Proposal for a PhD in mathematical/computational modeling for neuroscience

Modelling endocannabinoid-mediated synaptic plasticity and its implication in fast learning

Background: Synaptic plasticity is a dynamical process by which the weight of a synapse i.e., the efficacy of synaptic information transmission, changes as a function of the past activity of the neurons. These long-term changes in synaptic efficacy are considered the main cellular mechanism for learning and memory in the brain. Our focus here is on 'fast learning', a term that refers to learning and memory acquisition after a unique and brief experience.

Concretely, synaptic plasticity is implemented by a variety of biochemical reaction and gene expression systems, that alter the amount, activity status or residence time of the molecules and ionic channels involved in synaptic transmission. Among these systems, endocannabinoids (eCBs) are a molecule family of biolipids that mediates synaptic plasticity in several brain regions.

In previous collaborative works with the Venance Laboratory for experimental neuroscience (CIRB, Collège de France, Paris), Hugues Berry's Team at Inria Lyon has carried out an in-depth analysis of the biochemical reaction systems involved in eCB-mediated plasticity. In particular, we have shown that eCBs can mediate both an increase (potentiation) or a decrease (depression) of the synaptic weight, depending on its concentration in the synapse. In addition, we have gathered preliminary evidence that eCB-mediated plasticity could be the main molecular substrate for fast learning in a region of the brain called the striatum.

The ANR-funded project EngFlea (2022-2025), for "Engram of fast learning in the striatum", is a collaboration between the Venance Laboratory and the Berry Team. EngFlea is based on a strategy mixing experiments and mathematical modeling that aims at revealing the mechanisms underlying fast learning and the role of eCBs in this form of memory.

Proposed research: The proposed PhD will model eCB-mediated plasticity in fast learning both at the subcellular level and the neuronal network level. To uncover the molecular mechanisms by which the same molecular signal, eCB, can trigger potentiation or depression, we have set up experimental tools (fluorescent biosensors for cAMP, PKA, etc.) to measure in living neurons the spatial and temporal dynamics of biochemical reactions triggered by eCBs during fast learning.

The first stage of the PhD project will be to set up and study a reaction-diffusion model of the involved intracellular biochemical reactions, in accordance with the experimental data of the Venance Lab. The formalization of the model will be decided based on the first experimental results when available e.g., PDEs or individual-based models. The application of hybrid approaches with machine learning including equation discovery based on sparse/symbolic regression, will also be considered.

In a second stage, the PhD student will develop a spiking neural network model in collaboration with a postdoctoral researcher to be recruited. Incorporating the synaptic plasticity rule unveiled in the first stage, this model will be used to explore the impact of eCB-dependent plasticity at the network level in a fast learning framework. This stage will mainly be based on numerical simulations, but depending on the background of the PhD student and postdoctoral researcher, mathematical approaches (mean-field, macroscopic limits) will also be considered.

Environment: The PhD will take place at the recently inaugurated Inria research center of Lyon (campus de La Doua, https://www.inria.fr/en/centre-inria-de-lyon) under the supervision of Hugues Berry (http://www.inrialpes.fr/Berry/). In addition to interactions within his team, the intern is expected to build strong collaborative links with the Venance Lab at the Centre Interdisciplinaire de Recherche en Biologie (CIRB), Collège de France, Paris.

Starting date: between September and November 2022.

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