Cerebellar Network model reconstruction and simulation

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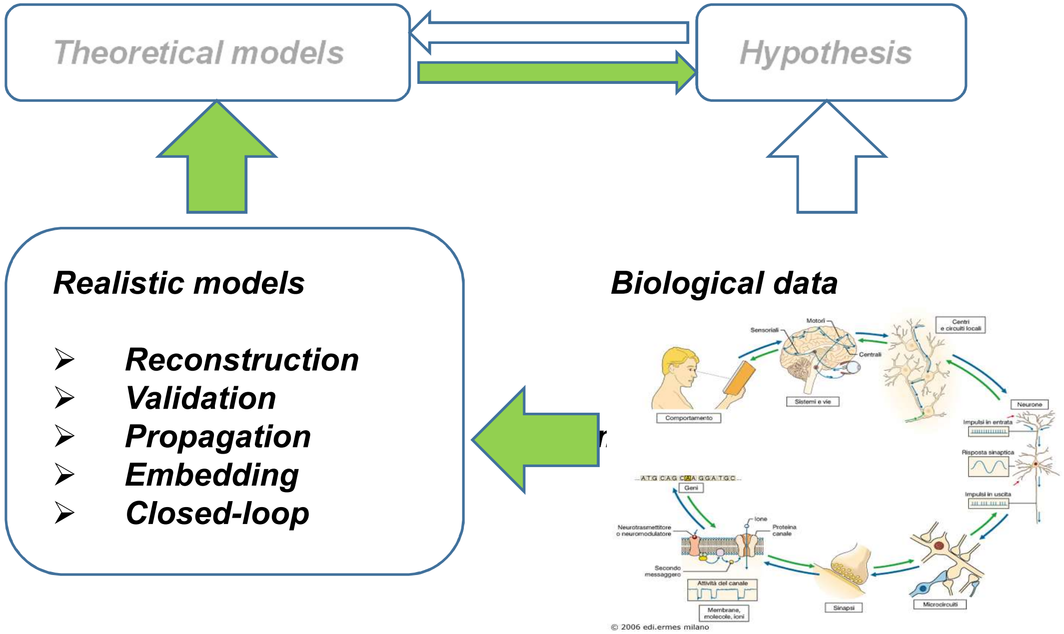
CodeJam* #10 Heidelberg - *28th Nov 2019

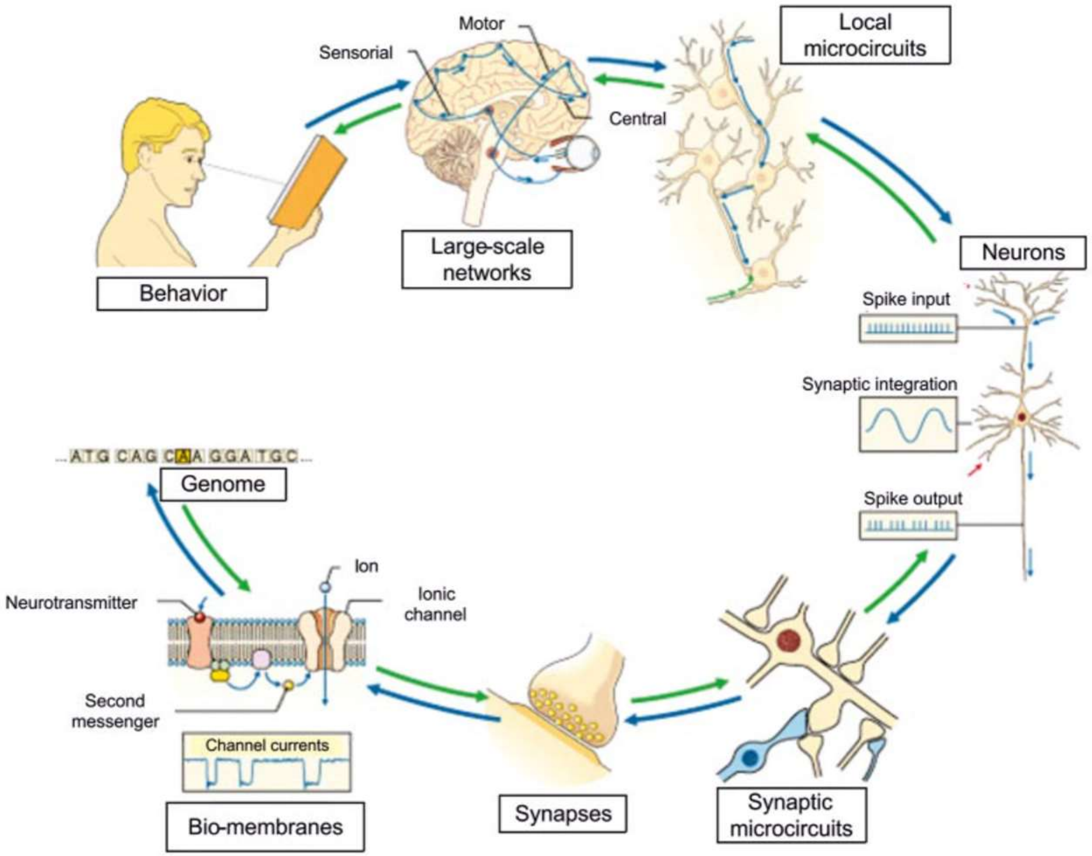
Modeling the brain

- **Fragmented** knowledge and data on the brain
- **Causal relationships** between mechanisms across scales still **unclear**



a combined bottom-up / top-down approach

Modeling the **cerebellar** circuit

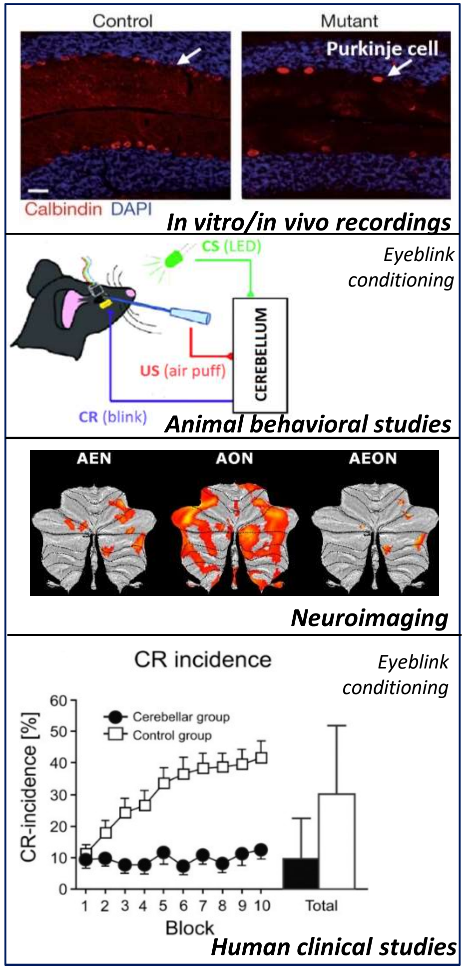


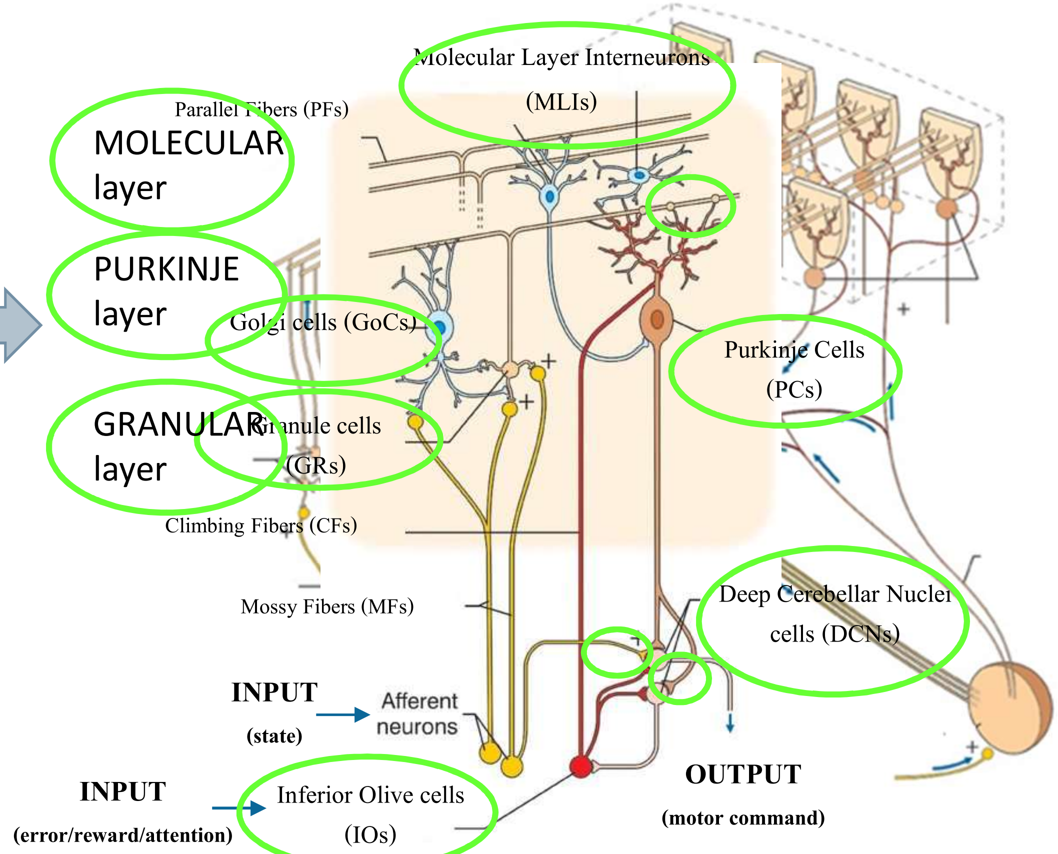
Multiscale investigation

- Experimental data at multiple scales
- Emergent functions (local network dynamics and global behavioral control schemes)
- …

<u>Olivo**cerebellar CIRCUIT**</u>:

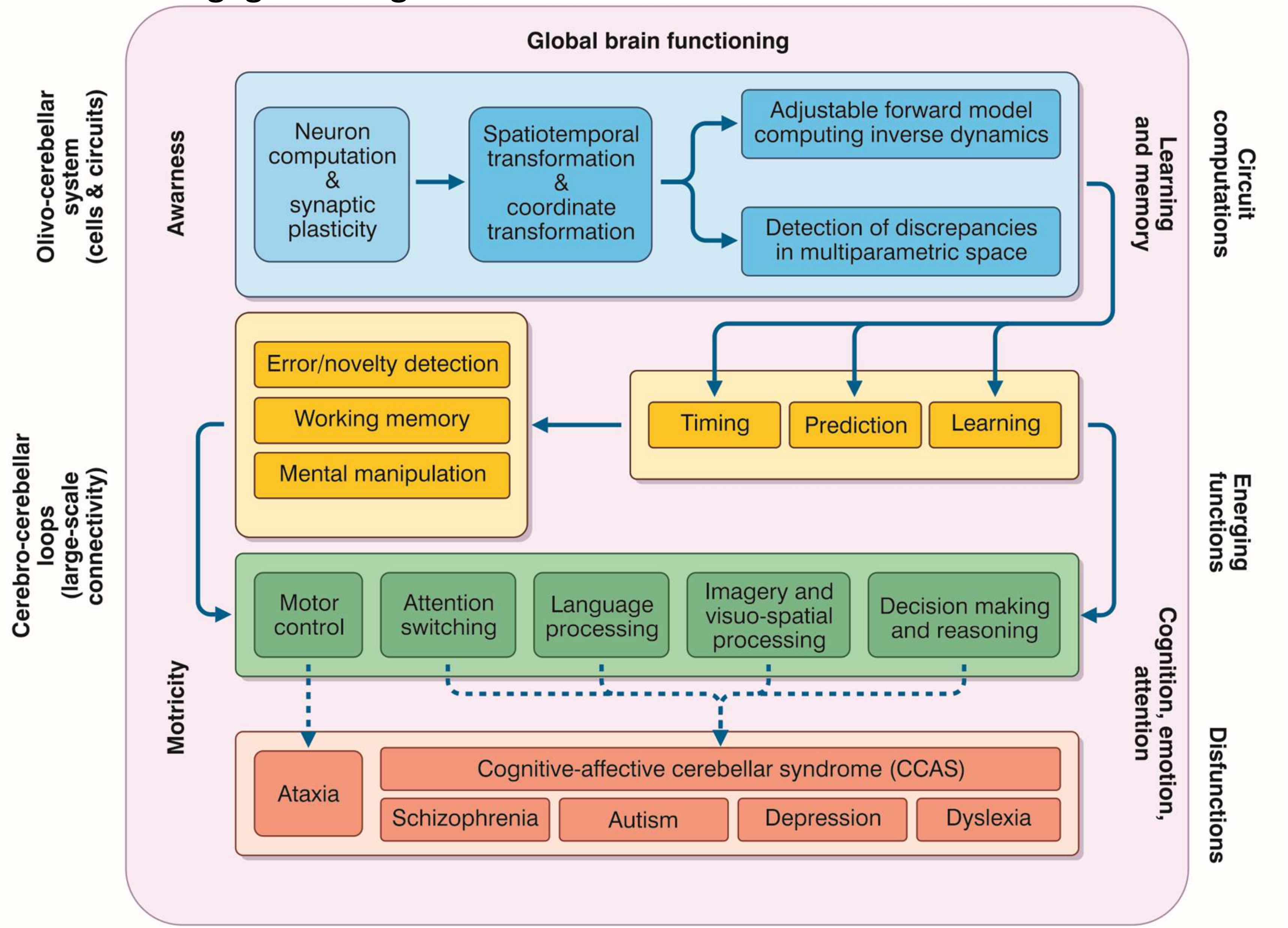
- *Modularity* (a generalized computational algorithm)
- Specific geometrical anisotropic organization and *connectome*
- Different *cell types* with specific complex dynamics
- Distributed *plasticity* (Long Term Potentiation/Depression – LTP/LTD)





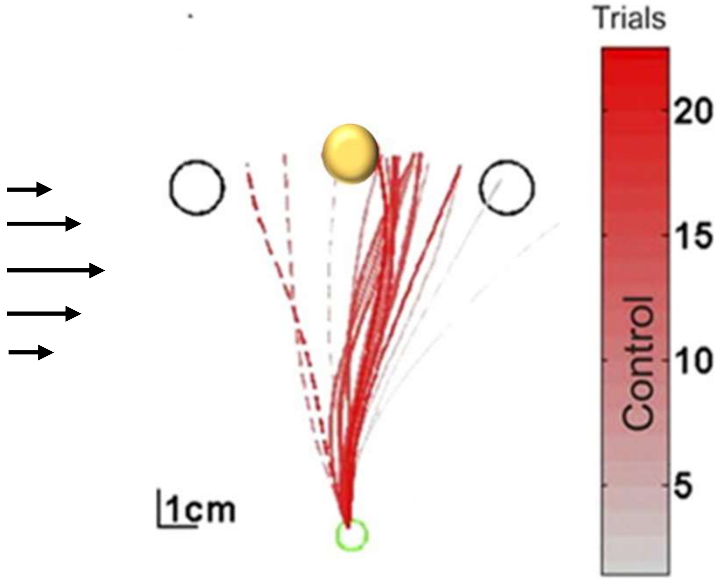
Adapted from [Tsai et al., Nature, 2012], [Piochon et al., Nat Comm, 2014], [Casiraghi et al, Cereb Cortex, 2010], [Dimitrova et al., Brain Res, 2008].

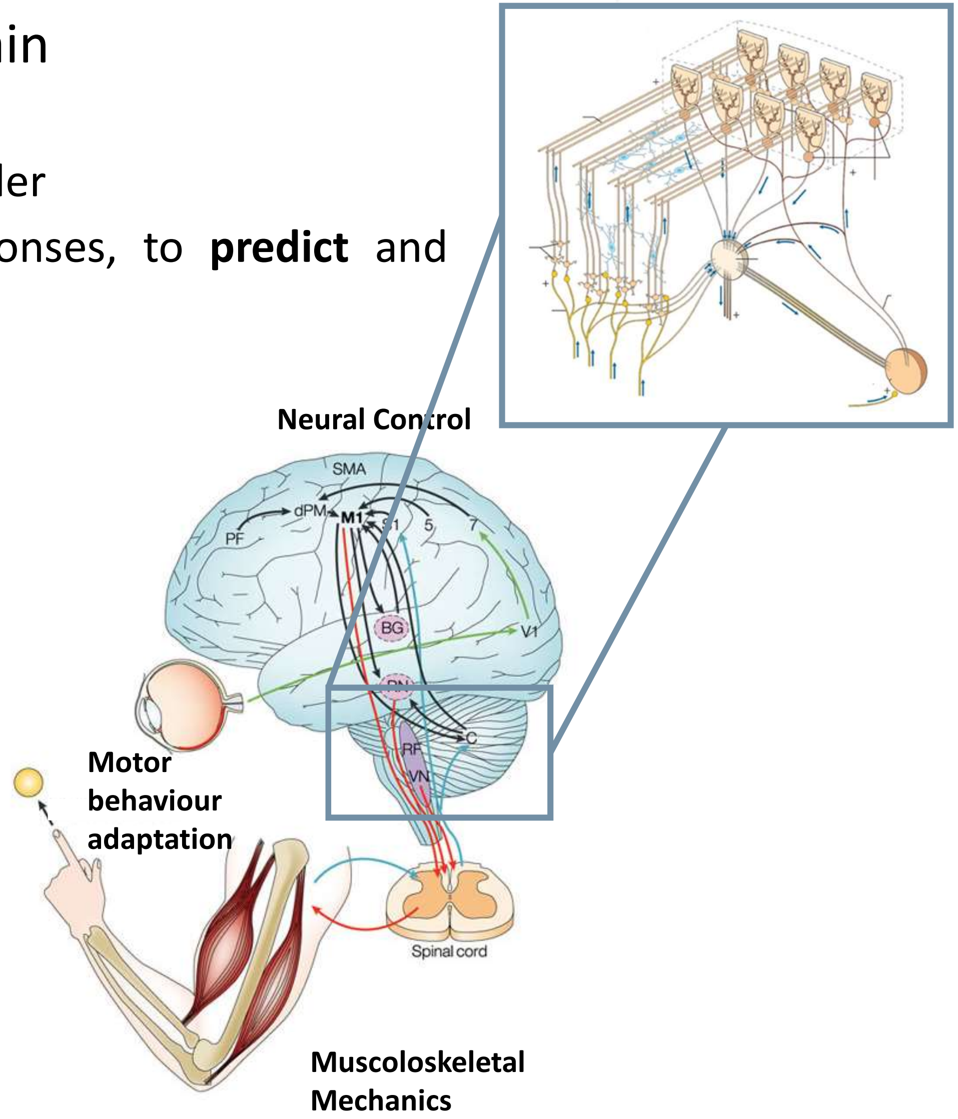
Behavioral emergent functions: the cerebellum takes part to large-scale networks engaged in cognitive and motor control …



Cerebellar FUNCTIONS in motor domain

- **motor learning**
- feedforward and feedback **adaptive** controller
- tuning *TIMING* and *GAIN* of motor responses, to **predict** and **compensate** for perturbations



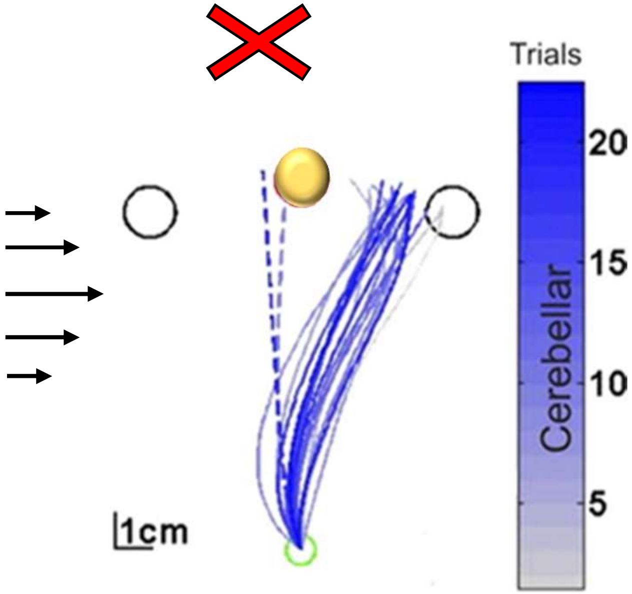


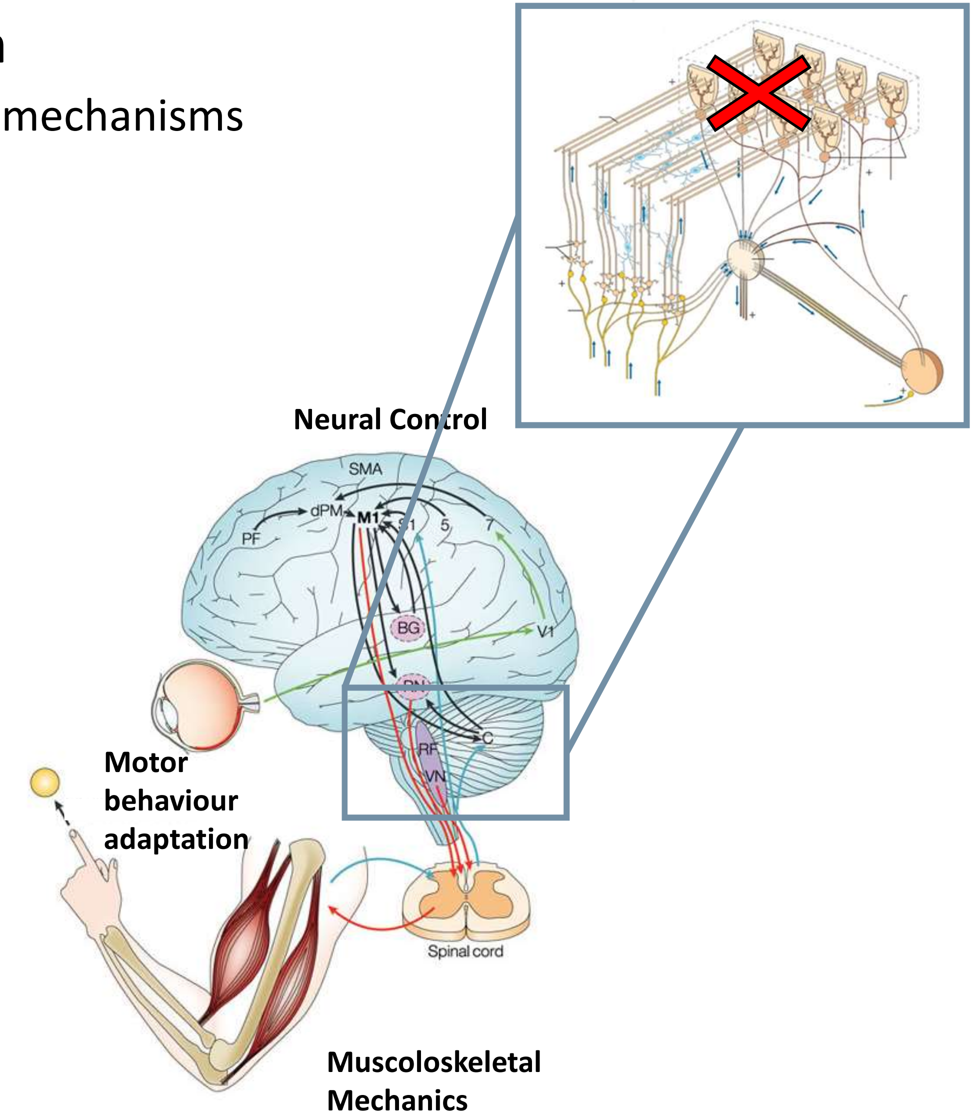
It is the cerebellum that deals with perturbations and errors!

[Scott, 2004; Rabe et al, 2009]

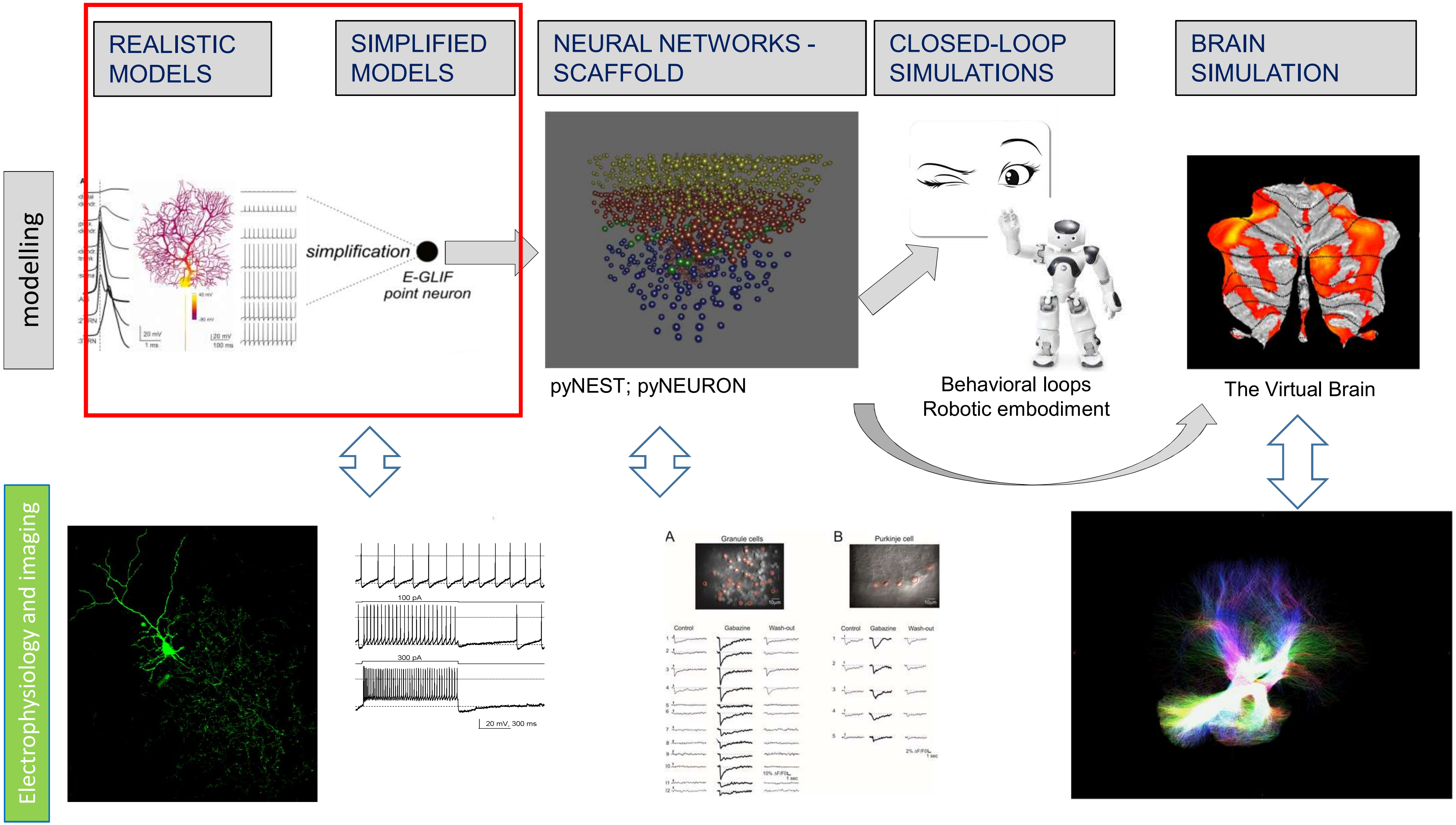
Cerebellar DISEASES in motor domain

- Damage to neural populations or plasticity mechanisms
- Impaired motor learning



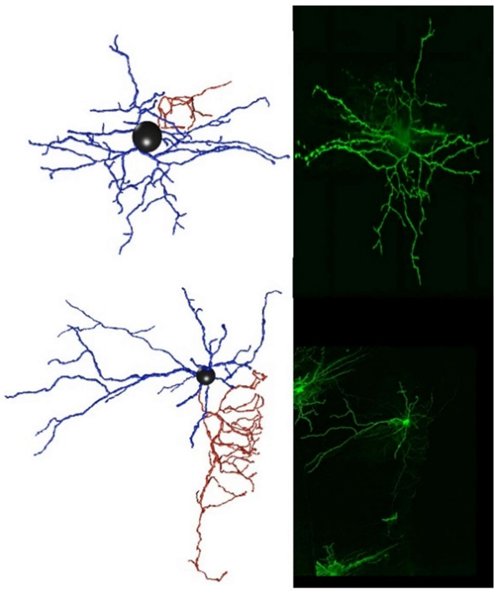


deficit in compensation!


REALISTIC MODELS
SIMPLIFIED MODELS
NEURAL NETWORKS - SCAFFOLD
CLOSED-LOOP SIMULATIONS
BRAIN SIMULATION
modelling
simplification
E-GLIF point neuron
pyNEST; pyNEURON
Behavioral loops
Robotic embodiment
The Virtual Brain
Electrophysiology and imaging
100 pA
300 pA
20 mV, 300 ms
Granule cells
Purkinje cell
Control
Gabazine
Wash-out

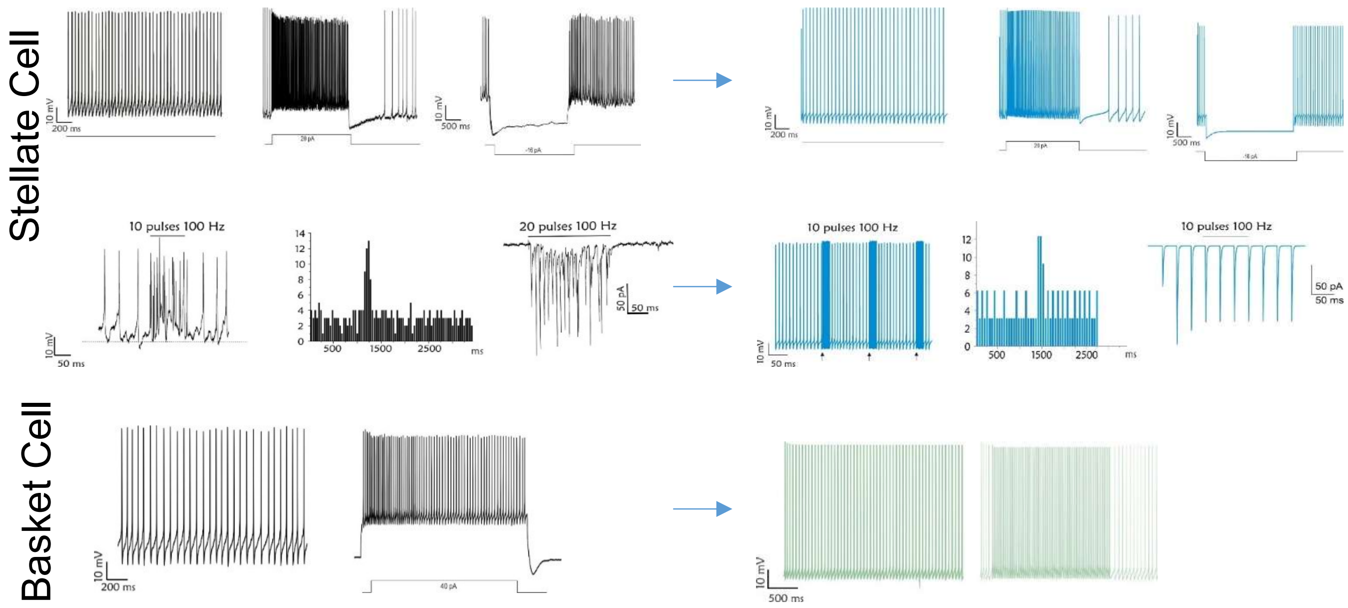
REALISTIC MODELS

Molecular Layer Inhibitory Interneurons

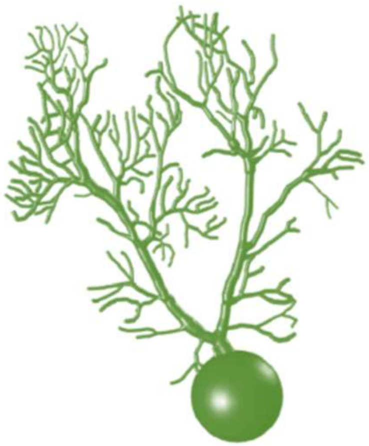


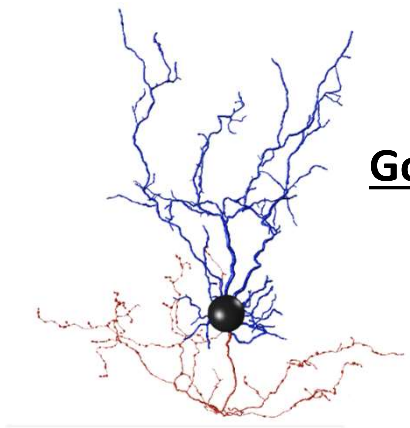
Patch-clamp recordings

Optimized models



Purkinje cell



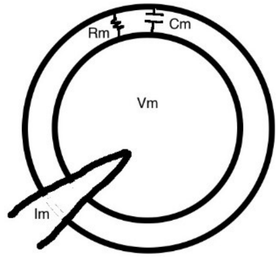


Golgi cell

NEURON

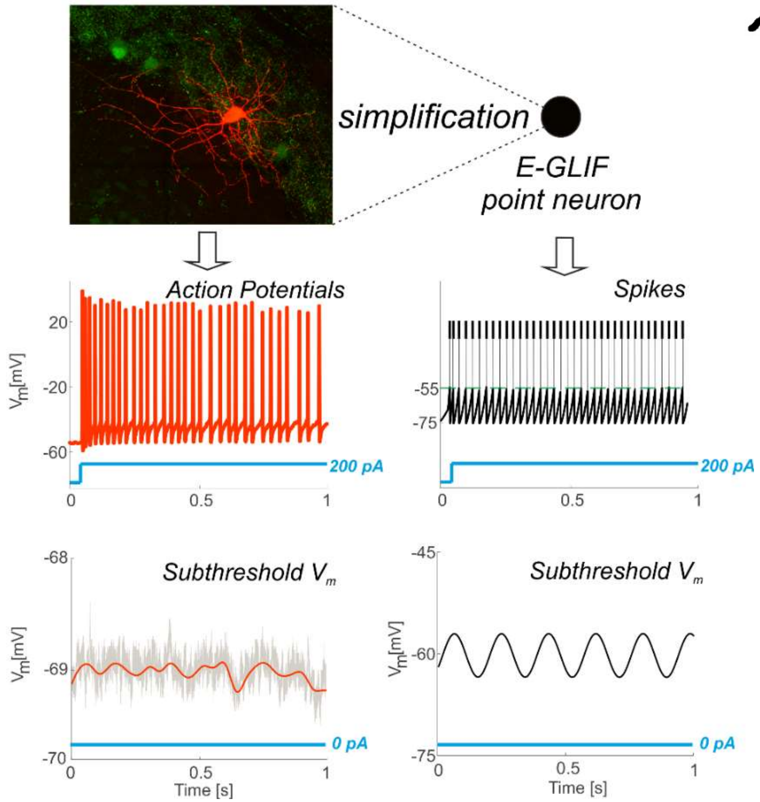
Complex Dynamics in Simplified Neuronal Models:

Extended Generalized Leaky Integrate and Fire models



rich electroresponsive phenotypes

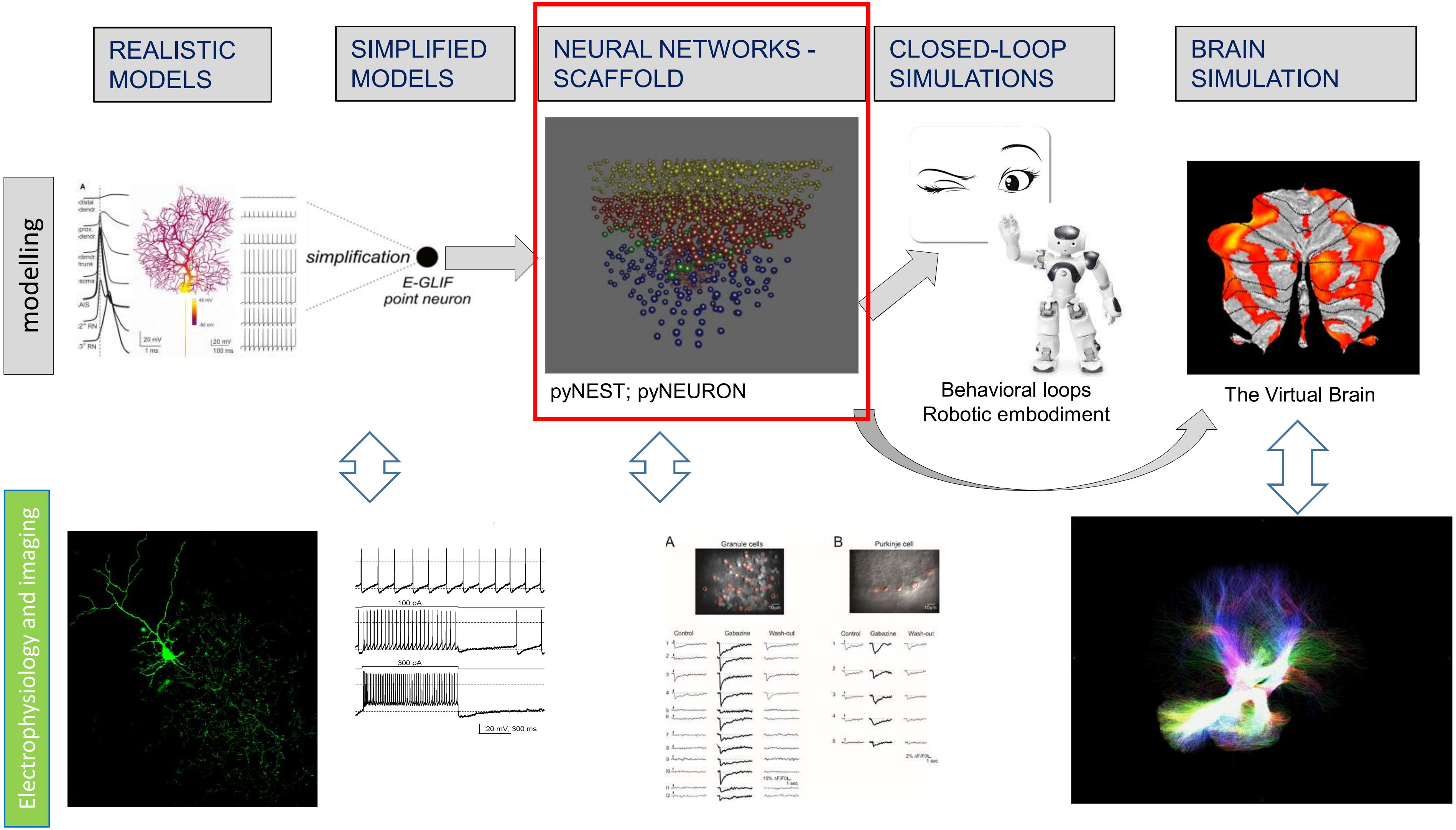
- autorhythm
- sub-threshold oscillations
- resonance
- phase reset
- depolarization-induced bursting
- spike-frequency adaptation
- post-inhibitory rebound bursting



nest:: simulated()

in *NEST model library*

[Geminiani et al., Front Neuroinform, 2018]
[Geminiani et al., Front. Comput. Neurosci 2019a]



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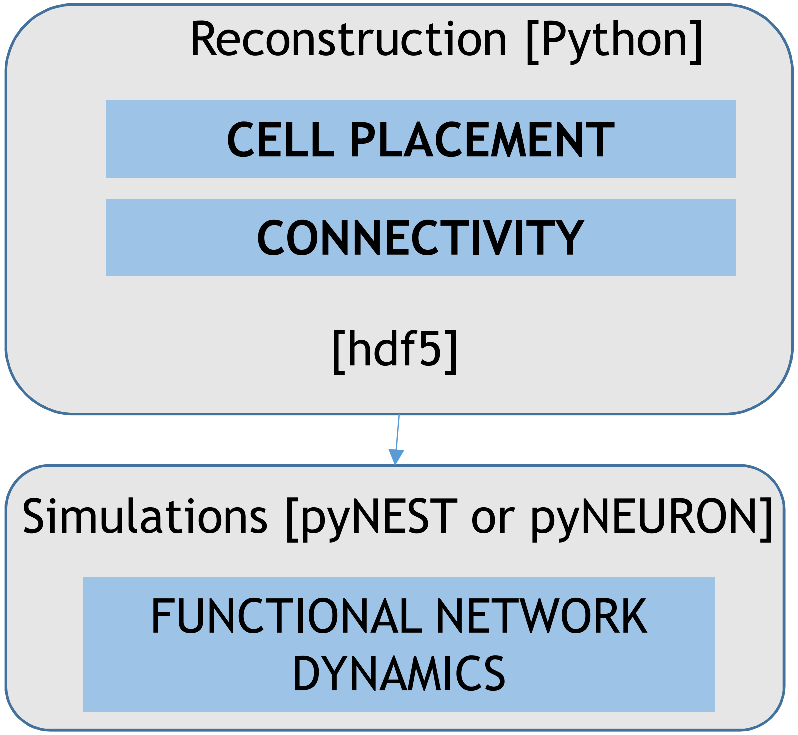
BOTTOM-UP APPROACH: integration of available details about neuronal properties and synaptic connectivity into computational models

NEURAL NETWORKS - SCAFFOLD




```
mouse_cerebellum.json
```

Configuration: parameters and method selections

```
scaffold -c=mouse_cerebellum.json compile
```

Compiles a network architecture: places cells in a simulated volume and connects them to eachother. All information then stored in a HDF5 file

```
scaffold  simulate SimName --hdf5=<file>
```

Run a simulation from a compiled network architecture (using an adaptor for the desired simulator)

- https://github.com/Helveg/cerebellum-scaffold
- dbbs-docs.rf.gd

[Casali et al. Front. in Neuroinformatics 2019]

mouse_cerebellum.json

- "network_architecture": {…
- "layers": {…
- "cell_types": {…
- "connection_types": {…
- "simulations": {…
  - simulator
  - neuron_model / params
  - synapse_model / params / plasticity
  - devices (stimulation, recording..)

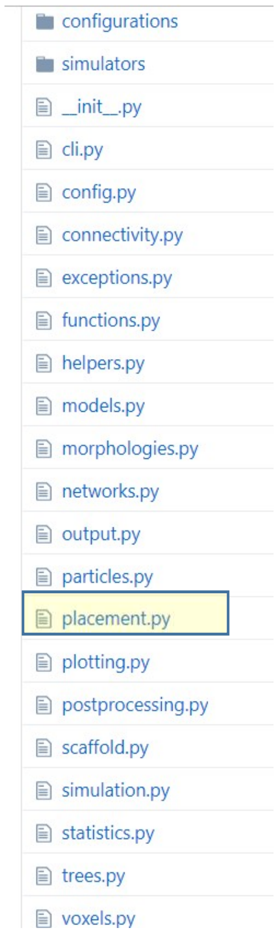
```
"network_architecture": {
    "simulation_volume_x": 400.0,
    "simulation_volume_z": 400.0,
```

```
"granular_layer": {
      "thickness": 150.0,
      "stack": {
        "stack_id": 0,
        "position_in_stack": 1
```

```
"granule_cell": {
      "placement": {
        "class": "scaffold.placement.LayeredRandomWalk",
        "layer": "granular_layer",
        "soma_radius": 2.5,
        "density": 3.9e-3,
        "distance_multiplier_min": 0.5,
        "distance_multiplier_max": 0.5
      },
      "morphology": {
        "class": "scaffold.morphologies.GranuleCellGeometry",
        "pf_height": 180,
        "pf_height_sd": 20,
        "pf_length": 3000,
        "pf_radius": 0.5,
        "dendrite_length": 40
```

```
"granule_to_golgi": {
     "class": "scaffold.connectivity.ConnectomeGranuleGolgi",
     "from_cell_types": [{"type": "granule_cell", "compartments": ["parallel_fiber", "ascending_axon"]}],
     "to_cell_types": [{"type": "golgi_cell", "compartments": ["dendrites"]}],
     "tag_aa": "ascending_axon_to_golgi",
     "tag_pf": "parallel_fiber_to_golgi",
     "aa_convergence": 400,
     "pf_convergence": 1200
```

CELL PLACEMENT



Cell types [json]

- **Geometric simplified features**
- **Density**

- Glom (Glomerulus -“ensemble”)
- GrC (granule cell)
- GoC (Golgi cell)
- PC (Purkinje cell)
- SC (Stellate cell)
- BC (Basket cell)
- DCN (Deep Cerebellar Nuclei cell)
- DCN interneurons
- IO (Inferior Olive cell)

Layered-volume [json]

- **Cerebellar cortex**:
  - user-defined volume base (x-z): e.g. 400 x 400 µm
  - fixed thickness (y): 150 (GCL) + 30 (PCL) + 150 (ML)
- **DCN volume and IO volume**: proportional sizes

3D placement strategies

- Self-avoiding random walk
- Particle placement
- Parallel array placement
- …

Output matrix hdf5:
neuron ID, cell type, 3D coordinates [x,y,z]

```
class LayeredRandomWalk(PlacementStrategy)
class ParticlePlacement(PlacementStrategy)
class ParallelArrayPlacement(PlacementStrategy)
```

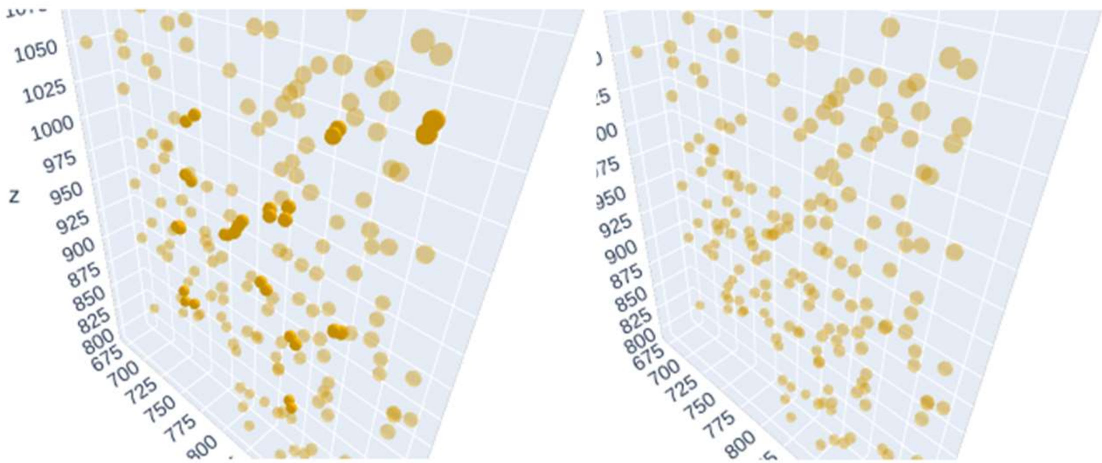
- ***Self-avoiding random walk***

Stellate cells

- ***Particle placement***

neurons are placed randomly in the 3D volume (defined by a set of voxels); then checks for collisions, using kd-tree partitioning of the 3D space. Colliding particles are placed at a distance to their original position that depends on their radius and the radius of the colliding particle (e.g. one small particle colliding to a big particle is replaced far from its original position - "higher repulsion force").

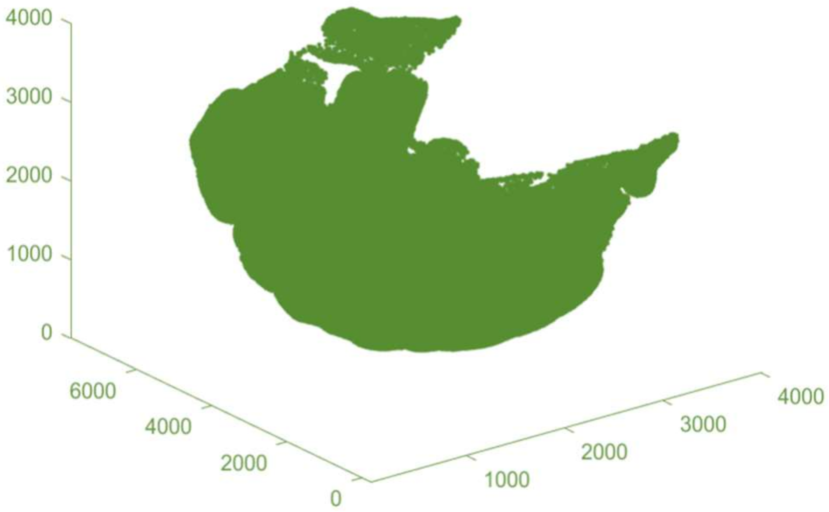
- computationally efficient
- uniform placement in 3D space
- even in a voxelized irregular volume

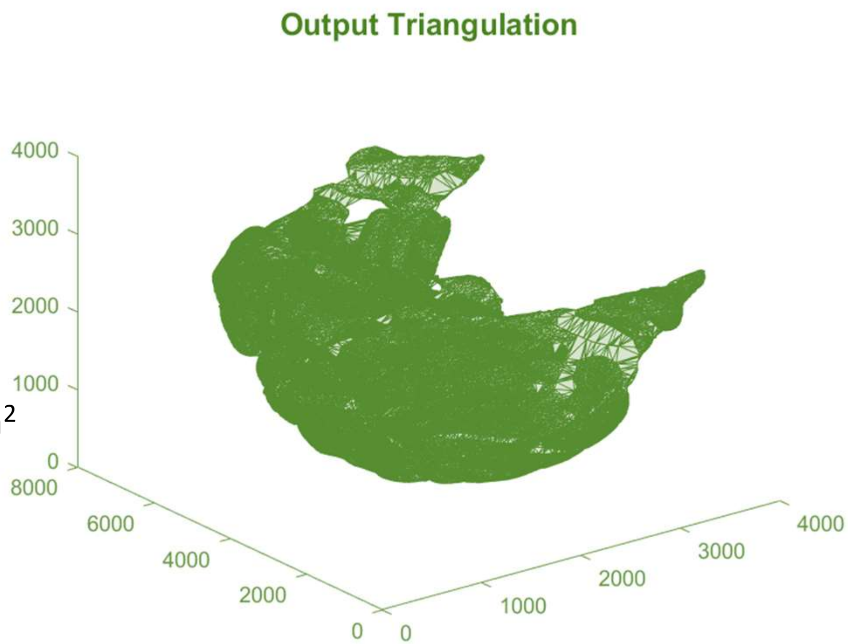


- *__Parallel array placement__* (planar grid of Purkinje cells)

    - planar density

All localized Purkinje cells in the cerebellum of a P10 L7-GFP mouse [Silvestri et al [Front Neuroanat](#). 2015]:
https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/HXM





From triangulation and area sum: Surface area = 129 mm^2 →

planar density = 221107 PCs / $129*10^{-6}$ μm^2 = 0.0017 #PCs/μm^2

- *Parallel array placement* (planar grid of Purkinje cells)

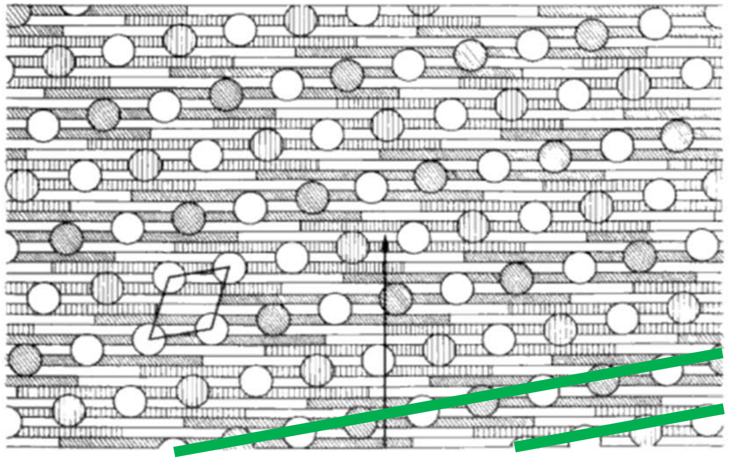
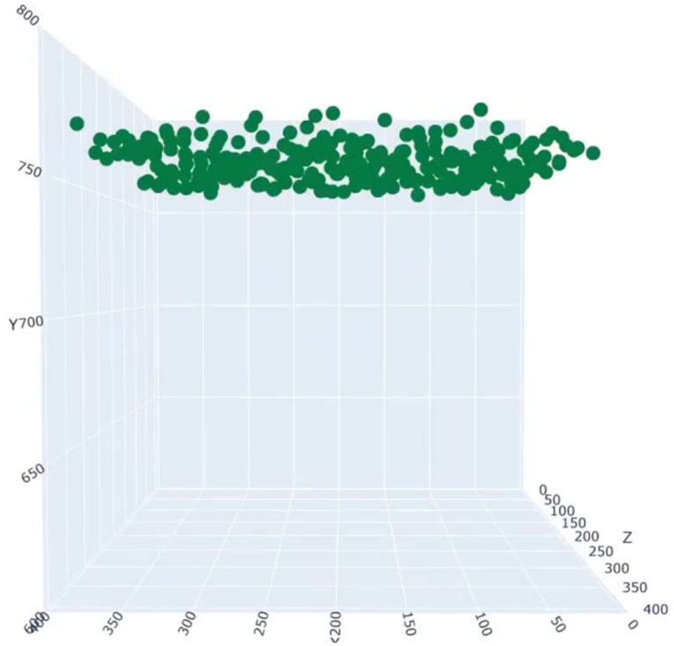


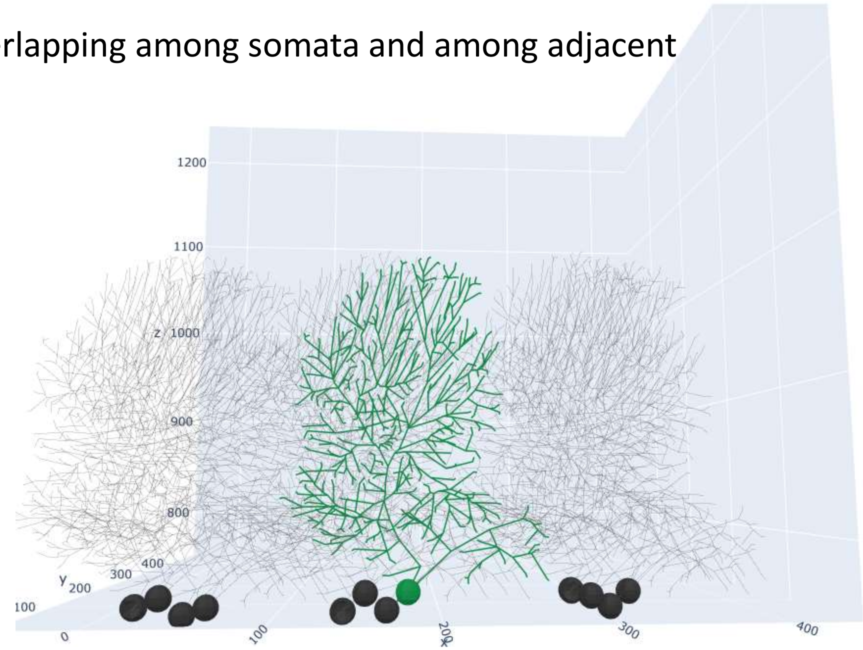
FIG. 10. Idealized model of Purkinje cell arrangement in the cerebellar cortex. *Circles*, Purkinje cell bodies. *Oblongs*, Purkinje dendrites. Corresponding cell bodies and dendrites are shown in the same pattern (*hatching and stippling*). *Arrow* indicates longitudinal axis of the folium (Palkovits et al., 1971a).

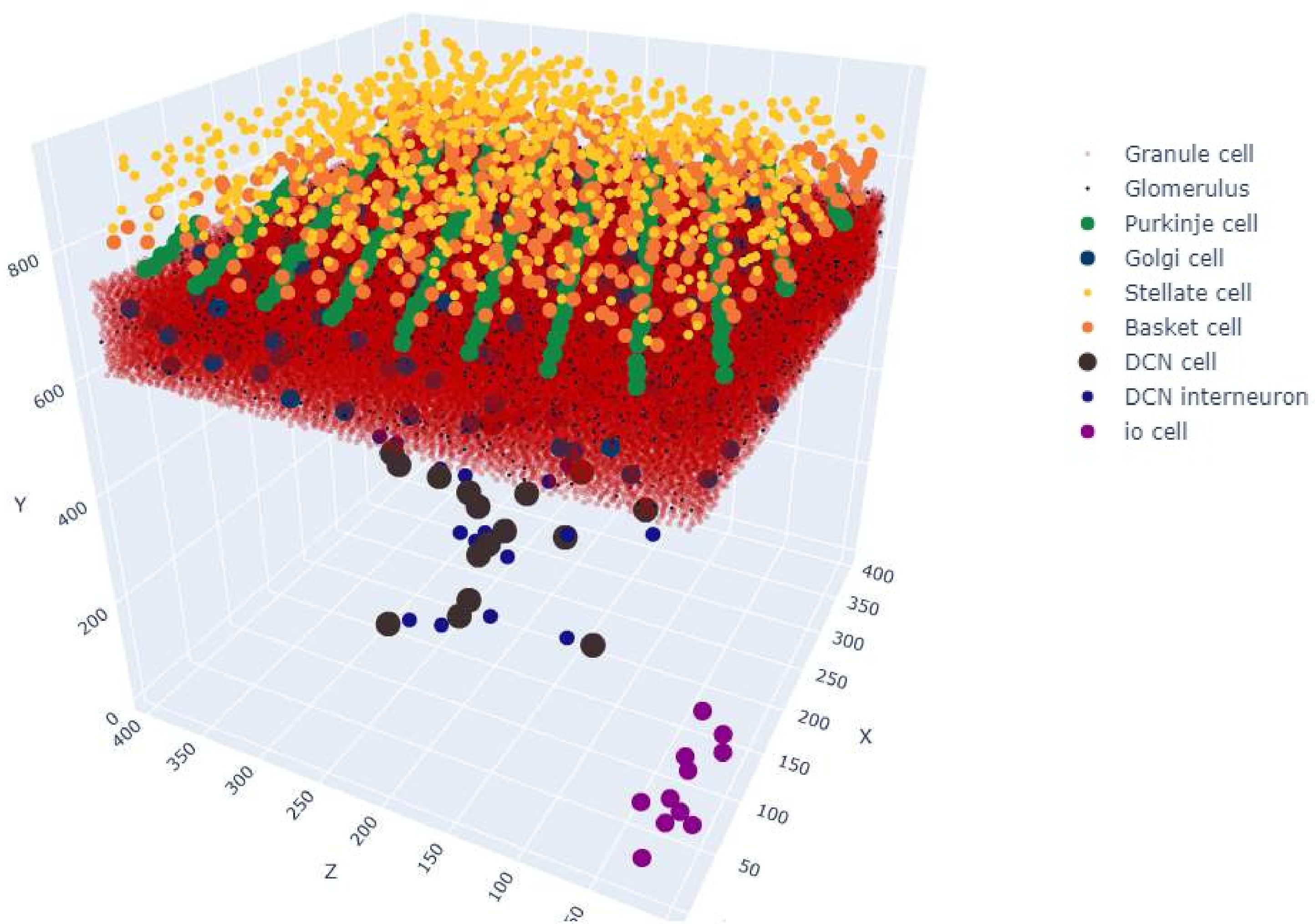
- planar density
- angle



Taking into account morphological features…

Check for not overlapping among somata and among adjacent dendritic trees





Granule cell
Glomerulus
Purkinje cell
Golgi cell
Stellate cell
Basket cell
DCN cell
DCN interneuron
io cell
Y
X
Z

CONNECTIVITY

3D positions from PLACEMENT

Connection types [json]

- ➢ `granule_to_golgi`
- ➢ …

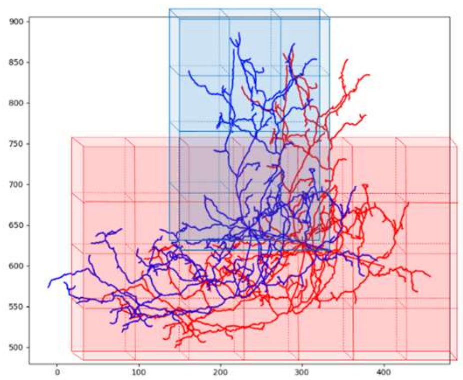
Connectivity strategies

- Field Intersection: axonal span / dendritic extensions (anisotropic) + statistical values (convergence and/or divergence)
- Touch detection (compartments intersection + desired number of synapses for each pair) [kd-tree]
- …

Output hdf5:
neuron ID pre-syn, neuron ID post-syn
[axonal compartment ID, dendritic compartment ID]

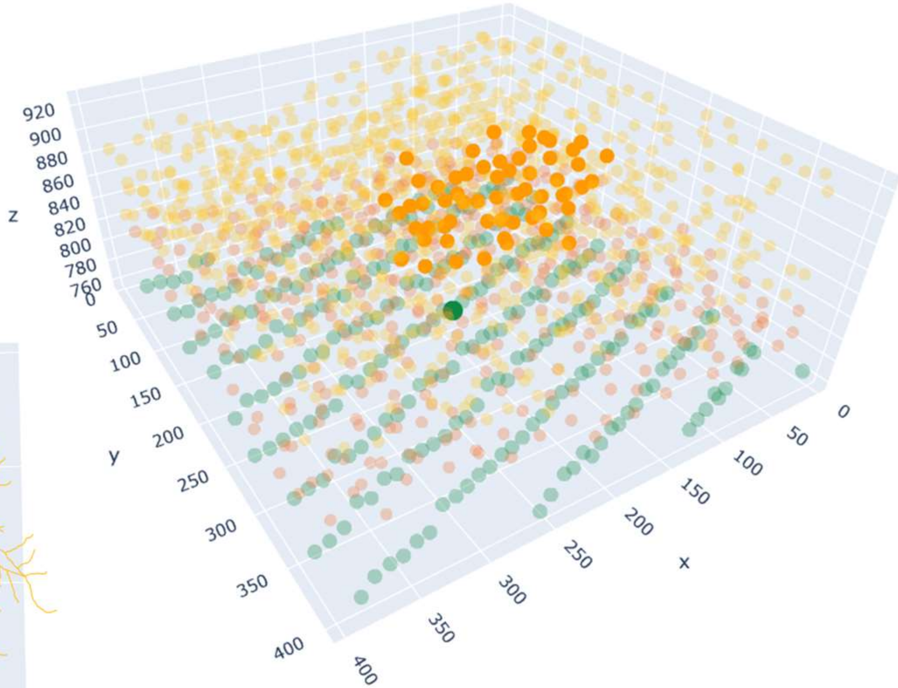
```
class TouchingConvergenceDivergence(ConnectionStrategy)
class TouchDetector(ConnectionStrategy)
```

- configurations
- simulators
- __init__.py
- cli.py
- config.py
- connectivity.py
- exceptions.py
- functions.py
- helpers.py
- models.py
- morphologies.py
- networks.py
- output.py
- particles.py
- placement.py
- plotting.py
- postprocessing.py
- scaffold.py
- simulation.py
- statistics.py
- trees.py
- voxels.py

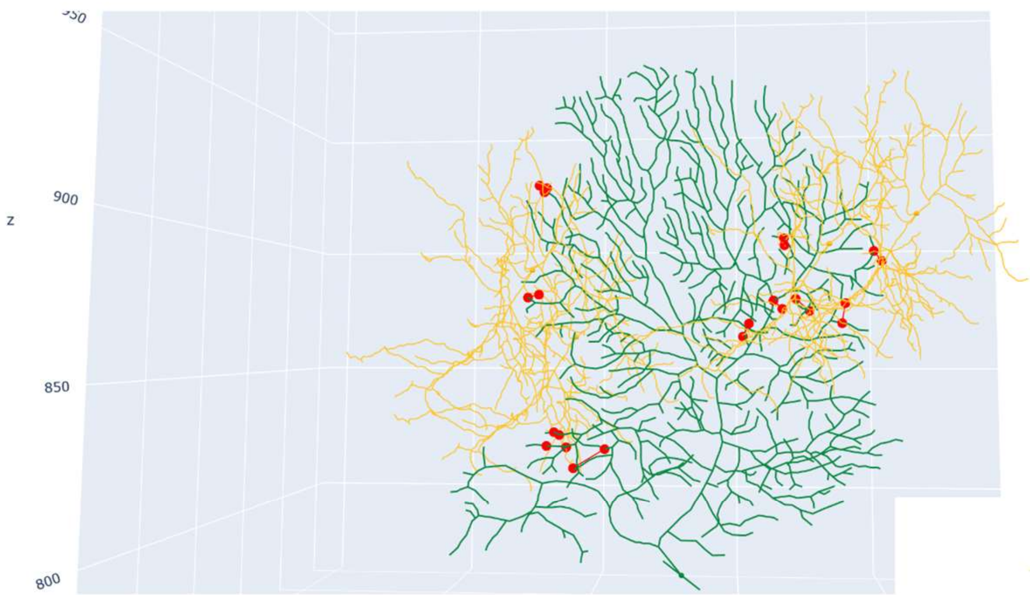


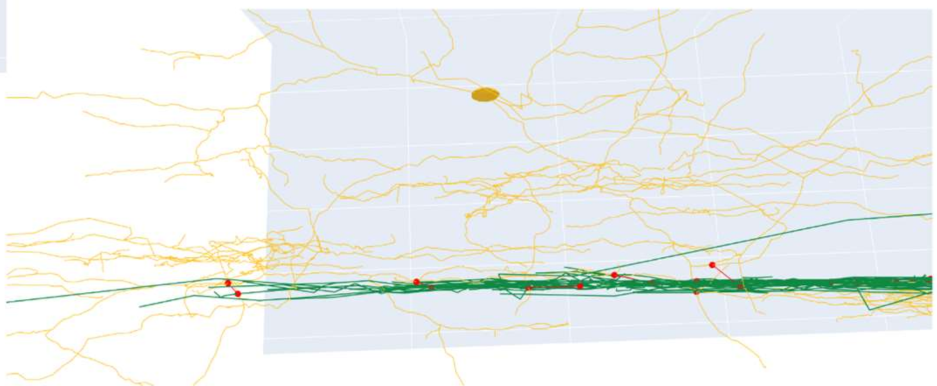
Connection type: Stellate cells to Purkinje cell

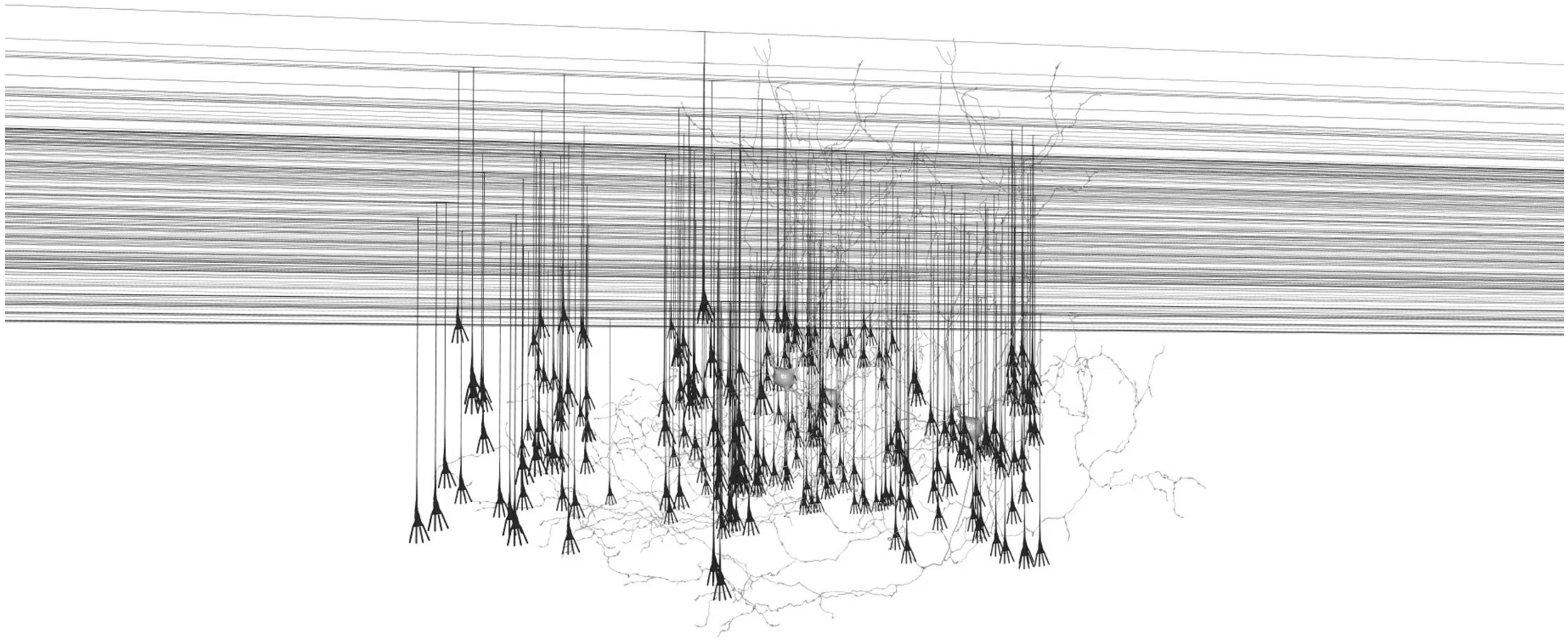
```
"to_cell_types": [{"type": "purkinje_cell", "compartments": ["dendrites"]}],
"divergence": 2,
"convergence": 20,
“limit_x": 500.0,
"limit_z": 100.0
```



Touch detection: synaptic locations on morphologies





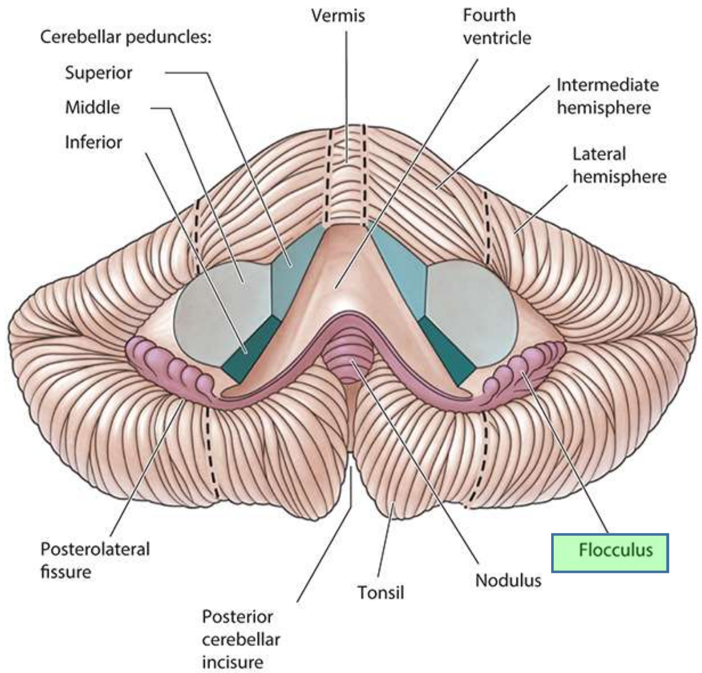


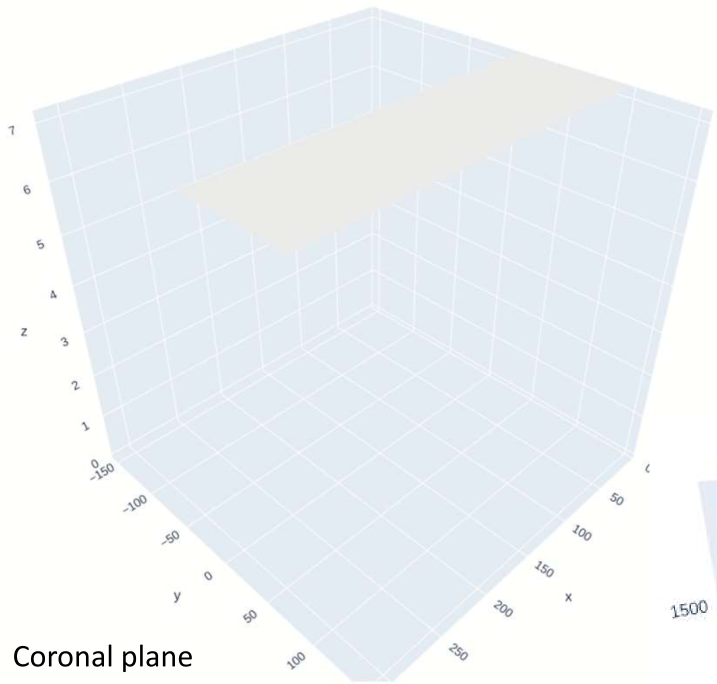
- **Golgi cells**, each 1726 dendritic compartments
- **Granule cells**, ascending axons and parallel fibers

Visualization tools (HBP):
http://gmrv.es/gmrvvis/

Full scale… on Brain Atlas geometry
flocculus

Total volume: 1,379 mm^3 – divided into 88316 voxels (25x25x25 μm^3)
Total cell numbers: 1.037.183

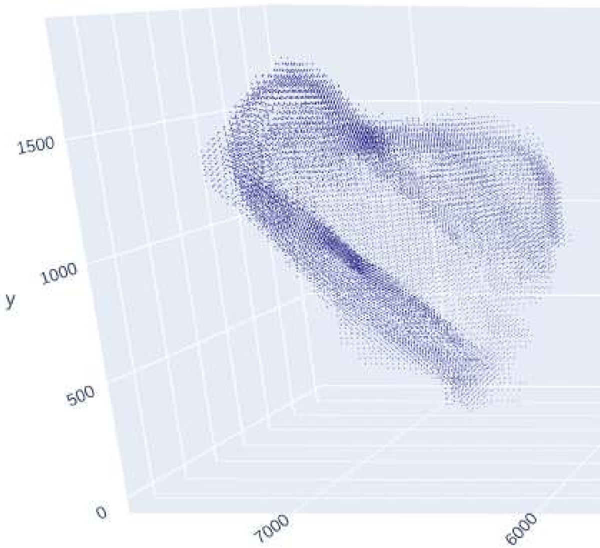


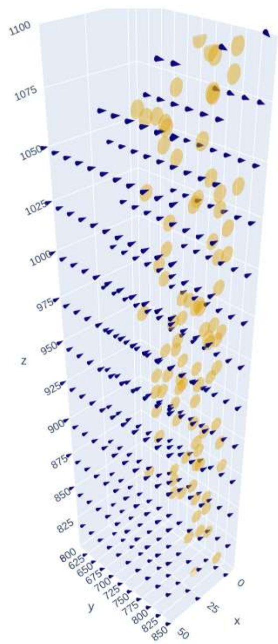


Coronal plane

3D placement by particle strategy

Vector field: orientation





Voucher #47
Collaboration with Dimitri Rodarie [EPFL]

FUNCTIONAL NETWORK DYNAMICS

nest :: simulated()

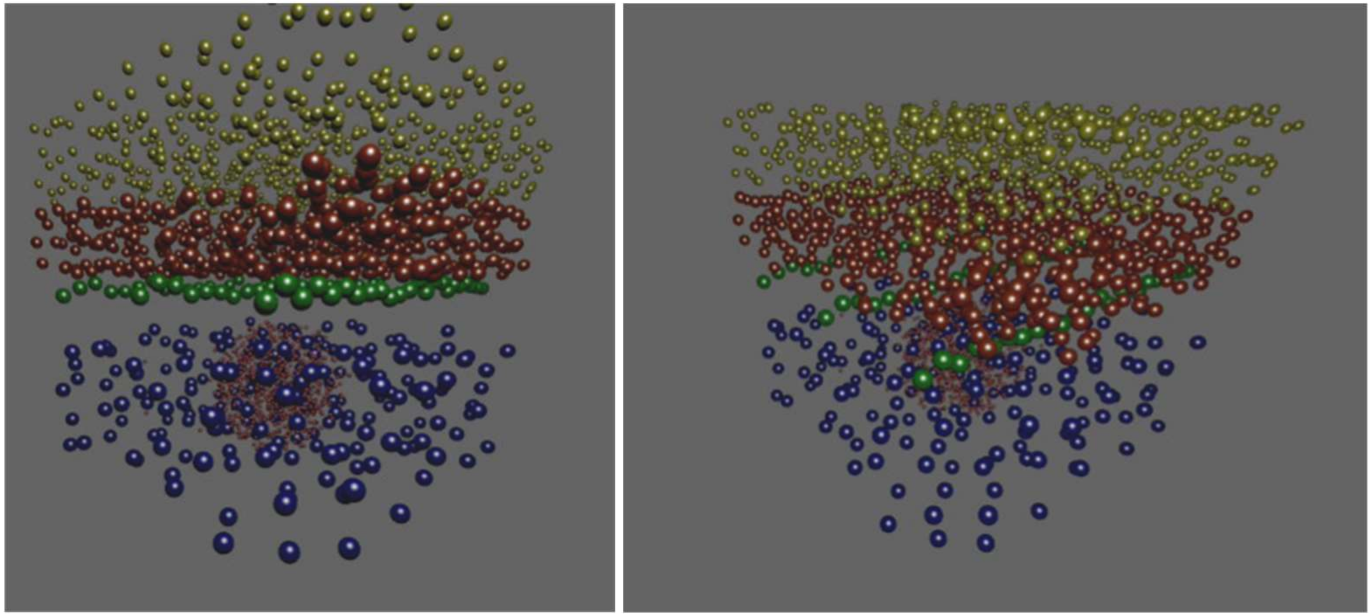
HPC resources

SIMPLIFIED MODELS

NEURAL NETWORKS - SCAFFOLD

Reconstruction: 0.077 mm^3 of mouse cerebellum with 96’767 neurons and 4’151’182 pair connections (conductance-based synapses – weight & delay)

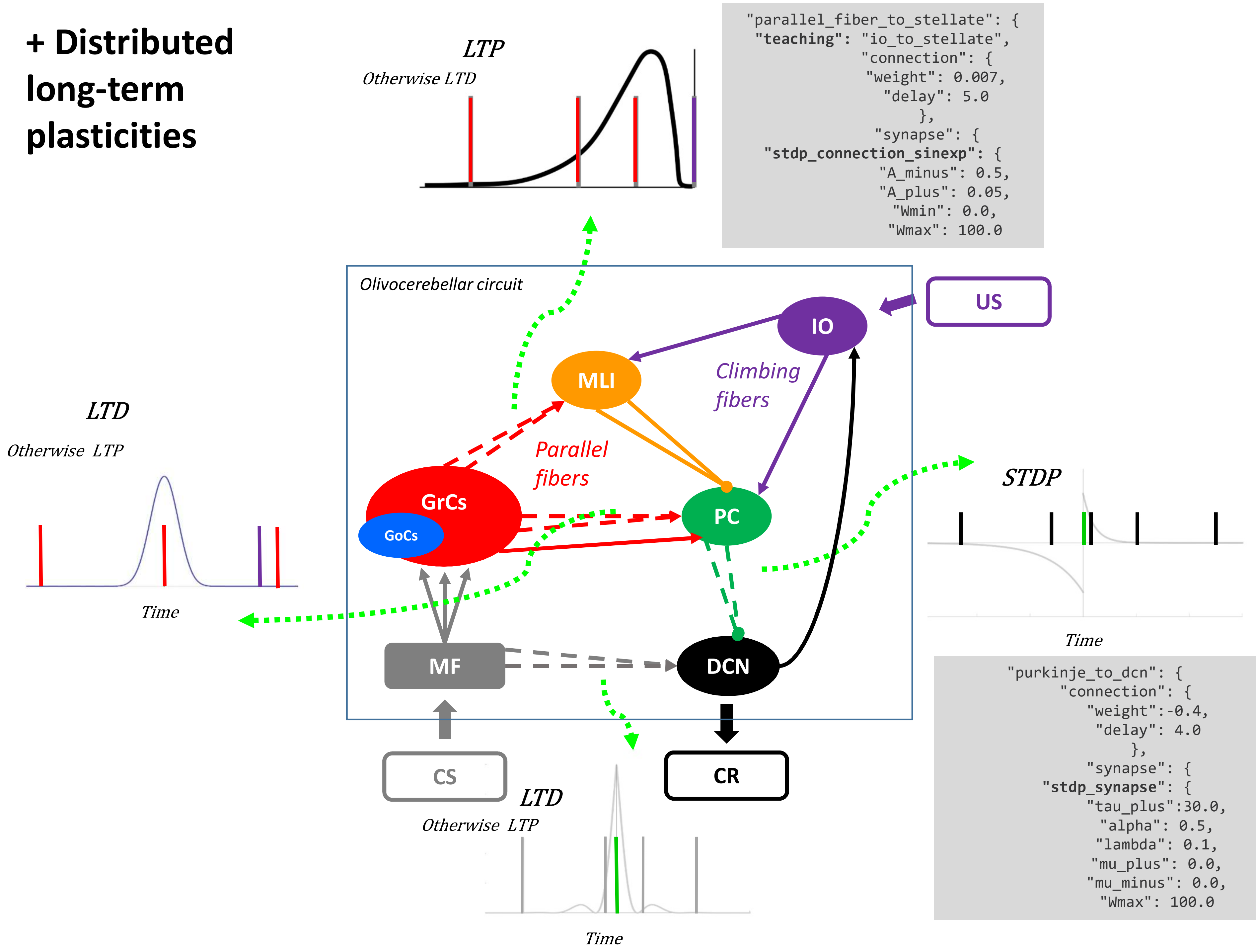
Simulation tests: spatio-temporal dynamics (e.g. center-surround, impact of specific synaptic inputs, oscillations,…)

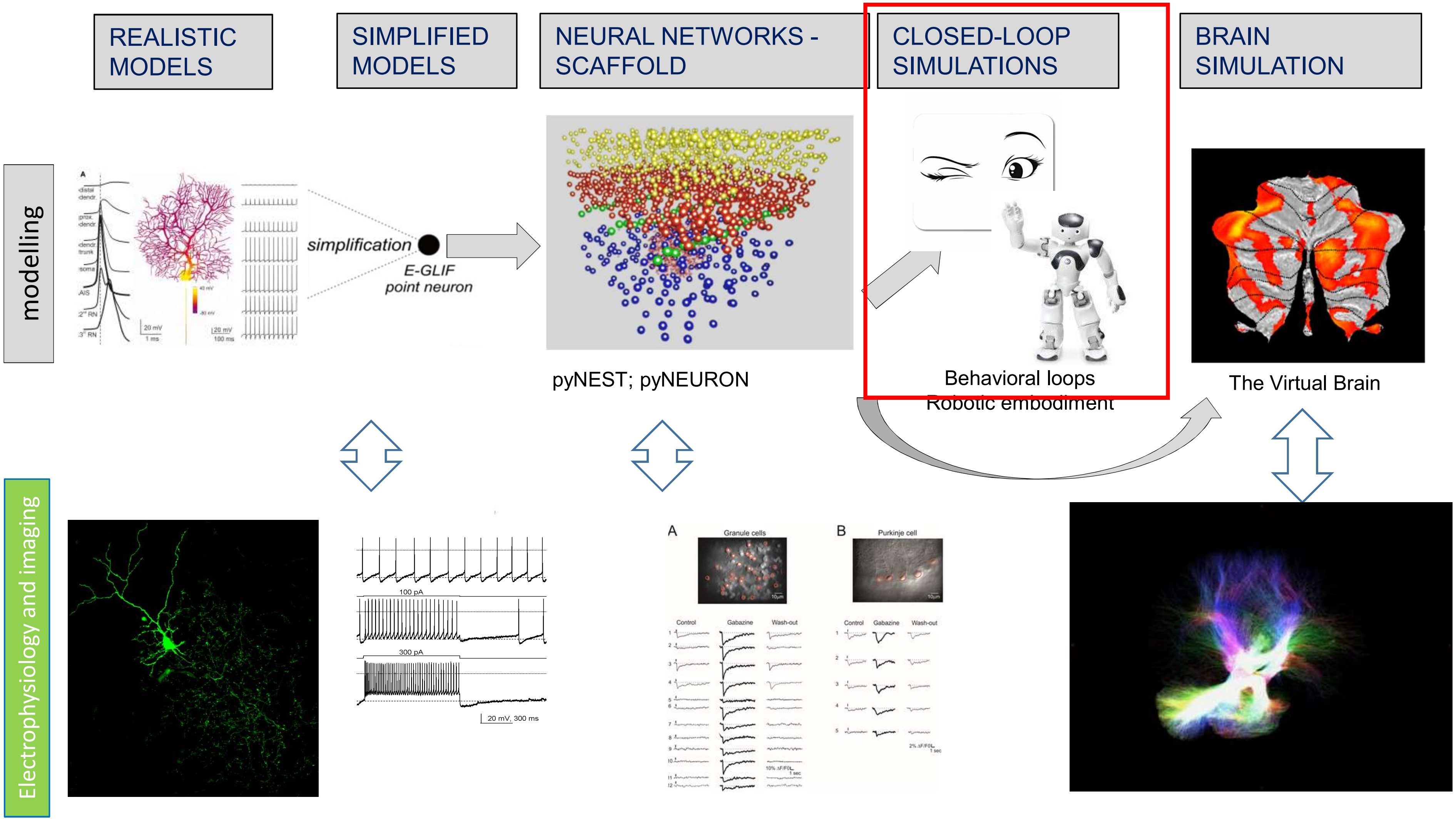


```
"simulations": {

"simulator": "nest“
"duration": 1000
"modules": ["cerebmodule"]
"cell_models": …
“connection models” ….
…

"center_stimulation":
"radius": 70.0,
"origin": [200.0, 70.0, 200.0]
"cell_types": ["glomerulus"]
“poisson generator”
          "parameters": {
            "rate": 150.0,
            "start": 300.0,
            "stop": 350.0
“background noise”
…
```

[Casali et al., 2019 Frontiers in Neuroinformatics]

[https://humanbrainproject.github.io/hbp-bsp-**live-papers**/2019/casali_et_al_2019/casali_et_al_2019.html](https://humanbrainproject.github.io/hbp-bsp-live-papers/2019/casali_et_al_2019/casali_et_al_2019.html)


+ Distributed long-term plasticities
LTP
Otherwise LTD
"parallel_fiber_to_stellate": {
"teaching": "io_to_stellate",
"connection": {
"weight": 0.007,
"delay": 5.0
},
"synapse": {
"stdp_connection_sinexp": {
"A_minus": 0.5,
"A_plus": 0.05,
"Wmin": 0.0,
"Wmax": 100.0
Olivocerebellar circuit
US
IO
MLI
Climbing fibers
LTD
Otherwise LTP
Parallel fibers
GrCs
GoCs
PC
STDP
Time
Time
MF
DCN
"purkinje_to_dcn": {
"connection": {
"weight":-0.4,
"delay": 4.0
},
"synapse": {
"stdp_synapse": {
"tau_plus":30.0,
"alpha": 0.5,
"lambda": 0.1,
"mu_plus": 0.0,
"mu_minus": 0.0,
"Wmax": 100.0
CS
CR
LTD
Otherwise LTP
Time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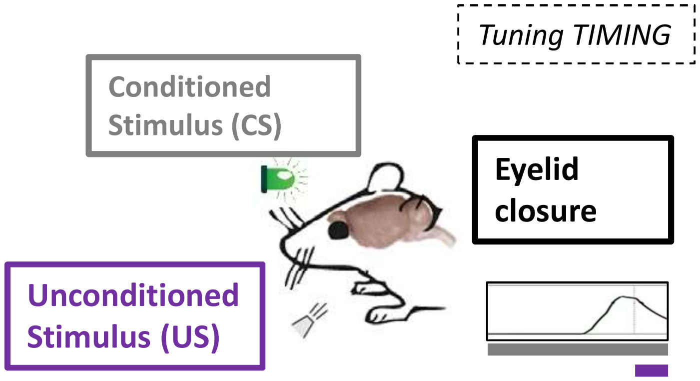
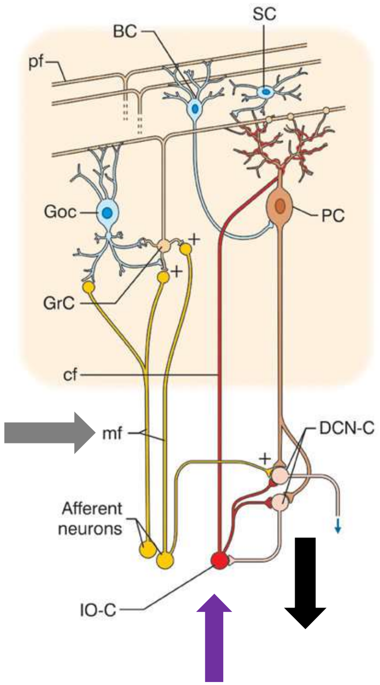
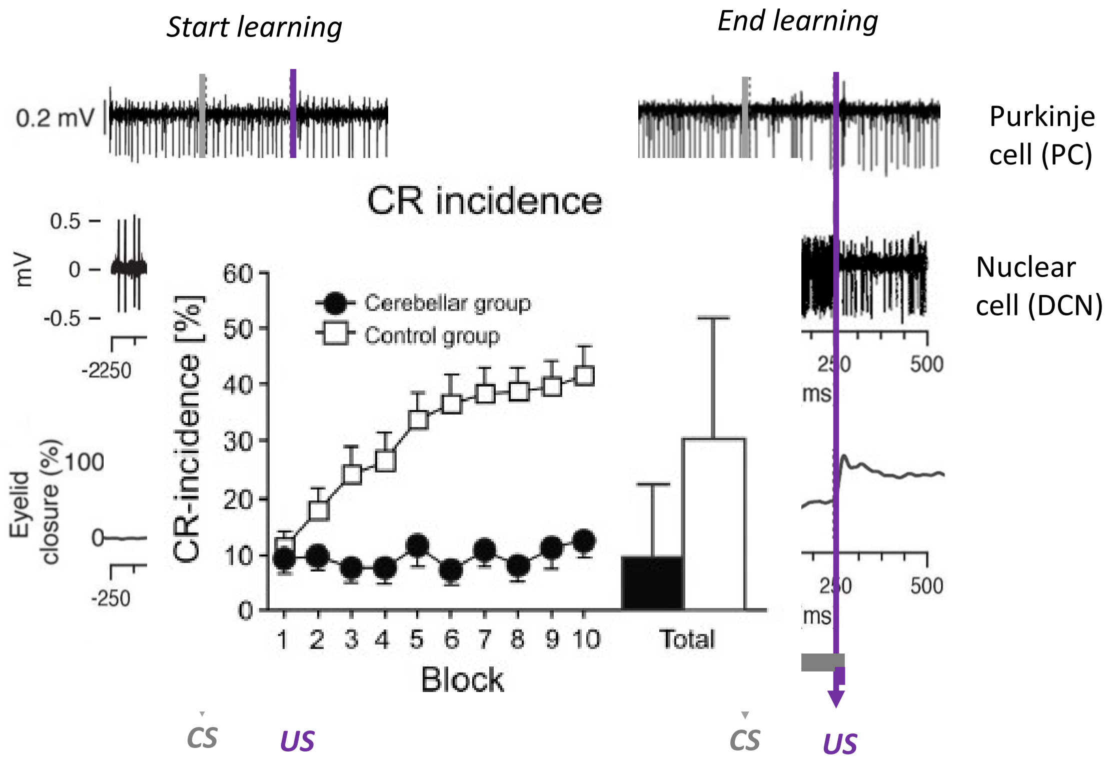
CLOSED-LOOP SIMULATIONS

Behavioral loops

Eye Blink Classical Conditioning (EBCC)







- relatively simple behavioral task
- experimental data on the underlying neural mechanisms are available
- biomarker for cerebellar disease

[Ten Brinke et al., 2015;2017]

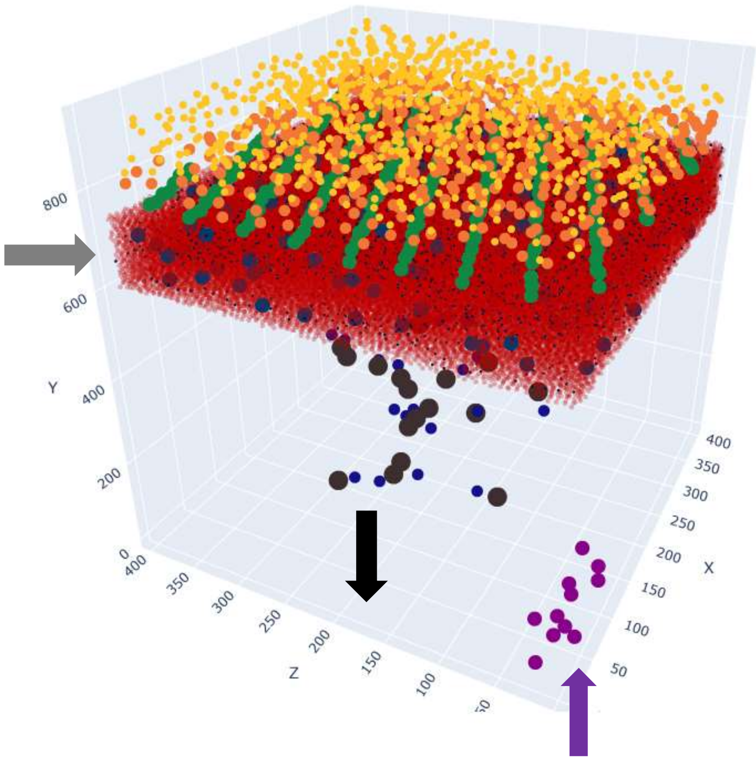
Complex dynamic responses in an olivocerebellar spiking neural network processing sensorimotor patterns

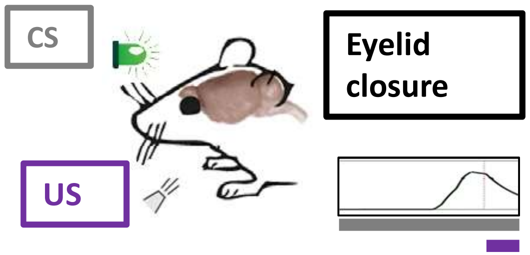
SIMPLIFIED MODELS

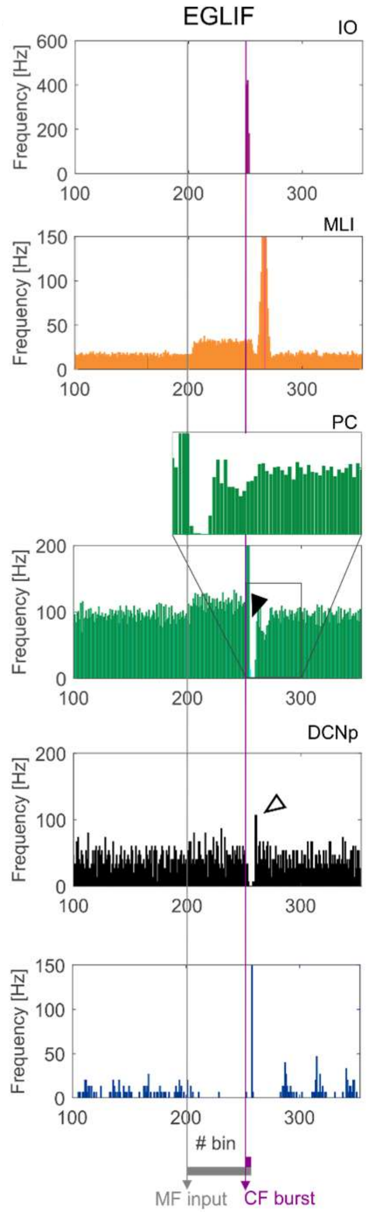
NEURAL NETWORKS - SCAFFOLD

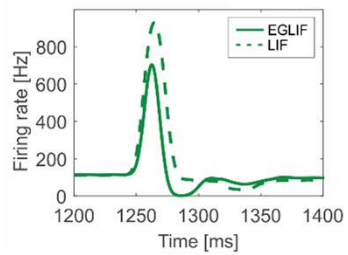
CLOSED-LOOP SIMULATIONS

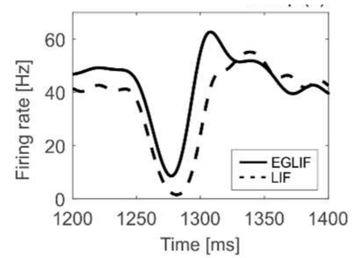
- **Healthy**
- **Start learning**











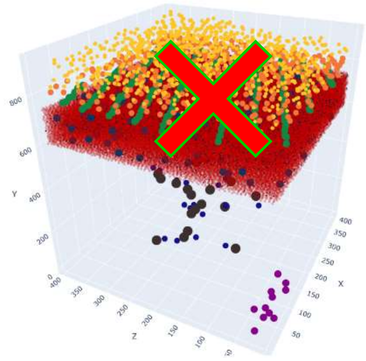
burst-pause and pause-burst responses in PC and DCNp neuronal populations → faster and more precise change of the overall population activity → enhancing time precision of motor output

[Geminiani et al., Front. Comput. Neurosci 2019b]

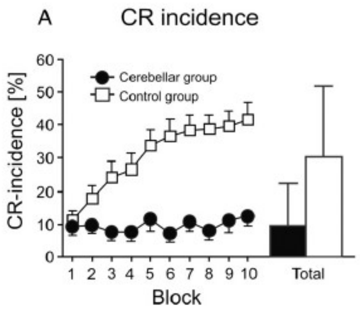
Modeling cerebellar diseases: Purkinje cell loss

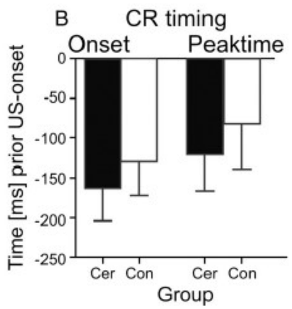
- <u>SpinoCerebellar Ataxia</u> patients reporting decreased cerebellar cortical volume
- In Eye Blink Classical Conditioning: prevented acquisition of the Conditioned Response (CR) and altered timing
  [Dimitrova et al., 2008]

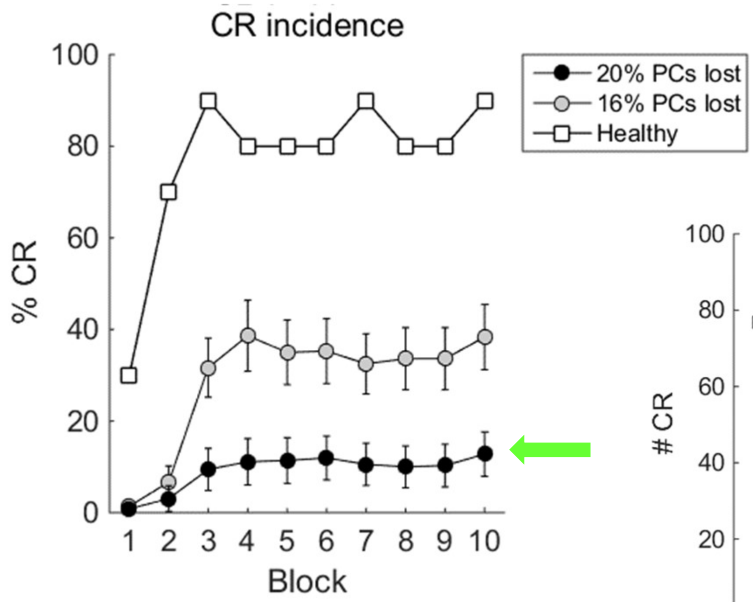
The model was able to reproduce the same **behavioural alteration (CR incidence)** as in the patient.
The model suggested **stability to low damages**

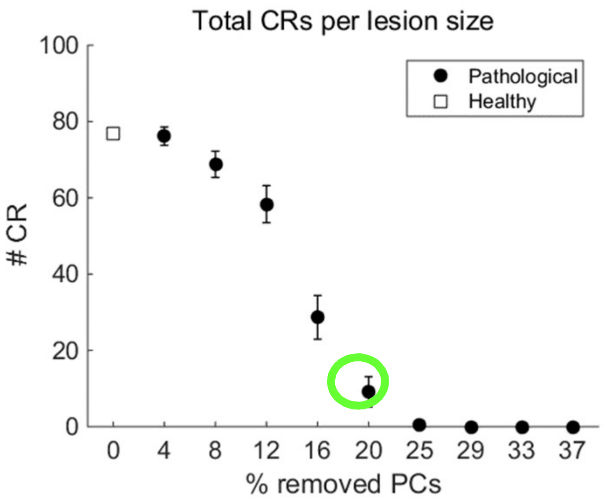


[Geminiani et al, Int J Neural Syst, 2018]









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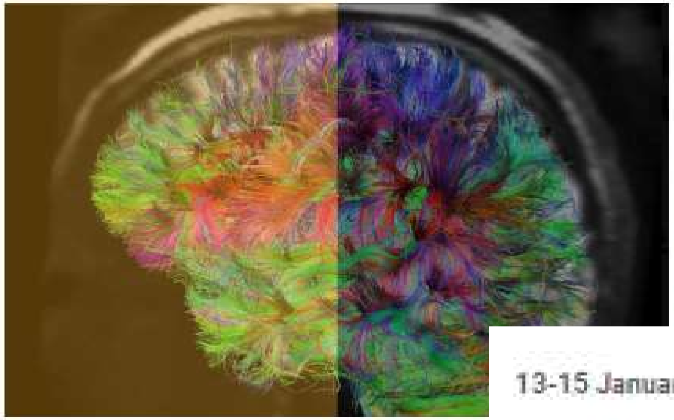
DAL 13 AL 15 GENNAIO – HACKATHON ON CEREBELLUM MODELLING

2019, 2020, cervello, Hackathon, Human Brain Project

13-15th January 2020, Pavia (Italy)



Cerca

Cerca...

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13-15 January 2020 Hackathon on cerebellum modelling

The event is organised by prof. **D'Angelo, Department of Brain and Behavioral Science**, and supported by the **Human Brain Project (HBP)**. The initiative will see the participation of international speakers and the organization of tutorials on the use of HBP infrastructures.

Attached the detailed program:

Programma Hackathon Cerebellum

The participation of researchers and students is recommended, with particular reference to those involved in modeling and computational studies and attending to PhD programs.

For registration and related information contact simona.tritto@unipv.it

http://news.unipv.it/wp-content/uploads/2019/10/Hackathon-Cerebellum-2019_program-2.pdf