**Spiking Model Summary**

Interactions between hippocampus and prefrontal cortex are thought to underlie the formation, the consolidation, and the retrieval of episodic memories. The hippocampal system, including subiculum, and adjacent parahippocampal regions, combined with prefrontal areas are known to play an important role in learning processes as well. To date only conceptual models have been offered to explain the potential interactions among these regions, but their extrinsic and intrinsic connectivity and synaptic regulation remain unknown. To better understand sequential learning and decision making during spatial navigation, a large scale biological model was needed to further guide experimental studies.

In our model, we first use hippocampal “place cells” and the associated entorhinal “grid cell” firing, which are well-established phenomena. We report the results of a putative entorhinal-hippocampal circuit level model that incorporates recurrent asynchronous-irregular nonlinear (RAIN) dynamics, in the context of recent *in vivo* findings showing specific intracellular-extracellular precession disparities and place field destabilization by entorhinal lesioning. In particular, during computer-simulated rodent maze navigation, our model demonstrated asymmetric ramp-like depolarization, increased theta power and frequency (that can explain the phase precession disparity), and a role for STDP and KAHP channels. Additionally, we propose distinct roles for two entorhinal cell populations projecting to hippocampus. Grid cell populations transiently trigger place field activity, while tonic “suppression-generating cell” populations minimize aberrant place cell activation, and limit the number of active place cells during traversal of a given field. Applied to place-cell RAIN networks, this tonic suppression explains an otherwise seemingly discordant association with overall increased firing.

We further propose a more complex model by adding hippocampal formation structures, including the subiculum, in a complete recurrent loop with prefrontal cortex to accomplish short-term memory of navigational sequences (Figure 1). The subiculum is used as “a winner-take-all”, which make the initial left or right decision for any given position in the maze. The prefrontal receives input from the hippocampus to execute the decision and reinforce it. In any pass through the multi-T maze, three binary left-right decisions must be made to reach a terminus, only one of which offers a reward. The sequence can be learned in as little as two passes through the maze, but more realistically is learned after four passes through. This computational model has been working successfully; but we are now enhancing the biological calibration of specific cell types and synapses to double the number of passes through the maze (assuming that an animal takes longer than four passes to learn this complete sequence of events). As of now, our model replicates the dynamics of the mammalian hippocampal-frontal loop microcircuitry, which demonstrated short-term memory during a sequential three binary decisions needed to receive a reward.

Additionally, phase-locking and coherence between hippocampus and prefrontal respective thetas have been observed in recent recordings studies. We propose that depending on specific connections between areas, phase synchrony (both phase and frequency coherence) of prefrontal cells to hippocampal theta oscillations during the performance of a task requiring working memory can be replicated (See Figure 2).

To demonstrate our computational model’s functionality, a graphic environment with a navigating virtual mouse will be used. Our brain model will process all the information, and will interact with this virtual environment for real-time experiment purposes.

The findings of this circuit level model suggest *in vivo* and *in vitro* experiments that could refute or support the proposed mechanisms of place cell dynamics, modulating influences of entorhinal cortex, decision making of subiculum, and memory consolidating of prefrontal cortex. Our first experiments are to test the types of extrinsic connectivity between the entorhinal cortex and the hippocampus, as well as the intrinsic connectivity in the subiculum.

**Figure 1: Model description**

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**Figure 2: Theta phase synchrony between HP and PF**