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Mechanisms of Coherent Activity in Hippocampus and Entorhinal Cortex

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***Abstract*—We consider the mechanisms by which coherent activity arises in the hippocampus and entorhinal cortex, two brain areas that are associated with episodic memory in humans and similar forms of memory in animal models. Our approach relies upon techniques from the theory of coupled oscillators. We show that such techniques can yield accurate predictions of the behavior of synaptically coupled neurons. Future work will expand upon these techniques to include real-world complications that better mimic the *in vivo* state.**

I. Introduction

COHERENT neural activity is extremely common in cortical structures of the mammalian brain. Such activity is strongly correlated with the behavioral state and with crucial aspects of brain function like learning and memory. In this paper, we review crucial findings related to the problem of neuronal synchrony from the last decade. The focus of the presented work is in the hippocampus and entorhinal cortex, two intimately related brain structures that are crucial for episodic (autobiographical) memory in humans and apparently very similar forms of memory in other mammals.

II. Results

A. Computational Models Suggest the Necessary Conditions for Neuronal Synchronization

Several lines of evidence suggest that synchronous neuronal activity is necessary for hippocampus-dependent episodic memory and "episodic-like" memory in animal models. Our computational modeling efforts [1]-[3] suggest that two factors are crucial for generating synchronous, quasi-periodic neuronal activity. *First*, one or more biophysical variables must serve as a "rate-limiting step" to stabilize the oscillatory period. In our modeling work, this biophysical variable often takes the form of a time constant associated with a set of voltage- or ligand-gated ion channels [1]-[3]. *Second*, the responses of neurons to perturbations from their neighbors should be such that the synchronous state, associated with simultaneous or near-simultaneous firing of the neurons, is stable. By stability we mean that the system returns to the synchronous state after being perturbed away from synchrony by noise or some other factor. We characterize stability in coupled neuronal networks using the theory of coupled oscillators [4]. This theory is most powerful in the limit of infinitesimally small coupling (synaptic) strengths, but often works well even with strong coupling. Computational studies [3],[5]-[6] have begun to elucidate how the biophysical properties of constituent neurons affect neuronal synchronization, at least in models.

B. Studies of Synchronization in Hybrid Networks

Spiny stellate cells (SCs) of the entorhinal cortex make an excellent test bed for studying neuronal synchronization. Under *in vitro* recording conditions, SCs generate intrinsic subthreshold oscillations in response to mild DC depolarization. With more depolarization, SCs generate action potentials that ride upon the depolarizing crest of the subthreshold oscillations. Because the slow oscillations match the frequency range of the synchronized 4-12 Hz theta rhythm in the entorhinal cortex, and because SCs are selectively sensitive to inputs in the theta-frequency range [7]-[8], it is reasonable to hypothesize that interactions among coupled SCs contribute to the theta rhythm.

To test this hypothesis, we recorded from SCs in the brain slice. We used a dynamic clamp system [9] to characterize the SCs in terms of coupled-oscillator theory. This manipulation involves inducing periodic firing, occasionally perturbing the SC with artificial synaptic input at a random phase of the oscillatory cycle, and measuring the degree of phase advance or delay induced by the synaptic input. Hundreds of such measurements from a given cell allow us to characterize the mean and variance of phase perturbations as a function of input phase. From these curves, under a set of testable assumptions, we can predict the degree of synchronization in a fully coupled network. Importantly, we can test such predictions by recording from two neurons simultaneously, using the dynamic clamp to couple them via virtual chemical synapses, and observe the outcome. In our work on SCs [10]-[11], we found that predictions match outcomes extremely closely, and that the properties of SCs are consistent with synchronization at theta frequencies via mutual synaptic excitation.

Our work on synchronization in SCs was predicated on the hypothesis that intrinsic oscillations in these cells serve as the rate-limiting step for theta oscillations. More recent work from our group [12] has challenged this underlying assumption. In the newer work, we found that bombardment of SCs with synaptic input at high rates fundamentally

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changes their integrative properties, apparently making them much less sensitive to inputs in the 5-12 Hz frequency range. This result suggests that other factors may set the pace of synchronous theta oscillations in the living entorhinal cortex. The most obvious other choice would be the decay time constant of chemical synaptic input. Current experiments are examining this possibility in networks that account for multiple cell types.

III. Conclusion

Our work suggests that phase-response techniques can be applied using dynamic-clamp technology to study the problem of neuronal synchronization. However, our original hypothesis that the cells behave as autonomous oscillators may be incorrect. Future work will explore the roles of synaptic decay time constants in pacing oscillations. We also hope to study population oscillations in neurons that fire sporadically and at firing rates substantially below the network oscillatory frequency.

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