SPACE AND TIME IN THE HIPPOCAMUS

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1 Introduction

How does the brain process, represent and store information relevant for making fast and reliable decisions supporting adaptive behavior in different animals? These are arguably the core questions in the field of neuroscience especially in computational neuroscience. The *hippocampus* is among the most intensively studied areas of the mammalian brain. Its relatively simple synaptic organization is well-conserved through the mammalian evolution, and its involvement in cognitive processes such as episodic memory or navigation makes the hippocampus an ideal candidate for studying neural information processing. The physical *location* of an animal is an abstract and hidden variable for them as they have to infer it based on their previous sequence of movements and the currently available set of sensory inputs. How the neural representation of the allocentric space changes in the hippocampus after environmental manipulations helps us understanding the information processing in the nervous system. Animals experience the continuous change of their environment on different *time* scales. Does the neural representation in the hippocampus reflect this continuous flow of information or the brain extracts discrete episodes in space, time and action? Although this question is still open, neural oscillations are naturally involved in binding and segmentation of the incoming information.

In the present dissertation we describe three lines of research focusing on different aspects of the questions posed in the previous paragraph. These three lines represent three different levels of hippocampal computations. First, on the microcircuit level, we give a new model for the generation of the septo-hippocampal theta oscillation and validate this model against experimental data. In the second line, on the macro-circuit level, we show that an integrated hippocampal spatial representation emerges from location dependent input, and we explore the interactions between entorhinal and hippocampal spatial representations under various experimental conditions. Finally, on the single-neuron level, we demonstrate that the dendritic morphology of different neurons shape their spatial receptive field within the hippocampus

2 Time: The Generation of the Septo-Hippocampal Theta Oscillation

2.1 The Problem

The medial septum-diagonal band (MSDB) complex is believed to play a crucial role in the generation and maintenance of the hippocampal theta oscillation, which is the dominant EEG pattern during exploratory behavior in the rodent hippocampus. Indeed, medial septal neurons fire rhythmic bursts phase locked to the hippocampal theta rhythm *in vivo*, and their theta-periodic, coherent spiking remains after isolation from the hippocampus, while lesions of the medial septal nuclei abolish hippocampal theta rhythm. However, under *in vitro* conditions medial septal cells do not exhibit sustained burst-firing activity but display either fast-firing, cluster-firing or slow-firing property. In this section we explore how the *in vivo* firing properties of these neurons emerge from their *in vitro* characteristics and their synaptic connections.

2.2 The Model

Medial septal neurons were described by detailed, conductance-based biophysical models based on *in vitro* recordings from MSDB slices. Glutamatergic neurons contained spike generating currents (I_{Na}, I_{K}) and a slowly inactivating potassium current (I_{KS}) responsible for the intrinsic cluster-firing behavior of these cells. GABAergic neurons contained only spike generating currents and displayed fast-firing property. Synaptic interactions among neurons were described by simple first-order kinetic equations.

2.3 Results

2.1. *Septal glutamatergic neurons, endowed with intrinsic cluster-firing property, form a pacemaker network for the septo-hippocampal theta rhythm.*

2.2. *Septal GABAergic fast-spiking neurons show bursting behavior due to emergent network dynamics: a subpopulation of these cells is driven* *by rhythmic EPSPs originating from the local glutamatergic pacemaker network; the other subpopulation is driven by IPSPs from the first GABAergic subpopulation.*

2.4 Conclusions

In this section we gave a model for the medial septal circuitry involved in the generation of the hippocampal theta oscillation. The model has been supported by experimental results as the two GABAergic subpopulations fire at opposite phases of the hippocampal theta rhythm and the firing rate of medial septal neurons depends on the modulation of the GABAergic synapses. We suggest that septal GABAergic subpopulations innervate different hippocampal interneurons and transmit the septal rhythm to the hippocampus. According to this model medial septal neurons are able to pace the hippocampal oscillations by rhythmically driving hippocampal interneurons during type II (atropine sensitive) theta. During type I (atropine resistant, locomotion related) theta medial septum is in a good position to intensify the hippocampal theta by resonance mechanism and to increase the coherence of the oscillation across the hippocampal formation.

3 Space I: Robust path integration in the entorhinal grid cell system with hippocampal feed-back

3.1 The Problem

Animals are able to update their knowledge about their current position solely by integrating the speed and the direction of their movement, known as path integration. Recent discoveries suggest that grid cells in the medial entorhinal cortex might perform some of the essential underlying computations of path integration. However, a major concern over path integration is that as the measurement of speed and direction is inaccurate, the representation of the position will become increasingly unreliable. In this section we study how integrated hippocampal place representation can be used to continually correct the accumulating error in the entorhinal path integrator system.

3.2 The Model

We set up the model of a mobile agent equipped with the entorhinal representation of idiothetic (grid cell) and allothetic (visual cells) information and simulated its place learning in a virtual environment. Due to competitive learning a robust hippocampal place code emerges rapidly in the model. At the same time, the hippocampo-entorhinal feed-back connections are modified via Hebbian learning in order to allow hippocampal place cells to influence the attractor dynamics in the entorhinal cortex.

3.3 Results

3.1. *Feed back connections from the integrated place cell representation in the hippocampus account for the robust, noise-free path integration realized by the grid cells in the entorhinal cortex.*

3.2. *Parametric changes in grid cell activity following morphing of the environment and remapping of place cells in a new environment are the result of a reciprocal interaction between hippocampal place- and entorhinal grid-cell activities.*

3.4 Conclusions

In this section we described an entorhino-hippocampal reciprocal loop where the integrated place representation in the hippocampus is used to correct for the accumulating noise in the entorhinal path integration system. Similarly, in our model the location of the animal can be continually recalled based on visual cues. Conversely, in the absence of vision (e.g., in darkness) the animal could retrieve visual landmarks associated with its location based on its position information coming from path integration.

4 Space II: Parallel Computational Subunits in Dentate Granule Cells Generate Multiple Place Fields

4.1 The Problem

The dentate gyrus has a pivotal role in the emergence of a robust place representation within the hippocampus, thus, in the third part, we explore the computations performed by dentate granule cells. Recordings from freely moving rats revealed that like pyramidal neurons, granule cells exhibit clear spatially selective discharge. However, granule cells had smaller place fields than pyramidal cells, and had multiple distinct subfields. It has also been recently shown that these subfields are independent, i.e., their distribution was irregular and the transformation of the environment resulted in incoherent rate change in the subfields. In this section we explore whether differences in the morphology of their dendritic arbor and thus in the corresponding single-neuron computations in granule cells versus pyramidal neurons may account for the differences in their spatial firing activity.

4.2 The Model

In this section we derived mathematical framework that can be applied to various neurons with different dendritic arborization. We set up a cascade model to study the somato-dendritic interactions in neurons, that is simple enough for mathematical analysis but can be adequately fitted to experimental data. The long, parallel branches of dentate granule cells are represented by distinct compartments connected to the somatic compartment of the model. We use linear and nonlinear dendritic transfer functions in order to model the integration of synaptic input arriving to the dendritic subunits. Using this model we define statistical criteria to measure if a single dendritic branch alone is able to trigger somatic spiking.

4.3 Results

4.1. *Triggering somatic firing by a relatively small dendritic branch requires the amplification of local events by dendritic spiking and synaptic plasticity.*

4.2. *The moderately branching dendritic tree of granule cells seems optimal for this computation since larger dendritic trees favor local plasticity by isolating dendritic compartments, while reliable detection of individual dendritic spikes in the soma requires a low branch number.*

4.3. *These parallel dendritic computations could contribute to the generation of multiple independent place fields of hippocampal granule cells.*

4.4 Conclusions

In this section we demonstrated that in certain neurons relatively small dendritic branches were able to independently trigger somatic firing. Therefore in these cells an action potential mirrors the activity of a small dendritic subunit rather than the input arriving to the whole dendritic tree. These neurons can be regarded as a network of a few independent integrator units connected to a common output unit. We demonstrated that a moderately branched dendritic tree of hippocampal granule cells may be optimized for this parallel computation. Finally, we showed that these parallel dendritic computations could explain multiple, independent place fields of hippocampal granule cells.

List of Publications

Publications on the results of this Dissertation

- **Ujfalussy, B.** and Kiss, T. (2006). How do glutamatergic and GABAergic cells contribute to synchronization in the medial septum? *J Comput Neurosci*, 21(3):343–57.
- **Ujfalussy, B.**, Kiss, T., Orban, G., Hoffmann, W. E., Erdi, P., and Hajos, M. (2007). Pharmacological and computational analysis of alpha-subunit preferential GABA(A) positive allosteric modulators on the rat septo-hippocampal activity. *Neuropharmacology*, 52(3):733–43.
- Samu, D., Erős, P., **Ujfalussy, B.**, and Kiss, T. (2009). Robust path integration in the entorhinal grid cell system with hippocampal feed-back. *Biol Cybern*, 101(1):19–34.
- **Ujfalussy, B.**, Kiss, T., and Erdi, P. (2009). Parallel computational subunits in dentate granule cells generate multiple place fields. *PLoS Comput Biol*, 5(9):e1000500.

Other related publications

- Érdi, P., Kiss, T., Tóth, J., **Ujfalussy, B.**, and Zalányi, L. (2006). From systems biology to dynamical neuropharmacology: proposal for a new methodology. *Syst Biol (Stevenage)*, 153(4):299–308.
- Diwadkar, V. A., Flaugher, B., Jones, T., Zalányi, L., **Ujfalussy, B.**, Keshavan, M. S., and Erdi, P. (2008). Impaired associative learning in schizophrenia: behavioral and computational studies. *Cogn Neurodyn*, 2(3):207–19.
- **Ujfalussy, B.**, Erős, P., Somogyvári, Z., and Kiss, T. (2008). Episodes in space: A modelling study of hippocampal place representation. In Asada, M., Hallam, J. C. T., Meyer, J., and Tani, J., editors, *From Animals to Animats 10*, volume 5040 of *Lecture Notes in Artificial Intelligence*, pages 123–136. Springer.
- Érdi, P., **Ujfalussy, B.**, and Diwadkar, V. A. (2009). The schizophrenic brain: A broken hermeneutic circle. *Neural Network Word*, 19(5):413–427.