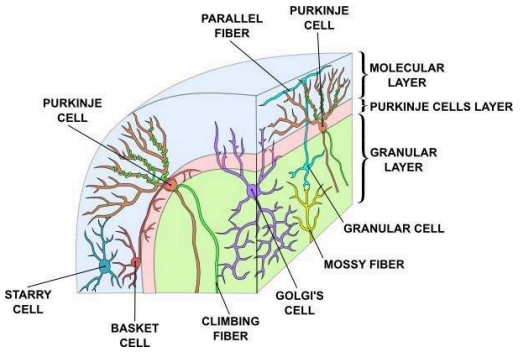
Cerebellar model simulation, a comparative study of spatial connectivity rules in the cerebellar cortex.

Introduction

The cerebellum is a complex structure in the brain, comprising half the total number of neurons but consisting only of a fraction of its volume. Part of its complexity is given by the variety of cells that populate it and their interactions, thus a good starting point is understanding the main cell types and how they synapse between one another.



The simplified models presented in this project take into account the following cell types:

- **Purkinje cells**: the ultimate destination of the afferent pathways to the cerebellar cortex. The Purkinje cells also receive a direct modulatory input on their dendritic shafts from the climbing fibers, all of which arise in the inferior olive.
- **Mossy fibers**: relay sensory information from the pons to the granule cells, then sent along the parallel fibers to the Purkinje cells for processing.
- **Granule cells**: receive mossy fiber input and generate parallel fiber signals to Purkinje cells. Held to be the most abundant class of neurons in the human brain and give rise to parallel fibers.
- **Climbing fibers**: regulate movement by modulating the effectiveness of the mossy-parallel fiber connection with the Purkinje cells.
- **Deep cerebellar nuclei**: situated in the white matter in the center of the cerebellum, receive inhibitory inputs from Purkinje cells and excitatory inputs from mossy fibers and climbing fiber pathways
- **Interneurons**: with interneurons in this case we are referring only to basket and stellate cells, which control the activity of Purkinje cells.
- **Golgi cells**: receive inputs from the parallel fibers and provide an inhibitory feedback to the cells of origin of the parallel fibers (the granule cells).

Goal

The aim of the project was to analyse the behaviour of a plethora of nervous cells in the cerebellar cortex, divided into categories according to biological morphology and to investigate whether a model with spatial connectivity rules performed better (in terms of biological realism) with respect to a model where connections between neurons weren't related to spatial constraints, but only to probability rules.

Structure of the project

To define cells we used two models on Nest, the poisson_generator, which simulates a neuron that is firing with exponentially distributed interspike intervals and the iaf_psc_alpha, a leaky integrate-and-fire model with a hard threshold, a fixed refractory period, no adaptation mechanisms and alpha-shaped input currents, which represents how neurons accumulate input until they reach a threshold and fire a spike.
The first was used to model mossy fibers and climbing fibers, which are inputs to the cerebellum carrying information from sensory and motor areas. These fibers do not behave like standard spiking neurons but rather relay incoming signals in a way that can be approximated as a stochastic process.
For the other cells - granule cells, Golgi cells, Purkinje cells, interneurons, and deep cerebellar nuclei - which integrate inputs, generate action potentials, and participate in computations that shape motor coordination and learning, the iaf model was chosen.

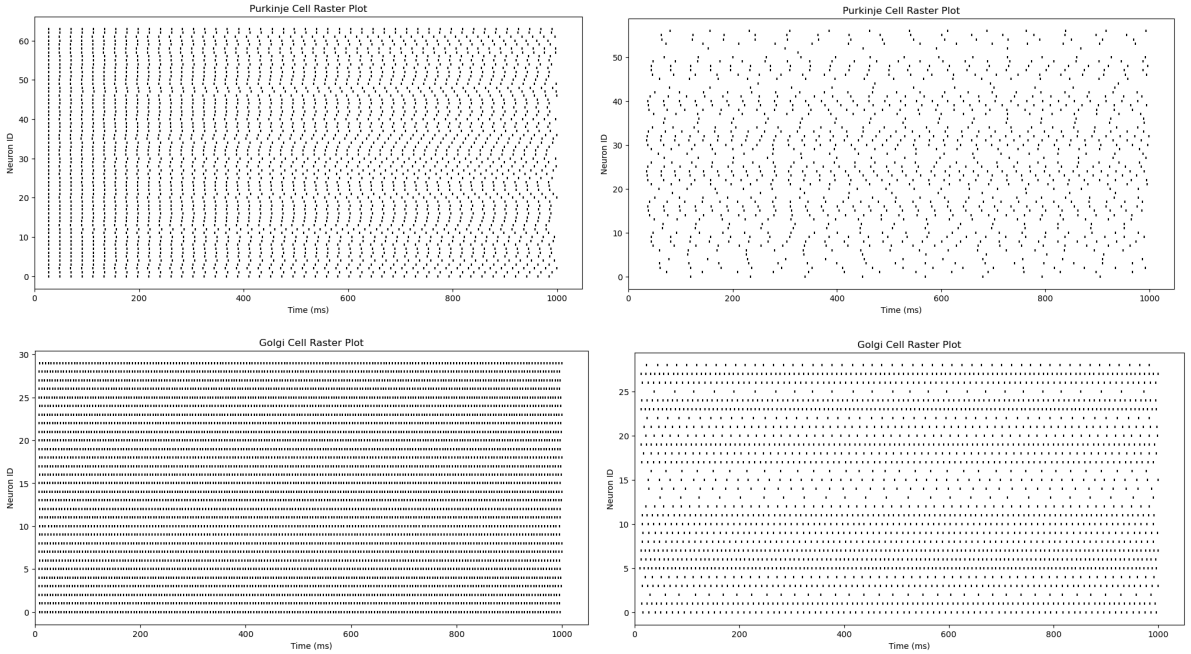
For the first model, each cell type was configured through the nest Create function with ad hoc parameters consisting of the *average rate* for mossy and climbing fibers, and of *membrane time constant*, *resting potential*, *firing threshold*, *reset potential* and *refractory period* for cerebellar cells in addition to the total number of each cell type for the final simulation.
To create connections between cells, the nest Connect function was used, taking connection and synaptic weights into account.
Regarding connections, for the most part the pairwise Bernoulli rule was used with varying probability value, based on the biological percentage of connectivity found experimentally between the two cell types being defined. The exceptions were for the connection between climbing fiber to the Purkinje cell, which was set as a one-to-one connection and the connection from Purkinje to deep cerebellar nuclear cell, set as a fixed outdegree rule, meaning that from each Purkinje cell, a fixed number of connections (outdegree value) to DCN is made.
Regarding synapses the parameters considered are weight (conductance value in nS) and delay.

The second model was set up in a way that had mossy fibers at the bottom and deep cerebellar nuclei at the top and with the connections accounting also for the spatial positions of the populations.
Using nest.spatial.free for most cells, with the exception of Purkinje which used nest.spatial.grid, the populations are located in random spatial positions within the section, and the Purkinje cells are placed in a grid.
For this model the connections are made as before mostly based on Bernoulli probability, except also the spatial constraint must be enforced (distance between the two cells involved).

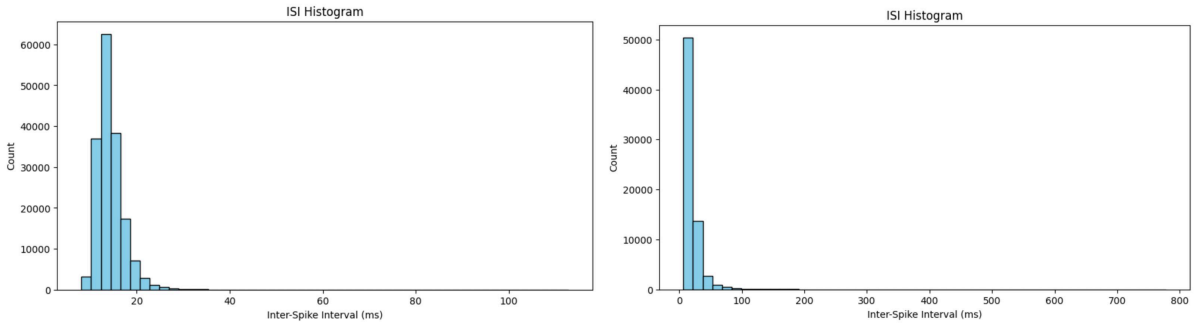
Analysis of results

In the simple model, neurons were connected probabilistically without spatial constraints and the network is more homogeneous in its connectivity, leading to relatively uniform firing properties across the population.
In the spatial model, neurons establish connections based not only on probability but also on spatial distance and neuronal type stratification and this creates local microcircuits where neurons interact more strongly with nearby cells, leading to heterogeneous firing behavior across different regions.

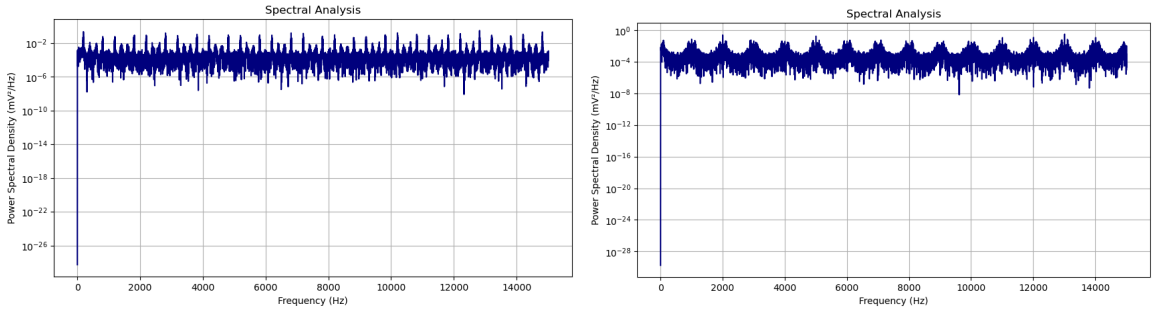
To visualize the results obtained we resorted to displaying raster plots, isi histogram graphs, voltage traces and spectral analysis plots of Golgi, granule and Purkinje cells for both models.



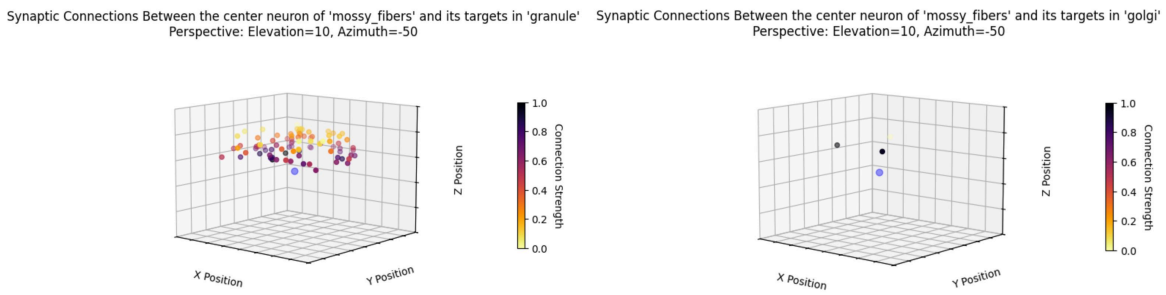
Raster plots of the simple model on the left and of the spatial model on the right. In the first model Purkinje cells exhibit regular firing, a behaviour which suggests uniform and strong excitatory input from granule cells, as well as a relatively balanced inhibitory drive. Also Golgi cells fire regularly, the raster plot shows evenly spaced firing events across all Golgi cells. In the spatial model, both cells fire irregularly and the raster plots show desynchronized spikes.



ISI histogram plots of granule cells produced from the simple model simulation on the left and of spatial model on the right. For the simple model, the ISI distribution is concentrated around a specific range (~10-20 ms), suggesting a relatively synchronous firing pattern, possibly driven by uniform excitatory and inhibitory inputs. In the spatial model the ISI distribution is more skewed, with a peak at low ISI values (~5-20 ms) and a longer tail extending to much larger values (~100-200 ms). This suggests bursty firing (increased number of very short ISIs) , likely due to recurrent excitatory loops within local clusters. The longer tail could be due to isolated neurons firing sparsely or due to regions with weaker excitatory drive.



Golgi cell spectral analysis, on the left the simple and on the right the spatial model. As expected the simple model shows a synchronized activity pattern, with sharp peaks, and the spatial model has more broad frequency components, which would indicate a more complex network dynamic, desynchronization and irregular spiking.



Visual representation of weight connection strength of a center mossy fiber neuron with respect to its granule (left) and Golgi (right) cell connections.

Comparison between the two models

The difference between the models is evident and can be analyzed through three different lenses.
First off, the first model's relatively uniform connectivity brings network synchronization effects, and can be seen in the narrower ISI distribution, whereas the second model breaks global synchronization, resulting in diverse firing patterns across different spatial regions. A second emergent element regards the influence of Purkinje cells, which are modelled on a grid in the spatial simulation, and may produce a more localized inhibition. This in turn may produce a stronger inhibition in some granule cells, leading to longer ISIs, while others may fire rapidly in disinhibited zones, explaining the increased number of very short ISIs. Thirdly and most importantly, in the structured model, neurons within close proximity might receive stronger recurrent excitation, leading to bursty activity. Conversely, neurons in low-connectivity regions might receive less excitation, leading to sparse, irregular firing.

Conclusions and future improvements

In conclusion, the goal was met and evident differences in the two models were encountered, leading us to make considerations aligning with theoretical knowledge.
The project could be further developed by considering a larger neuron population, which would require a higher computational cost.
The most important addition would be to further tune parameters to obtain a simulation biologically more realistic. Our parameters (present in config.py), were set arbitrarily, drawing inspiration from the data and images shown in the lectures.
Another interesting modification would be to implement some other neuron models: we only used the iaf_psc_alpha model, but some others could be considered, such as the hh_psc_alpha (the Hodgkin-Huxley model that is present in the NEST simulator). Although we have to consider that this would surely increase the computational complexity of the model.