Intracellular Dynamics of Virtual Place Cells

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The pattern of spikes recorded from place cells in the rodent hippocampus is strongly modulated by both the spatial location in the environment and the theta rhythm. The phases of the spikes in the theta cycle advance during movement through the place field. Recently intracellular recordings from hippocampal neurons (Harvey, Collman, Dombeck, & Tank, 2009) showed an increase in the amplitude of membrane potential oscillations inside the place field, which was interpreted as evidence that an intracellular mechanism caused phase precession. Here we show that an existing network model of the hippocampus (Tsodyks, Skaggs, Sejnowski, & McNaughton, 1996) can equally reproduce this and other aspects of the intracellular recordings, which suggests that new experiments are needed to distinguish the contributions of intracellular and network mechanisms to phase precession.

Hippocampal place cells encode spatial position with elevated firing rates in certain areas of the environment called place fields (O'Keefe & Dostrovsky, 1971; O'Keefe, 1976). Relative to 4–12 Hz theta rhythm, the spikes occur at a steadily advancing phase as the animal crosses through the place field, a rare example of temporal coding (O'Keefe & Recce, 1993). Harvey, Collman, Dombeck, and Tank (2009) recorded intracellularly from hippocampal neurons in mice in order to uncover the mechanisms underlying phase precession. Explanations for phase precession can be broadly divided between network and intracellular mechanisms. The authors argued that their results supported intracellular mechanisms and not network ones (Tsodyks, Skaggs, Sejnowski, & McNaughton, 1996). We show here that

the intracellular recordings presented in their article cannot distinguish between these two classes of models.

The intracellular models (Kamondi, Acsady, Wang, & Buzsaki, 1998; Magee, 2001; Harris et al., 2002) are based on a combination of intracellular recordings in slices and single-cell conductance-based modeling. A superposition of oscillating excitatory and inhibitory currents applied respectively to dendrites and soma of a neuron can result in phase precession of the output spike train. Conditions for precession are phase opposition between the two currents and a gradual increase of both the baseline and oscillation amplitude of the excitatory current as the animal enters the place field. Possible sources of the excitatory and inhibitory currents are not included in the models.

In the network model (Tsodyks et al., 1996), excitatory cells were mutually interconnected with connection strength biased in the direction of motion and decreasing with the distance between the place fields. Phase precession emerged in the network from fast propagation of activity in the direction of movement that begins at the rising phase of the theta cycle and terminates on the descending phase (see Figure 1A). As the animal proceeded into the place field, the initial position of the wave advanced, and the cell fired earlier in the phase.

Harvey et al. (2009) observed an increase of amplitude in membrane potential oscillations when the animal was within a place field. They argued that this observation was consistent with intracellular models but not with network models, which produce the same oscillation amplitudes within and outside the place field. In order to test this claim, we computed excitatory and inhibitory synaptic currents in one of the cells as the simulated animal passed through the place field (Tsodyks et al., 1996). The currents in the network model had the same features assumed in the intracellular models (Kamondi et al., 1998; Magee, 2001; Harris et al., 2002): excitatory and inhibitory currents oscillated out of phase with approximately the same frequency. The amplitude of oscillations in the excitatory current increased within the place field, as expected, because the neighboring cells generating this current had increasing firing rates. A closer inspection of Figure 1B shows that the network-generated inputs exhibited some features that were more similar to the experimental observations than those in the intracellular models (Kamondi et al., 1998; Magee, 2001; Harris et al., 2002): The ramp in the current was asymmetric, reaching the peak at about two-thirds of the distance from the beginning of the field, compatible with observations and similar to previous work (Mehta, Lee, & Wilson, 2002). In Figure 2, we compare the timings of spikes emission, the maxima of the filtered membrane potential, and the theta-modulated input during a single run in a neuron's place field. Spikes were emitted near maxima of the membrane potential, which advanced compared to the theta rhythm, in accordance with the results reported in Harvey et al. (2009). The advance of the total synaptic current and membrane potential relative to the external rhythm, together
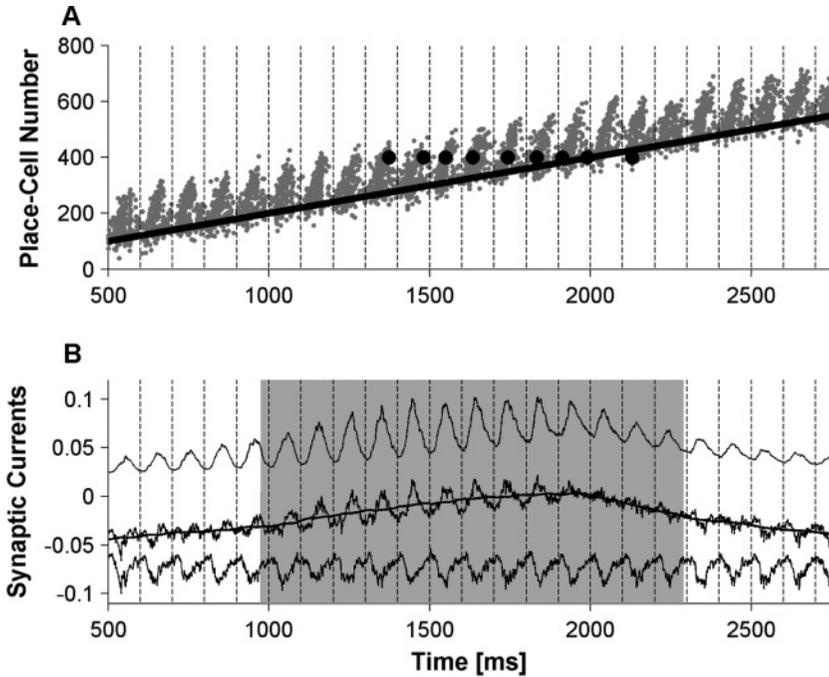
Figure 1: Network model of phase precession (Tsodyks et al., 1996). (A) Spiking activity during a single run through a linear environment. Excitatory neurons are ordered according to their place fields position. Inhibitory neurons are not shown. Each row of gray dots represents spikes emitted by one place cell. An external moving input (maximum on the solid black line) drives the recurrent network. A propagating wave of activity emerges between the maxima of theta-modulated input to the inhibitory subpopulation (vertical dashed lines); the wave originates at each cycle at the location dictated by the external input and propagates forward, producing spike advancement with respect to the underlying oscillations. The black dots are the spikes emitted by a single neuron at the middle position. (B) Membrane currents, relative to spiking threshold, for the single neuron illustrated in A, averaged over 50 runs. The excitatory current (upper curve), consisting of the sum of the recurrent and external input, and the inhibitory current (lower curve) were summed to produce the net drive (middle curve) and moving average (smooth black line) with a time window of 100 ms. Vertical dashed lines as in A. The shaded area corresponds to the firing duration of the neuron. The simulation parameters are identical to those in the original model: $\tau = 20$ ms, $\tau_{ex} = 6$ ms, $\tau_{in} = 4$ ms, $V_{res} = 0.85$, $\theta = 1$, $J_1 = 0.015$, $J_2 = 0.02$, $\sigma = 1.8$, $s^{ex} = 0.2$, $s^{in} = 0.7$, $I_0 = 1.02$, $l = 0.15$, $\lambda_e = 0.03$, $\lambda_i = 0.02$ (see Tsodyks et al., 1996, for methods). Refractory period was 2 ms for both excitatory and inhibitory neurons (not reported in Tsodyks et al., 1996).
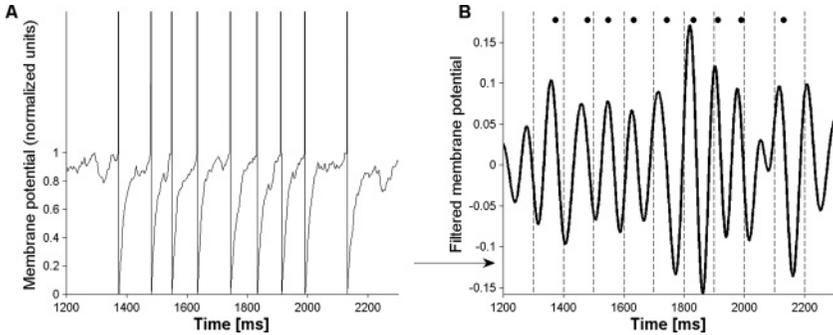
Figure 2: Single neuron membrane potential dynamics and spikes emission. Data from the single neuron illustrated in Figure 1. (A) Membrane potential trace during a single trial in the place field. The potential was rescaled and shifted; values of reset and threshold potential are normalized to 0 and 1, respectively. Spikes added for illustrative purposes. (B). The filtered membrane potential. The potential in windows from 1 ms before to 24 ms after each spike was substituted with a linear interpolation and then bandpass filtered in 5 to 15 Hz (thick black curve). Vertical dashed lines are at maxima of theta-modulated input to the inhibitory neurons. Black circles denote the times when the spikes were emitted by the neuron. Note the phase precession of the spikes with respect to the underlying theta input and the fixed phase relationship between the spikes and the maxima of the filtered membrane potential.

with the asymmetric ramp in the current, contributed to the robustness of phase precession in the spiking output from the model neuron. Neurons were simulated with an integrate-and- fire model with fixed threshold and instantaneous voltage reset after spike, which affects the shape of the voltage trace (see Figure 2A and Tsodyks et al., 1996, for details). However, the phase precession is inherited primarily from the precession of the current peaks and is thus independent of the details of the spiking model.

Thus, contrary to the claim made by Harvey et al. (2009), their intracellular measurements were also consistent with an existing network model of phase precession. More generally, this illustrates the difficulty of separating the influence of the intrinsic properties of neurons from network effects in accounting for the responses of neurons.

Acknowledgments _____

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