Programme Doctoral Interfaces Pour le Vivant 2022

Projet de thèse

"Memory formation and neurogenesis: from experiments to computational models and back"

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Description of the project

Introduction. Storing and recalling distinct memories of similar information are essential brain functions that play key roles in guiding our day-to-day behavior. For example, a familiar room may change its appearance when the light is switched on, yet it needs to be recalled from memory as one and the same room. In turn, two different rooms may strongly resemble each other, but need to be stored as separate memories so that behavior can be adapted to contextual changes.
The hippocampus is thought to tackle the challenge of forming distinct neuronal population activity patterns ("memory representations") of similar objects or events. Experiments in rodents have revealed that as information enters the hippocampus, small differences between environments are first amplified in the dentate gyrus. The downstream regions CA3 and CA1 then combine these distinct inputs with additional information from other brain regions about the saliency or unexpectedness of the present environment. As a result, either a new and distinct memory representation is stored (neuronal discrimination or "pattern separation") or an existing familiar memory representation is recalled even from partial or disrupted cues (neuronal generalization or "pattern completion") [1].
Intriguingly, the dentate gyrus is also one of the few mammalian brain regions where new neurons are continuously generated throughout life, though the issue is debated in humans [2,3]. Newborn granule cells integrate into the adult neural circuit over a period of several weeks after mitosis. During this integration period, they are highly excitable and show an enhanced degree of synaptic plasticity [4]. The finding that specific neural circuits in the adult brain can integrate newborn neurons represents a fundamental and fascinating new principle in neuroscience. However, how these new neurons contribute to the pronounced neuronal discrimination in the dentate gyrus and to the shaping of memories in downstream hippocampal areas remains poorly understood. Our project will specifically assess the contribution of adult-born neurons to hippocampal function through a combination of computational and machine-learning-based modelling with "all-optical" recording and stimulation of functionally identified adult-born and mature neuronal subpopulations in the hippocampus of mice performing memory-guided behavioral tasks in virtual reality.

Objectives. Indirect methods, including ablation or promotion of adult neurogenesis, have yielded partially conflicting results, but they converge towards the view that new neurons contribute to the

neuronal discrimination function of the dentate gyrus [7–9]. While a number of computational models have been developed to explain how adult neurogenesis may contribute to dentate gyrus function [10,11], it has been impossible to empirically evaluate these hypotheses, as we know very little about how adult-born granule cells encode information. Furthermore, it is unclear how their activity relates to behavior.

To address these questions, we aim to record (with 2-photon imaging of neurons expressing genetically encoded calcium indicators) and manipulate (with optogenetic tools) the activity of precisely birth-dated adult-born and mature neuronal populations in the hippocampus. Targeting birth-dated adult-born neurons for functional imaging has been a challenge in the past, as they are highly sensitive to viral vectors for gene delivery [12]. Most studies to date have therefore been limited to recording from a broad range of relatively mature, coarsely birth-dated adult-born neurons [13]. We have developed a new tool that tackles this challenge: a retrovirus carrying a bi-cistronic construct expressing both a structural marker and a genetically encoded calcium indicator (Fig. 1). This construct can also be used to deliver a red-shifted opsin instead of a structural marker for all-optical experiments. This novel tool will allow us to draw causal links between the spatiotemporal activity pattern of adult-born neurons and performance in a memory-guided task, to finally reveal the computational role of adult-born neurons in the mammalian brain.

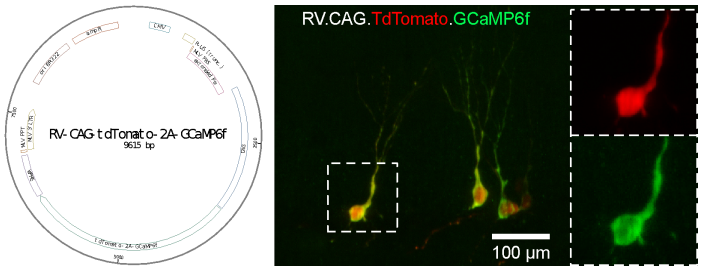

***Figure 1**. Left, A bi-cistronic construct for expression of the structural marker tdTomato and the genetically encoded calcium indicator GCaMP6f was encapsulated into a retro-virus. Middle, Fluorescence image of a fixed hippocampal brain slice showing adult-born granule cells expressing tdTomato (red) and GCaMP6f (green). Right, magnified views of one of the neurons. Unpublished pilot data from the C.S.-H. group.*

In parallel to these experimental investigations, the functional role of the dentate gyrus in the learning of new memories will be elucidated through a combination of modelling, information-theoretic and abstract agent-based approaches.

(a) As a preliminary step we have proposed an abstract computational mechanism, in which the transient increase in the DG activity observed in our pilot data as an animal is introduced to a novel environment drives the downstream CA3 attractor network from a familiar map to a new state that gets progressively consolidated upon learning[14] (Fig. 2). We will investigate how the temporally-tagged inputs due to adult-born neurons in the DG, quantitatively characterized in C.S.-H.'s group, can affect existing memories or yield new representations. We will study how varying the amplitude of DG inputs can modulate the similarity between the existing and new memories, extending our previous theoretical works on the resolution of multiple continuous attractors[15].

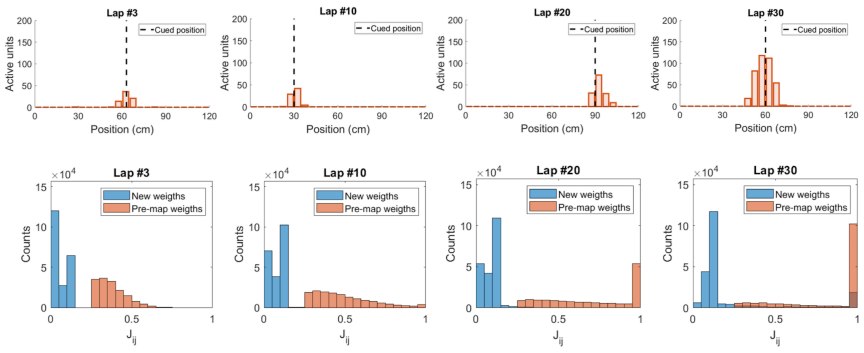

***Figure 2**. Learning of a new continuous attractor in CA3 under a novelty signal from DG[14]. A naive map is initially formed with normally distributed weights (mean=0.3, std=0.01), and is consolidated through hebbian learning. Top: Snapshots of network activity vs. number of laps. Red bars represent the number of active cells in the consolidating map with a place field center in the corresponding 5 cm bin. Black dashed lines locate the position cued through the MEC. Bottom: Distributions of synaptic weights, with the appearance of new connections (blue bars) and the strengthening of the naive couplings (red bars).*

(b) Building on our experience in modelling the effect of neurogenesis in the olfactory epithelium in response to environmental changes[16] we propose to extend Barlow's efficient-coding framework developed for sensory areas to the processing of new spatial and contextual information by the dentate gyrus. This will allow us to interpret the transient high excitability-high plasticity nature of adult-born cells and their differential processing of LEC and MEC mediated inputs[17], in relation to the representational state of mature neurons. We will derive biologically plausible learning and apoptosis[18] rules maximizing the efficient-coding objective function, and compare to the most recent computational models for neurogenesis in the DG[19].

(c) We will develop, on a more abstract level, a deep reinforcement learning-based approach in which an artificial agent learns to associate a change of behavior to a change of environment, along previous works on navigation and path integration by others[20] and us[21]. The nature of the solutions (circuits and representations) will be investigated and compared to the experimental outcomes of the project.

Interdisciplinary nature of the project

Rémi Monasson is director of research at CNRS, working in the Department of Physics at Ecole Normale Supérieure, and professor at Ecole Polytechnique. He is developing statistical-physics and machine-learning based approaches for biological data analysis and modelling, in neuroscience (representation of space in the mammalian brain, coding of olfactory and auditory information, sensory-motor computation in zebrafish) and in genomics.
Christoph Schmidt-Hieber leads the G5 Research Group "Neuronal Circuits for Spatial Navigation and Memory" at the Institut Pasteur. He is an expert in the synaptic integrative mechanisms underlying memory formation and has pioneered electrophysiological and optical recording methods from animals navigating in virtual reality.

The interdisciplinary nature of the PhD project requires that the candidate shares his/her time between the two laboratories. We are primarily looking for a PhD candidate with a strong background in statistical and computational physics, and deep interest towards neuroscience. From the computational point of view, he/she will in charge of designing new models, analyzing their properties through a combination of analytical, numerical and machine-learning methods. From the experimental point of view, he/she will help collect, preprocess and analyze the data. However, candidates with a very strong background in experimental neuroscience and willing to devote a part of their time to data analysis/modeling will be welcome. This PhD will strengthen the fruitful collaboration already existing between the partners: A previous PhD student from R.M.'s group has contributed to a publication from the C.S.-H. laboratory [1]. Furthermore, a common manuscript on the role of DG in pattern separation is currently submitted for publication[14].

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