Reconstruction and simulation of the cerebellar microcircuit:
a scaffold strategy to embed different levels of neuronal details

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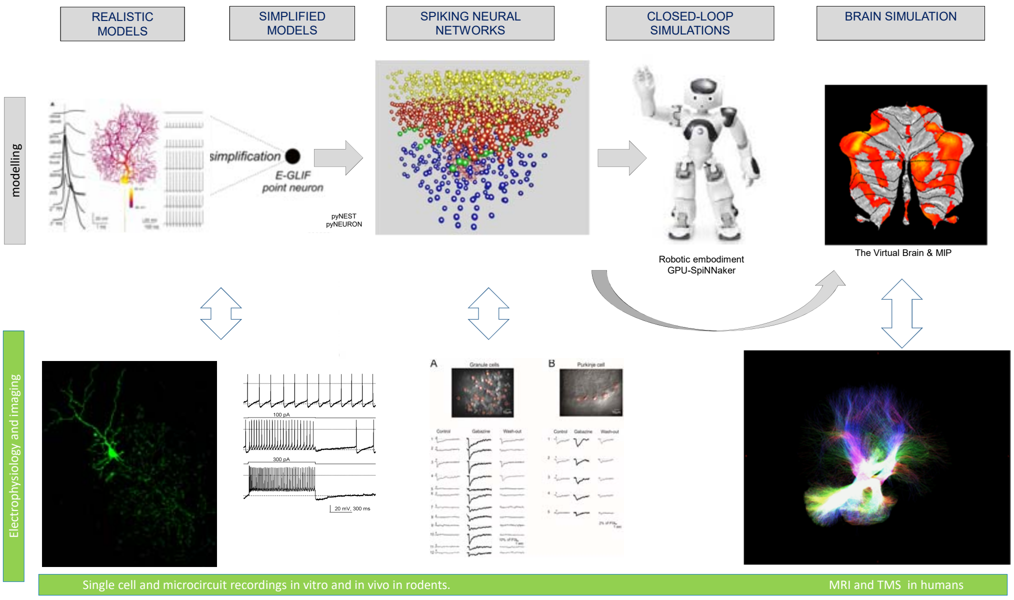
Computational models allow propagating microscopic phenomena into large-scale networks and inferencing causal relationships across scales. Here we reconstruct the cerebellar circuit by bottom-up modeling, reproducing the peculiar properties of this structure, which shows a quasi-crystalline geometrical organization well defined by convergence/divergence ratios of neuronal connections and by the anisotropic 3D orientation of dendritic and axonal processes [1]. Therefore, a cerebellum scaffold model has been developed and tested. It maintains scalability and can be flexibly handled to incorporate neuronal properties on multiple scales of complexity. The cerebellar scaffold includes the canonical neuron types: Granular cell, Golgi cell, Purkinje cell, Stellate and Basket cells, Deep Cerebellar Nuclei cell. Placement was based on density and encumbrance values, connectivity on specific geometry of dendritic and axonal fields, and on distance-based probability.

In the first release, spiking point-neuron models based on Integrate&Fire dynamics with exponential synapses were used. The network was run in the neural simulator pyNEST. Complex spatiotemporal patterns of activity, similar to those observed in vivo, emerged [2]. For a second release of the microcircuit model, an extension of the generalized Leaky Integrate&Fire model has been developed (E-GLIF), optimized for each cerebellar neuron type and inserted into the built scaffold [3]. It could reproduce a rich variety of electroresponsive patterns with a single set of optimal parameters [4].

Complex single neuron dynamics and local connectome are key elements for cerebellar functioning. Then, point-neurons have been replaced by detailed 3D multi-compartment neuron models. The network was run in the neural simulator pyNEURON. Further properties emerged, strictly linked to the morphology and the specific properties of each compartment.

This multiscale tool with different levels of realism has the potential to summarize in a comprehensive way the electrophysiological intrinsic neural properties that drive network dynamics and high-level behaviors.

The model has been tested in a sensorimotor loop of EyeBlink Classical Conditioning (EBCC) [5], letting emerge fundamental operations ascribed to the cerebellum: prediction, timing and learning of motor commands.



CONCLUSIONS and NEXT STEPS

The reconstruction and the simulations with task-dependent signals, in a behavioral context, are needed to allow the cerebellum *to learn to predict the **precise timing** of correlated events*, setting the basis for cerebellar contribution to motor and cognitive control. According to the modular organization of the cerebellum, these microcomplexes could be multiplied and reconnected to investigate how input signals are integrated and elaborated to control complex movements, for example in whisking and locomotion. Scaling-up the network modular architecture would require to re-organize connectivity among microcomplexes, which can determine fundamental properties of cerebellar functioning, such as somatotopic organization, fractured somatotopy mapping and multimodal sensory fusion.

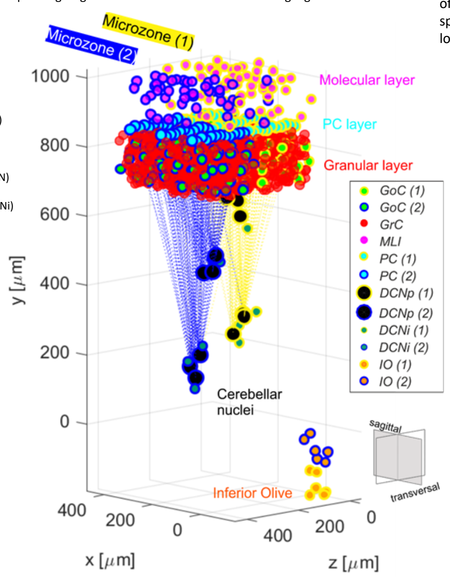
Since the model satisfactorily captures fundamental properties of microcomplexes, it can help shedding light on the links between **structure, function and dynamics** in the cerebellum **under physiological and pathological conditions** and during learning. These extended applications are warranted by the flexible structure of the scaffold and the tunable nature of EGLIF neurons.

Future work will endow the EGLIF-SNN cerebellum models with mechanisms for synaptic plasticity in order to evaluate the impact of single neuron and network properties on motor learning. Eventually, the model may be exploited to mimic pathological conditions at multiple scales providing new insights into the role of cerebellum in brain diseases. It is also envisaged that the EGLIF scaffold strategy could be customized to model and simulate other brain regions (like the cerebral cortex, hippocampus or basal ganglia).

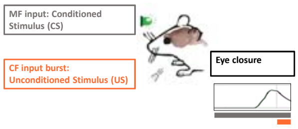
Olivocerebellar scaffold: reconstructed volume includes 96'767 neurons and 4'151'182 total synapses and represents a portion of two cerebellar microcomplexes with the corresponding olivary nuclei. The two microcomplexes are labelled in yellow (1) and blue (2).

Connectivity: specific cell-specific morphologies (extension of axon span and dendritic tree along x, y and z) + statistical rules (convergences/divergence ratios). Here only connections between PCs from each microzone and the corresponding target cells in the cerebellar nuclei are highlighted.

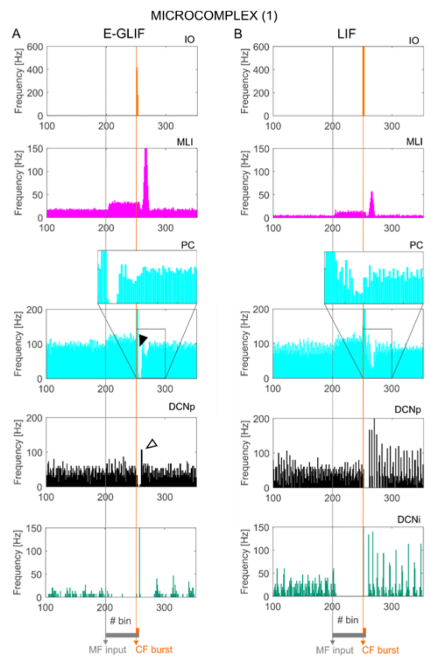
- Mossy fiber (MF)
- Granule cell (GrC)
- Golgi cell (GoC)
- Molecular Interneuron (MLI)
- Purkinje cell (PC)
- Inferior Olive (IO)
- Climbing fiber (CF)
- Deep Cerebellar Nuclei (DCN)
  - •non-GABAergic (DCNp)
  - •GABAergic interneuron (DCNi)



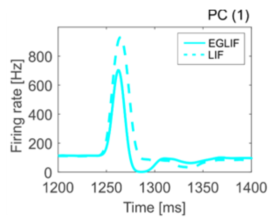
EBCC protocol: CS excited the granular layer across microzones, consistent with the operation of signal analysis (through recombinatorial expansion) carried out by the granular layer. The granular layer output was then synthesized and further processed in the PC layer. **US** influenced individual microcomplexes through specific IO projections, segregating the attention (or error) signal within the network. These modular activation patterns represent the most elementary instantiation of cerebellar functioning, i.e. the ability to correlate neural signals transmitted along different afferent pathways, the MFs and CFs.

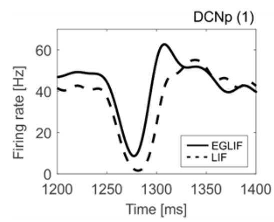


PSTH (bin 5 ms) of IO, MLI, PC and DCN neurons in microcomplex (1) in EGLIF-SNN (A) and LIF-SNN (B). The first stimulus (CS, i.e. MF input) increases the firing rate in MLI, PC and DCNp neurons during the 260-ms interval, while DCNi cells that do not receive MF inputs, get inhibited by the increased PC firing. The air puff (US) is encoded as a burst from CFs. MLIs receive the CF stimulus through the IO pathway causing a delayed protracted increase in firing rate about 70 ms after the stimulus, due to neurotransmitter spillover from CFs. At PC level, CF stimulation results in a complex spike (burst-pause, black arrow). The presence of causing a pause-burst in DCN neurons (white arrow). These dynamic behaviors are observed only in the EGLIF-SNN due to the complex intrinsic dynamics of EGLIF neuron models. In LIF-SNN, the PC burst caused by CF input is not followed by the pause, while in DCNp neurons the pause due to PC complex spike inhibition is followed by a synchronous restart of firing (causing the increased instantaneous frequency) without any rebound burst. Note that the lower irregularity of firing in LIF-SNN simulations resulted in apparent higher firing rates, due to non-physiological synchronization of population spikes.



Mean instantaneous population firing rate of PC and DCNp neurons from microcomplex (1), averaging all neurons (35 PC and 6 DCNp) and all simulations (n=5), comparing EGLIF-SNN (continuous line) and LIF-SNN (dashed line). **The presence of burst-pause and pause-burst responses in EGLIF PC and DCNp neuronal populations, results in a faster and more precise change of the overall population activity → enhancing the time precision of the motor output**





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