CAJAL BLUE BRAIN PROJECT

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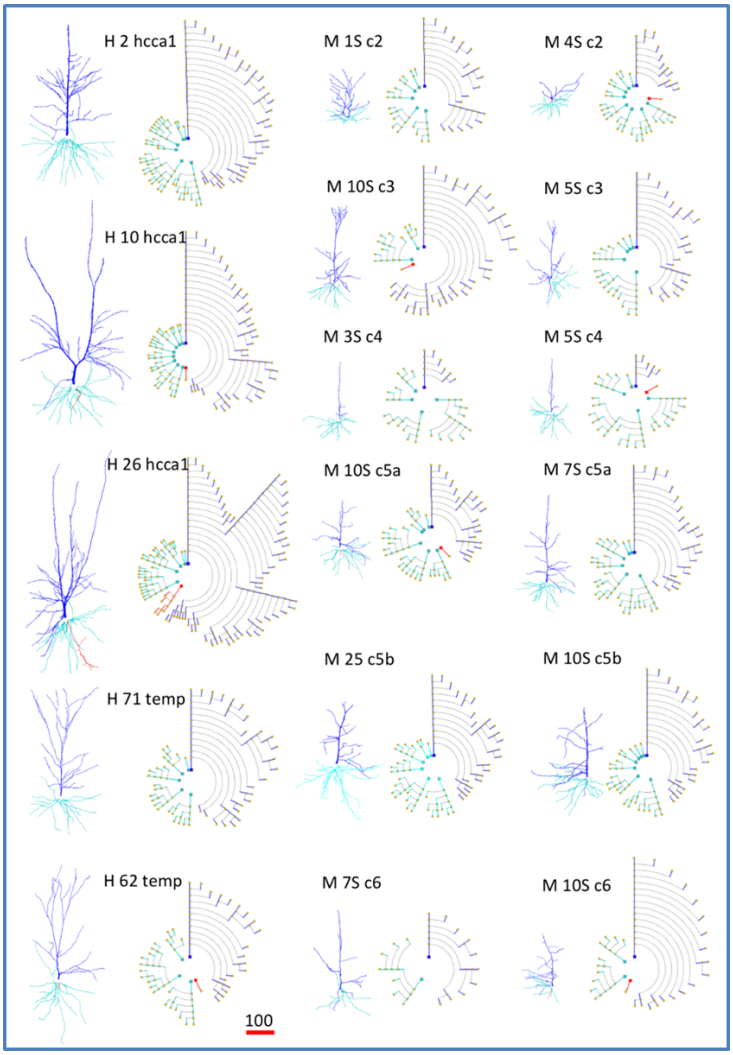
- IT Tools and Models developed in 2018

Cajal Blue Brain Project: Year Ten

During 2018 we have we have completed and finished the main objectives that we intended to achieve during the previous years of the project. Furthermore, we have obtained anatomical and physiological data data from the brain of both rat and mouse which is particularly relevant for the comparative studies. This is important because most of the models used to examine the cerebral cortex are based on data generated on rats, and the challenge now is to apply all the informatics tools to a different species, the mouse. Furthermore, during this year we have particularly focusing on the comparative study of the human **cerebral cortex** with the mouse. As we originally planned for the final phase of the project. The significance of this goal is very high since understanding the human brain is extremely challenging — not only because of its complexity and the technical difficulties involved, but also because ethical limitations do not allow all of the necessary datasets to be acquired directly from human brains. Consequently, most of our present knowledge of brain structure and behavior has been obtained from experimental animals, particularly the mouse. The problem is that data from nonhuman brains cannot fully substitute information on humans since there are fundamental structural and behavioral aspects that are unique to humans as well as to any other species. Accordingly, the question remains as to how much of this nonhuman brain information can be reliably extrapolated to humans, and indeed it is important to establish what the best strategy currently is for obtaining the missing data. Thus, it is critical to determine the differences and similarities in brain organization. Therefore, choosing appropriate experiments to obtain strategic data that could be extrapolated to the human brain should be another major goal. The CBBP has created an infrastructure and a reaserch team which is very well positioned to leader these studies in collaboration with other projects such as the BBP and the HBP. For example, thaks to this collaboration, we have provide the most comprehensive model of any human neuron to-date demonstrating the biophysical and computational distinctiveness of human cortical neurons.



Cajal BLUE BRAIN

2018 Main Achievements

2018 Main Achievements in Neuroscience

Neuroanatomy

- Mitochondria play a key role in energy production and calcium buffering, among many other functions. We found that dendrites are proportionally richer in mitochondria with respect to axons, supporting the notion that most energy consumption takes place at the postsynaptic side. We also found a positive correlation between the volume fraction of mitochondria located in neuronal processes and the density of synapses.
- We have used focused ion beam milling and scanning electron microscopy (FIB/SEM) to obtain stacks of serial sections from the six layers of the juvenile rat. We segmented in three-dimensions 6184 synaptic junctions and determined whether they were established on dendritic spines or dendritic shafts. This study provides a new large quantitative dataset that may contribute not only to the knowledge of the ultrastructure of the cortex, but also towards defining the connectivity patterns through all cortical layers.
- Changes in the size of the synaptic junction are thought to have significant functional consequences. We have used FIB/SEM to segment in 3D a large number of synapses. This study provided three main findings. Firstly, the mean synaptic sizes were smaller for asymmetric than for symmetric synapses in all cortical layers. Secondly, most cortical synapses had disc-shaped postsynaptic densities. Thirdly, the curvature was larger for symmetric than for asymmetric synapses in all layers.
- The study of neuronal dendritic orientation is of interest because it is related to how neurons grow dendrites to establish the synaptic input that neurons receive. We found that the orientation of basal dendritic arbors of pyramidal cells is variable and asymmetric, although a majority has a single orientation with a preference for the anterior direction.
- We have generated detailed models of pyramidal cells from human neocortex, including models on their excitatory synapses, dendritic spines, dendritic NMDA- and somatic/axonal Na+ spikes that provided new insights into signal processing and computational capabilities of these principal cells. Our study provides the most comprehensive model of any human neuron to-date demonstrating the biophysical and computational distinctiveness of human cortical neurons.

Physiology and Modelling

- We have examined the physiological properties of the cortical circuits in the hindlimb somatosensory cortex in juvenile (P14-P16) and adults rats. The data obtained is critical to validate the models obtained in silico experiments, which are mainly based on data generated in juvenile animals. The main achievements are the following:

⇒ We have obtained catalogs of FP generators in juveniles and adult rats using spatial discrimination techniques. These catalogs contain the spatial distribution, mean power, and relation to slow wave activity in the cortex.

⇒ These generators clearly differ in the two age groups. The different spatial distribution indicates that the active synaptic pathways within the column atP14-P16 are different from those that are active in adults.

Cell Physiology

- We have aimed to decipher the role of astrocytes in the sensory information processing in the primary somatosensory cortex in vivo in wildtype mice and a mouse model of Alzheimer´s disease (AD). We have monitored simultaneously the astrocyte calcium signal through two-photon microscopy imaging and neuronal electrical activity through electrocorticogram (ECoG) recordings in vivo in wildtype mice and APP/PS1 mice, and AD animal model.

⇒ In healthy physiological conditions, we have found:

- ♦ Cortical astrocytes respond with calcium elevations to the sensory stimulation.
- ♦ The extension of the astrocyte population response depends on the frequency, intensity and duration of the sensory stimulation.
- ♦ Astrocyte activity is associated with changes in the gamma oscillations of the cortical neuronal network during sensory stimulation.
- ♦ Selective stimulation of astrocyte activity modulates cortical neuronal network activity.
- ♦ The astrocyte regulation of cortical neural network activity is bidirectional and depends on the functional state of the circuit.
- ♦ These findings indicate that cortical function in vivo results from the coordinated activity of astrocytes and neurons.

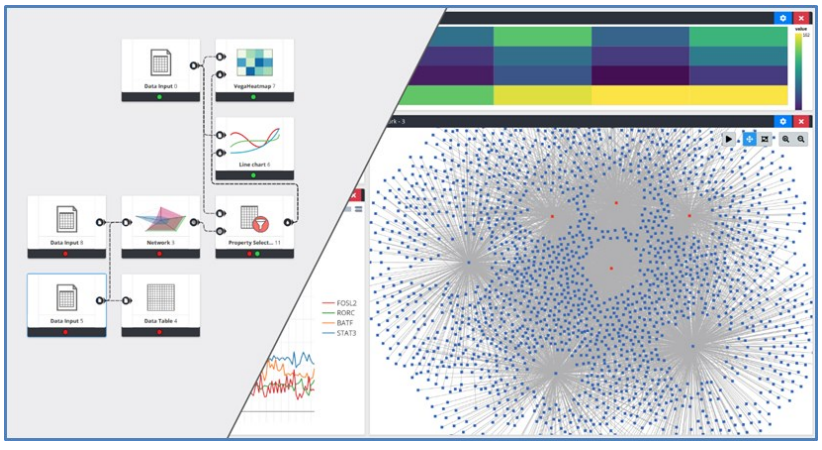
⇒ In the AD mouse model, we have found:

- Astrocytes in the cortex of mice displaying conspicuous β-amyloid (Aβ) plaques respond to sensory stimulation, but with different properties than healthy animals.
- Astrocyte population response depends on the intensity, frequency, and duration of the sensory stimulus, but with significantly different stimulus-dependent curves than healthy animals.
- Relative to control wildtype animals, sensory-evoked astrocyte calcium responses are prolonged.
- Preliminary data to be confirmed suggest that astrocytes regulation of cortical neuronal network activity in AD is dysregulated.
- These findings indicate that the alteration of the properties of the astrocytes and their interaction with neurons may contribute to cognitive impairments in AD, suggesting that astrocytes may be a potential target for therapeutic intervention to treat AD.

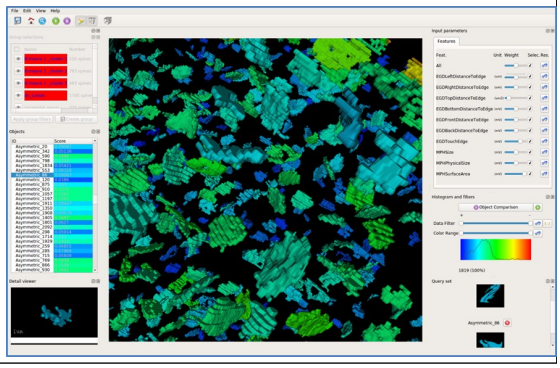
IT Tools and Models

Some examples of the IT Tools and models developed in 2018 are as follows:

- 3D morphology-based clustering and simulation of human pyramidal cell dendritic spines (Luengo-Sanchez et al. 2018, PLoS Computational Biology)
- A supervised classification of neocortical interneuron morphologies (Mihaljevic et al. 2018, BMC Bioinformatics)
- MultiMap: A tool to automatically extract and analyze spatial microscopic data from large stacks of confocal microscopy images (Varando et al. 2018, Frontiers in Neuroanatomy)
- A regularity index for dendrites –local statistics of a neuron's input space (Anton-Sanchez et al. 2018, PLoS Computational Biology)
- Bielza, C., Larrañaga, P. (2019). Data-Driven Computational Neuroscience. Cambridge University Press, in press. > 700 pages
- Development of *Melvin,* a new platform for designing interactive and coordinated view visualization applications able to deal with different neuroscience data types (https://gmrv.es/gmrvvis/melvin/app/):



- The prototype of the integrated framework for the interactive exploratory analysis and visualization of neuroscience data has been successfully carried out, being based on *Vishnu* (https://gmrv.es/gmrvvis/vishnu/). *Vishnu* provides a single access point to DC Explorer, Clint Explorer and Pyramidal Explorer, enabling each of these tools to acquire data coming from different origins.



2018 Main Achievements

CTB

The Cajal Blue Brain Project is hosted by the Universidad Politécnica de Madrid (UPM) in the Scientific and Technological Park of Montegancedo Campus. Computational needs and support infrastructure required by CajalBBP are provided by two of the Research Centers of the Park, the Centro de Tecnología Biomédica (CTB) and the Centro de Supercomputación y Visualización de Madrid, CeSViMa, which is focused on the massive storage of information, high-performance computing and advanced interactive visualization.

More information: www.ctb.upm.es

Sponsorship