PhD PROJECT PROPOSAL

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Title of the project

Neuronal network model of the early Sharp Waves in the neonatal rodent hippocampus

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Abstract

During development, neuronal networks display peculiar patterns of activity, directly involved in the formation of neuronal circuits. Early Sharp Waves (eSPWs) are the predominant structured activity pattern in the developing entorhinal-hippocampal network of neonatal rodents, which is thought to be essential for the formation of the connections between the entorhinal cortex (EC) and the hippocampus. Considerable amount of data on cellular, synaptic and network aspects of EC-driven eSPWs in the neonatal hippocampus has been accumulated recently in the Khazipov team at INMED, yet the generative mechanisms of eSPWs remain elusive. One of the central hypotheses involves the different modes of operation of the early vs late EC-hippocampal network, which is enabled by delated development of GABAergic inhibition and large temporal integration window of excitatory inputs from EC or other hippocampal subnetworks. The aim of this project is to identify the generative mechanism of eSPWs by developing a biologically accurate circuit model of EC-driven eSPWs based on recent data, and formulate specific predictions that will be experimentally tested in the Khazipov lab.

Keywords

Sharp waves, hippocampus, entorhinal cortex, rodents, generative mechanism, synchronization, GABAergic synapses, network model, inhibition, development, biophysical model, neural oscillations

Objectives

1. Construct a comprehensive circuit model of the EC-hippocampal network incorporating cellular, synaptic, and population data to simulate network activity during development, and particularly the genesis of eSPWs.
2. Identify the key network components of the EC-hippocampal circuit in the generation of eSPW via model predictions.
3. Test the different hypotheses regarding the generative role of developing EC-hippocampus connectivity in eSPW onset, considering the role of delayed GABAergic inhibition and temporal integration windows of network inputs.

Proposed approach (experimental / theoretical / computational)

We will pursue a combined experimental and theoretical project to determine the developmental mechanisms of activity formation in the EC-hippocampal system. To do so, we will construct a neural circuit model of the EC-Hippocampal networks together with the tegmental glutamatergic and cholinergic inputs. This modelling will be methodologically based on our previous work on the role of GABA and glutamate maturation in neural circuits, synaptic integration, multi-frequency coupling, and cholinergic neuromodulation. We will build upon *exact reduced network models* and use machine learning methods to align the model quantitatively with the obtained data. We will combine computer simulations with the analytical approach based on fast-slow analysis to elucidate the dynamical mechanisms for the onset and the generation of eSPWs, and the role of the developing synaptic and circuit properties. The modelling and analysis will be integrated to generate testable experimental hypotheses and drive the design of new experiments.

Interdisciplinarity

This project will directly combine modelling and analysis methodology from physics and applied mathematics with experimental electrophysiology, in a team spanning all these disciplines. The doctoral student will be physically based at INMED within an interdisciplinary environment including both experimental neuroscience (R. Khazipov) and theory (L. Fontolan), with inputs from the B. Gutkin. The doctoral student will be trained in modelling methods, network analysis, and machine learning approaches to data-based model development. The student will also learn the biophysics of neurons, with a particular attention to hippocampal circuits during development. For what concerns the machine learning part of the project, the student may also receive support from the CENTURI multi-engineering platform. We anticipate that the project will result in multiple publications in physics/applied mathematics/neurocomputing journals as well as top-notch journals in neuroscience.

PhD student’s expected profile

The Ph.D. student should hold a Master’s degree in physics/applied mathematics/electrical engineering/computational neuroscience. Basic skills in modelling of neural/biological systems can be of additional advantage. Of high importance are: i) the ability to work in an interdisciplinary environment, ii) the willingness to dig into the biological intricacies of neural circuits, and iii) to combine analytical and numerical approaches that incorporate experimental data.

Is this project the continuation of an existing project or an entirely new one?

It is an entirely new project.

Two to five references related to the project

Leinekugel X, Khazipov R, Cannon R, Hirase H, Ben Ari Y, Buzsaki G. (2002) Correlated bursts of activity in the neonatal hippocampus in vivo. Science 296(5575):2049-52

Valeeva G, Janackova S, Nasretdinov A, Rychkova V, Makarov R, Holmes GL, Khazipov R, Lenck-Santini PP. (2019) Emergence of Coordinated Activity in the Developing Entorhinal-Hippocampal Network. Cereb Cortex 29(2):906-20.

Fontolan L, Hyafil A, Krupa M, Gutkin B. (2013) Analytical insights on theta-gamma coupled neural oscillators. J Math. Neuroscience 3(1):16.

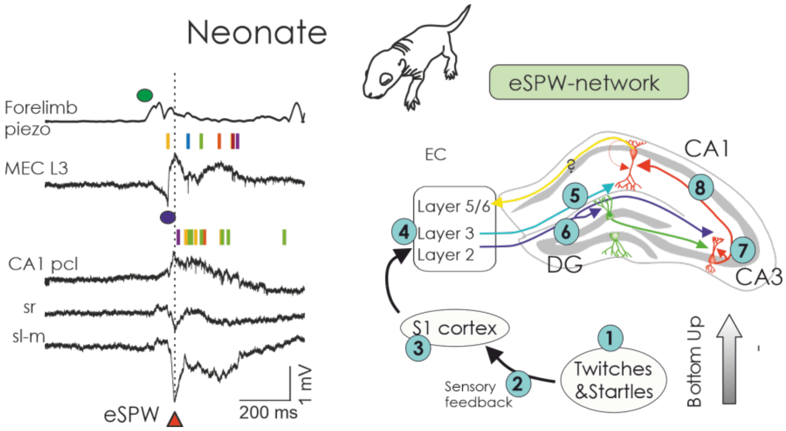
Finkelstein A, Fontolan L, Economo MN, et al. Attractor dynamics gate cortical information flow during decision-making. Nat Neurosci 24, 843–850 (2021). https://doi.org/10.1038/s41593-021-00840-6

Romagnoni A, Colonnese, M, Touboul J and Gutkin B (2020) Progressive Alignment of Inhibitory and Excitatory Delay May Drive a Rapid Developmental Switch in Cortical Network Dynamics, J. Neurophys, 123(5):1583-1599. Doi: 10.1152/jn.00402.2019

Two main publications from each PI over the last 5 years

1. *Finkelstein A, **Fontolan L,** Economo MN, et al. Attractor dynamics gate cortical information flow during decision-making. Nat Neurosci 24, 843–850 (2021). https://doi.org/10.1038/s41593-021-00840-6*
2. *Inagaki, H. K., **Fontolan, L.,** Romani, S., & Svoboda, K. (2019). Discrete attractor dynamics underlies persistent activity in the frontal cortex. Nature, 566(7743), 212-217.*
3. *Cossart R, Khazipov R. (2022) How development sculpts hippocampal circuits and function. Physiol Rev 102(1):343-78*
4. *Nasretdinov A, Vinokurova D, Lemale CL, Burkhanova-Zakirova G, Chernova K, Makarova J, Herreras O, Dreier JP, Khazipov R. (2023) Diversity of cortical activity changes beyond depression during Spreading Depolarizations. Nat Commun. 14(1):7729.*
5. *Perez-Cervera A, Thomas P, **Gutkin B.S**. & Lindner, B (2023) A Universal Description of Stochastic Oscillators, PNAS, i 120 (29) e2303222120*
6. *Dumont G, Perez A, **Gutkin B.S.** (2022) A Framework for Macroscopic Phase-Resetting Curves for Generalized Spiking Neural Networks. PLOS Comp. Biol. 18(8), e1010363*

Project's illustrating image



Early sharp waves (eSPWs) in the neonatal rat hippocampus.

Left, Example traces of the forelimb twitch (green circle), population burst in MEC-L3 (blue circle) and eSPWs (red triangle) recorded from CA1 pyramidal cell layer (pcl), stratum radiatum (sr) and stratum lacunosum-moleculare (slm) in a P5 rat pup. Vertical color bars above traces indicate single-unit activity. *Right*, eSPW network model. Note that sequential activation of various structures in this scheme follows the bottom-up information transfer from the spinal cord to hippocampus. Adapted from *Cossart and Khazipov, 2022 Physiol. Rev.*