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A phase code for memory could arise from circuit mechanisms in entorhinal cortex

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ABSTRACT

Neurophysiological data reveals intrinsic cellular properties that suggest how entorhinal cortical neurons could code memory by the phase of their firing. Potential cellular mechanisms for this phase coding in models of entorhinal function are reviewed. This mechanism for phase coding provides a substrate for modeling the responses of entorhinal grid cells, as well as the replay of neural spiking activity during waking and sleep. Efforts to implement these abstract models in more detailed biophysical compartmental simulations raise specific issues that could be addressed in larger scale population models incorporating mechanisms of inhibition.

1. Introduction

The parahippocampal cortices play an important role in memory function. In humans, the severe anterograde amnesia seen in patient HM was associated with bilateral removal of both the hippocampus and the entire entorhinal cortex (Corkin, Amaral, Gonzalez, Johnson, & Hyman, 1997). In monkeys, lesions of parahippocampal cortices without damage to the hippocampus cause severe memory impairments on delayed matching to sample tasks in both the visual and tactile modalities (Suzuki, Zola-Morgan, Squire, & Amaral, 1993; Zola-Morgan, Squire, Amaral, & Suzuki, 1989), and anterograde memory impairments caused by damage to the hippocampus are increased when accompanied by damage to parahippocampal cortices (Zola-Morgan, Squire, Clower, & Rempel, 1993). Damage to the entorhinal cortex alone causes a transient impairment in delayed match to sample at long delays (Leonard, Amaral, Squire, & Zola-Morgan, 1995), suggesting that it normally plays a crucial role in this task until other structures can compensate. In rats, lesions of the entorhinal cortex impair spatial memory in the water maze (Steffenach, Witter, Moser, & Moser, 2005) and in the 8-arm radial maze (Otto, Wolf, & Walsh, 1997) and cause impairments of memory for odors in delayed matching tasks (Otto & Eichenbaum, 1992; Staubli, Le, & Lynch, 1995; Young, Otto, Fox, & Eichenbaum, 1997). Note that a large number of these memory impairments involve impairments in delayed matching to sample tasks with delays on the order of seconds. This indicates a role for entorhinal cortex in the maintenance of memory representations.

2. Cellular mechanisms in entorhinal cortex

How do local circuits in the entorhinal cortex mediate this role in memory function? The connectivity of entorhinal cortex is summarized in Fig. 1A, showing that input from other neocortical areas arrives in the superficial layer II (Witter & Moser, 2006; Witter et al., 2000a; Witter, Wouterlood, Naber, & Van Haeften, 2000b). The recurrent connectivity between neurons in layer III and V appears to be stronger than in layer II (Dhillon & Jones, 2000), but recent studies have demonstrated excitatory recurrent connectivity in layer II as well (Kumar, Jin, Buckmaster, & Huguenard, 2007). There are strong interactions with both the hippocampus and the subiculum. Layer II projects to the dentate gyrus and region CA3, whereas layer III projects to region CA1 and subiculum in the rat (Witter, Griffioen, Jorritsma-Byham, & Krijnen, 1988), and layer V receives feedback from the hippocampal formation and subiculum (though layers II and III also receive input from subicular subregions).

Here we review data suggesting how cellular and circuit mechanisms might allow the relative phase of neural firing to code memories. These intrinsic cellular mechanisms have been

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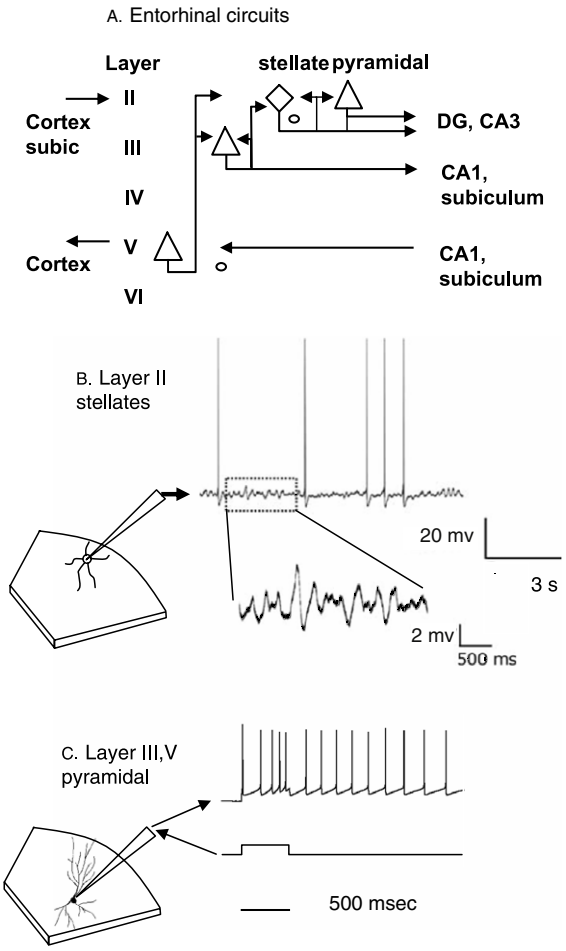

Fig. 1. A. Summary of the circuitry of medial entorhinal cortex. Input from other cortical areas (Cortex) and subiculum (sub) enters in layer II and III. Layer II contains both stellate and pyramidal cells, and these cells send recurrent connections to layer II and afferent connections to dentate gyrus and CA3. Layer III has recurrent connections to layer II and III and afferent connections to CA1 and subiculum. Region CA1 and subiculum send return connections to layer V which projects to other cortical regions. B. Whole cell patch recording in slice preparations shows that layer II entorhinal stellate cells generate subthreshold membrane potential oscillations in between the generation of action potentials (Giocomo & Hasselmo, 2008b). Blowup focuses on subthreshold oscillations. C. Whole cell patch recording in the presence of cholinergic or mGlulr agonists shows that layer III and V pyramidal cells exhibit persistent spiking that is maintained after the termination of a square pulse current injection (Yoshida et al., 2008).

demonstrated using intracellular sharp electrode or whole cell patch recording in entorhinal cortex neurons. Fig. 1B and C illustrate important intrinsic properties of entorhinal neurons that could contribute to the phase coding of memory.

2.1. Membrane potential oscillations

Entorhinal layer II stellate cells show subthreshold membrane potential oscillations when depolarized near firing threshold (Alonso & Klink, 1993; Alonso & Llinas, 1989; Giocomo, Zilli, Fransen, & Hasselmo, 2007). An example is shown in Fig. 1B (Giocomo & Hasselmo, 2008b). These are small oscillations of a few millivolts in amplitude that can influence the timing of action potentials (Fransen, Alonso, Dickson, Magistretti, & Hasselmo, 2004; Pervouchine et al., 2006; Rotstein, Oppermann, White, & Kopell, 2006) and may contribute to network theta frequency oscillations (Acker, Kopell, & White, 2003; Alonso & Garcia-Austt, 1987; Mitchell & Ranck, 1980). The frequency of membrane potential oscillations differs systematically along the dorsal to ventral axis of the medial entorhinal cortex (Giocomo et al., 2007). The oscillations appear to be due to a hyperpolarization activated cation current or *h*-current (Dickson et al., 2000), that differs in time constant along the dorsal to ventral axis (Giocomo & Hasselmo, 2008b). Membrane potential oscillations appear less frequently in layer II or layer III pyramidal cells (Alonso & Klink, 1993), but are observed in layer V pyramidal cells, where they may be caused by M-current (Yoshida & Alonso, 2007). The layer V membrane potential oscillations also show a gradient in frequency from dorsal to ventral medial entorhinal cortex (Giocomo & Hasselmo, 2008a). Membrane potential oscillations do not appear in neurons of the lateral entorhinal cortex (Tahvildari & Alonso, 2005).

2.2. Persistent spiking

In slices, pyramidal neurons in different layers of entorhinal cortex demonstrate the capacity to display persistent spiking activity after a depolarizing current injection or a period of repetitive synaptic input (Egorov, Hamam, Fransen, Hasselmo, & Alonso, 2002; Fransén, Tahvildari, Egorov, Hasselmo, & Alonso, 2006; Klink & Alonso, 1997; Tahvildari, Fransen, Alonso, & Hasselmo, 2007; Yoshida, Fransen, & Hasselmo, 2008), as illustrated in Fig. 1C. Some pyramidal neurons in layer II of medial entorhinal cortex show persistent spiking, whereas others show spiking that self-terminates over periods of many seconds (Klink & Alonso, 1997). Pyramidal cells in layer III show stable persistent spiking that can last for two minutes or more (Yoshida et al., 2008). Pyramidal neurons in deep layers of entorhinal cortex can maintain spiking at different graded frequencies for many minutes (Egorov et al., 2002). The persistent spiking appears to be due to muscarinic or metabotropic glutamate activation of a calcium-sensitive non-specific cation current (Fransén et al., 2006; Shalinsky, Magistretti, Ma, & Alonso, 2002; Yoshida et al., 2008). This graded persistent firing could allow these neurons to integrate synaptic input over extended periods. Persistent firing has also been shown in layer III of lateral entorhinal cortex (Tahvildari et al., 2007).

The mechanism of persistent spiking could code memories either in terms of the graded magnitude of firing rate (Egorov et al., 2002; Fransén et al., 2006), or in terms of the phase of spiking relative to the phase of a stable baseline frequency (Hasselmo, 2008a). Many models of cortex code memory in the form of the firing rate of individual neurons. For example, models of working memory based on recurrent connections code the previous presence of a specific stimulus by inducing and maintaining a different level of firing frequency in a population of neurons (Amit & Brunel, 1997; Lisman, Fellous, & Wang, 1998; Zipser, Kehoe, Littlewort, & Fuster, 1993). These types of models can also code and maintain the location of a simulus over time by maintaining a "bump" of activity in a set of neurons responding selectively to a particular location (Miller, 2006; Miller & Wang, 2006; Samsonovich & McNaughton, 1997). In contrast, other models have used phase to code the memory for a specific item. For example, sequences of spiking at different phases have been proposed to represent different items in a model of short term memory (Jensen & Lisman, 1996a, 1998, 2005), and the spiking phase arising from oscillatory interference has been proposed to code spatial location for path integration (Burgess, 2008; Burgess, Barry, & O'Keefe, 2007; O'Keefe & Burgess, 2005).

Here we focus on how the phase of rhythmic spiking activity relative to a reference phase could code memory, due to intrinsic cellular properties of neurons (Giocomo & Hasselmo, 2008a, 2009; Giocomo et al., 2007; Hasselmo, 2008a) or network dynamics. The mechanism can be used in models to encode the spatial location of a rat (Burgess, 2008; Burgess et al., 2007; O'Keefe & Burgess, 2005), or it could be extended to encode the spatial location of a stimulus, the magnitude of a stimulus or the temporal duration of a stimulus.

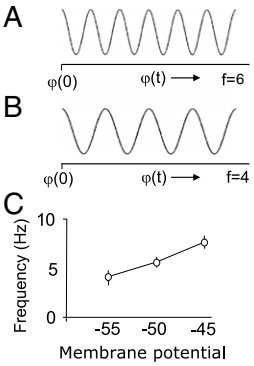

Fig. 2. Schematic representation of oscillations with different frequencies that could be regulated by neuronal input. A. Higher frequency oscillation ($f = 6$ Hz). B. Lower frequency oscillation ($f = 4$ Hz). C. Experimental data from different populations of stellate cells recorded at different membrane potentials shows a difference in mean oscillation frequencies (Giocomo & Hasselmo, 2008a).

3. Phase code for memory

The phase code of memory will first be illustrated in a simple example using an abstract representation of oscillations. These modelled oscillations can represent a range of different physiological phenomena. They could represent subthreshold membrane potential oscillations (MPO) arising from interactions of voltage-dependent membrane currents within single neurons. With a simple threshold function, trigonometric functions could represent rhythmic persistent spiking activity with a stable firing frequency regulated by calcium-sensitive membrane currents. These oscillations could also represent network level oscillations based on the interactions of sub-populations of stellate cells, pyramidal cells and inhibitory interneurons.

Consider a single oscillation with constant frequency over time:

$$V(t) = \cos(2\pi ft). \tag{1}$$

The number of cycles of the oscillation per unit time is determined by the frequency f, and the time duration of one cycle is the period $T = 1/f$. Examples of oscillations are shown in Figs. 2–4. Note that the oscillations can also be described by their instantaneous phase angle (the term "angle" is commonly dropped). The instantaneous phase corresponds to the angle being used at each point of time in the cosine function, as follows:

$$\varphi(t) = 2\pi ft. \tag{2}$$

Thus, for frequency $f = 1$ and time $t = 0.25$, the phase angle is $\varphi(t) = \pi/2$. Note that this description of instantaneous phase differs from the initial phase $\varphi(0)$ that would shift the entire oscillation from the starting time, as in $\cos(2\pi ft + \varphi(0))$.

The phase code described here focuses on the relative phase of one oscillation versus a baseline oscillation. The frequency of the baseline oscillation keeps a constant value f, as described by Eq. (2) above.

The memory mechanism described here can encode a new input through the influence of that input on the frequency of an oscillation holding the memory, thereby causing the oscillation holding the memory, labelled as $\varphi_m(t)$ in Figs. 2 and 3 to have a different relative phase. The instantaneous phase changes constantly, but the relative phase difference caused by a memory input can be quantified when compared to a reference phase. The new input will cause a change in frequency of the oscillation at different time points. The instantaneous phase $\varphi(t)$ at each new time step can be computed by adding the old phase angle at time t to the change in phase angle for each time interval Δt. When the frequency of an oscillation changes as a function of time $f(t)$, then the phase angle needs to be updated with different values of $f(t)$ for each time interval Δt, as follows: $\varphi(t+\Delta t) = \varphi(t) + 2\pi f(t)\Delta t$. Updated continuously, this results in the phase integrating the function of frequency over time $\varphi(t) = \int_0^t 2\pi f(\tau)\mathrm{d}\tau$. For the baseline oscillation with constant frequency f, this integration simply yields the baseline phase $\varphi(t) = 2\pi ft + \varphi(0)$.

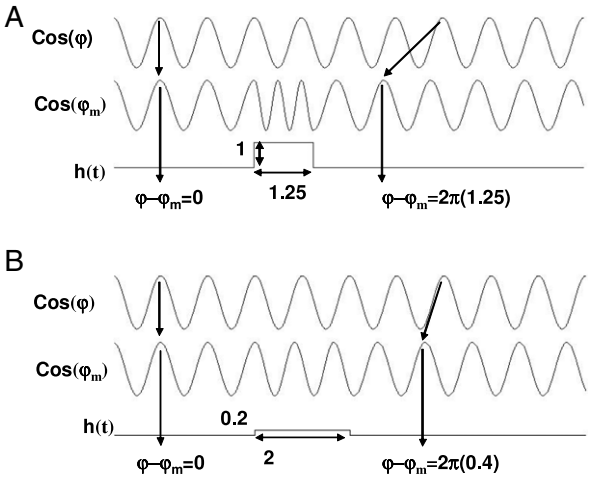

Fig. 3. Plot of the phase of membrane potential oscillations in a single cell $\cos(\varphi_m(t))$ interacting with the network theta rhythm oscillation $\cos(\varphi(t))$. A. Input $h(t)$ with magnitude 1.0 and duration 1.25, causes a shift in the frequency and phase of $\cos(\varphi_m(t))$ relative to $\cos(\varphi(t))$ that is proportional to the magnitude and duration of input. Thus, the input associated with a prior item input can alter the phase representation, providing memory for the item in the form of a shift in phase that is maintained over time. B. Example of the shift in frequency and phase caused by input $h(t)$ with magnitude 0.2 and duration 2.0.

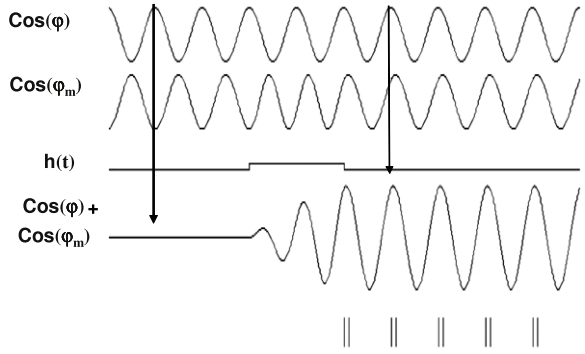

Fig. 4. The phase code of memory can be read out by spiking activity due to interference between oscillations. The top row shows two oscillations that start out in antiphase with each other. The depolarizing input $h(t)$ to $\cos(\varphi_m(t))$ causes the frequency of the oscillation to increase and the phase to shift relative to the reference oscillation $\cos(\varphi(t))$. The sum of the oscillations then shifts from showing destructive interference at the start to showing constructive interference. This constructive interference brings the summed oscillation over threshold, generating spiking activity.

4. Memory as phase angle

Neural oscillations in single neurons have the potential capacity to hold memory for prior inputs in the form of the relative phase angle of the oscillation. In the simplest example, the memory being encoded would consist of some stimulus causing a shift in the frequency of an oscillation for the period of time that the stimulus is present. The change in frequency will shift the relative phase angle compared to the baseline oscillation. Thus, the stored memory takes the form of a difference in the phase angle of a neural oscillation relative to a reference phase angle. The shift in phase

angle will be proportional to the magnitude and duration of the encoded input.

Experimental data from stellate cells shows differences in the oscillation frequency observed in different individual cells recorded at different membrane potentials in dorsal entorhinal cortex (Giocomo & Hasselmo, 2008a), as summarized in Fig. 2. This suggests that oscillation frequencies may change with depolarization, though direct measures of changes in oscillation frequency with depolarization in single neurons do not always show clear frequency changes. The frequency is difficult to analyze across many membrane potential values in single neurons, because the amplitude of oscillations becomes small near resting potential, and the oscillations are obscured when cells are depolarized enough to generate spikes. In persistent spiking cells, additional depolarizing or hyperpolarizing current injection will increase or decrease the spiking frequency from the baseline persistent firing frequency (Yoshida and Hasselmo, unpublished data).

A potential difficulty for implementing a phase code with membrane potential oscillations concerns the tendency for oscillations within different parts of a single neuron to synchronize, as shown in computational studies (Remme, Lengyel, & Gutkin, 2007). Previous models have proposed that the relative phase of two oscillations could differ if one is an intrinsic oscillation in the dendrites of a neuron, and the other is a network oscillation altering the somatic membrane potential (Burgess et al., 2007; Lengyel, Szatmary, & Erdi, 2003; O'Keefe & Recce, 1993). As an alternative, persistent spiking of different individual neurons with the same baseline frequency could allow maintenance of separate phases (Hasselmo, 2008a), or the oscillation encoding the memory could also arise from network dynamics within a population of neurons.

Consider a neuron holding memory for the magnitude and duration of a previous movement. The shift in phase angle can be induced by changing the frequency of the oscillation for a period of time according to $h(t)$, representing some sensory input influencing frequency. For example, as shown in Fig. 3, imagine there is no initial movement until time $t = 3$, when movement occurs with magnitude 1 until time $t = 4.25$, at which time movement stops. This input causes a shift in the frequency of the oscillation that results in a shift in the phase of the oscillation as follows:

$$\varphi_m(t + \Delta t) = \varphi_m(t) + 2\pi(f + h(t))\Delta t. \quad (3)$$

This difference can be seen in Fig. 3 when comparing the phase φ_m of the oscillation holding the memory to the phase φ of the baseline oscillation. Before the movement occurs, the phase difference between the two oscillations is zero. During the movement, the phase difference increases by $2\pi h(t)\Delta t$, so that at the end of the movement the phase difference is $2\pi(1)(1.25)$. The total phase shift is proportional to the integral of $h(t)$ over the interval of input. In the absence of further input, this phase shift persists in the network over all of the subsequent cycles of oscillation.

The phase shift can integrate any function $h(t)$ over any interval. Another example is shown in the bottom of Fig. 3. In this case, $h(t)$ increases from zero to 0.2 for a period of 2 s, resulting in a phase shift of $2\pi(0.2)(2) = 2\pi(0.4)$. This is visible as a shift in the peak of φ_m to an earlier phase that precedes the peak of the baseline oscillation by about 4/10 of a full cycle. Thus, the figure illustrates how memory of a previous input can be maintained in the form of a shift in the phase of one oscillation relative to a baseline oscillation.

By integrating the magnitude and duration of previous input, the phase shifts described here encode a continuous representation of previous input and maintain this memory by holding the phase (in the absence of further input). However, this leaves open the problem of reading out the phase angle difference coding the memory.

5. Interference provides memory read-out

The memory encoded by phase shift in the previous section must be accessible for read-out. A potential mechanism for reading out the difference in phase is through the interference of oscillations (Burgess et al., 2007; O'Keefe & Recce, 1993). In the example in Fig. 4, the input causes a difference between the phase of the oscillation holding the memory and the phase of the baseline oscillation. This can be read out in the form of interference between these two oscillations.

As shown in Fig. 4, the sum of two oscillations that are out of phase with each other will undergo destructive interference so that the summed oscillation is a flat line. However, if one of the oscillations is shifted by input of magnitude 0.2 for 2 time steps, the integral of the shift is 0.4. Thus, the phase has shifted by about half a cycle. This brings the two oscillations closer in phase with each other. In this case, the sum of the oscillations now shows constructive interference, resulting in a large amplitude oscillation. If we consider a neuron that spikes whenever the oscillation crosses a threshold of 1.4, this results in regular spiking that indicates that a previous input of a particular magnitude was presented.

This read out specifically indicates the integral of prior input, giving the same response for a magnitude of 0.8 for 0.5 time steps or a magnitude of 0.1 for 4 time steps. In addition, it codes magnitude in a repeating manner, responding the same for 0.4 and 1.4. However, the readout can be made more specific by utilizing oscillations with different sensitivity to input that shifts them by different amounts. For example, consider a second pair of oscillations in which the input is scaled by 2/7. This second pair of units will respond to 0.4 and 1.4 with 0.11 and 0.4, thereby distinguishing the two states. The interaction of different coding scales can effectively code very large ranges according to the least common denominator of interactions (Gorchetchnikov & Grossberg, 2007). Different scales could arise from the differences in intrinsic frequency in neurons at different anatomical positions in medial entorhinal cortex (Giocomo & Hasselmo, 2008a, 2008b, 2009; Giocomo et al., 2007) that may underlie differences along the dorsal to ventral axis in the size and spacing of grid cell firing fields as well as the size of place cell firing fields in the hippocampus (Hasselmo, 2008b; Kjelstrup et al., 2008). This raises the intriguing possibility that anatomical differences in intrinsic frequencies in other structures such as prefrontal cortex and piriform cortex could underlie differences in the scale of coding for different behaviours (Hasselmo, 2008b).

This section described how a shift in phase of oscillations can provide a memory for prior input, and shows how interference between shifted phases can provide read-out of the prior memory. This process could code memory for the temporal duration and magnitude of a stimulus or stimulus feature. For example, neurons responding to different stimulus features could create a phase code for individual sample stimuli that would be maintained over a delay period by maintenance of the relative phases of oscillations.

Alternately, this process could code memory for the velocity of self-motion in an environment, providing a mechanism for path-integration (Burgess, 2008; Burgess et al., 2007). Velocity can be coded by head direction cells (Taube, Muller, & Ranck, 1990b) combined with cells responding to speed of translational motion (O'Keefe, Burgess, Donnett, Jeffery, & Maguire, 1998). Starting from an initial relative phase, input coding the direction and speed of movement will shift the phase of firing in proportion to velocity. The shift in phase integrates velocity, so that at the end of the movement, the relative phase codes the relative difference in position between the starting location and the end location. The interference of different oscillations will show repeated patterns of spiking dependent upon the movement. This phenomenon forms

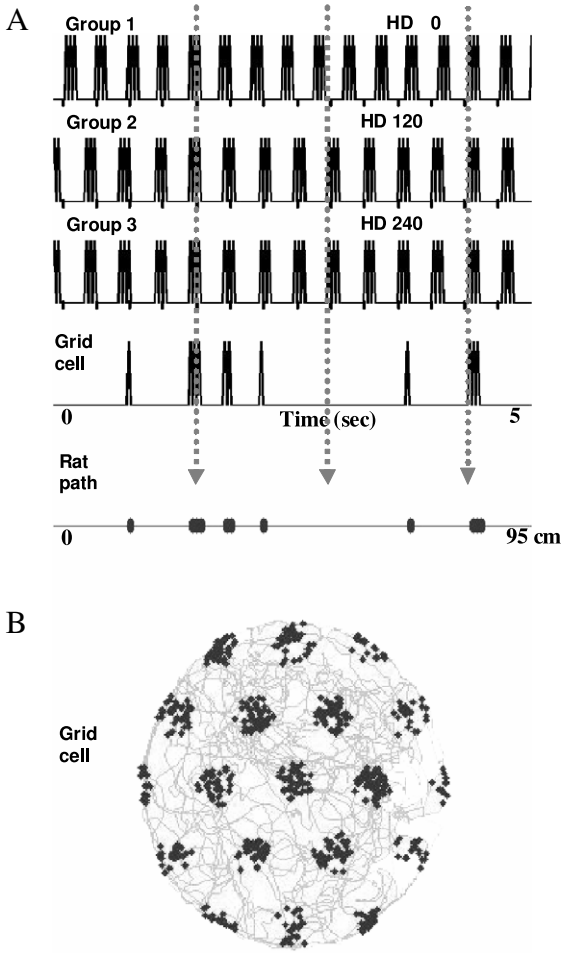

Fig. 5. Mechanism for interaction of persistent firing cells to cause grid cell firing. A. Spiking activity over time of three different groups of persistent firing neurons. Here, each group consists of three persistent spiking cells firing with a baseline frequency of 3 Hz with different phases. Cells receive input from head direction (HD) cells with 0 degree preferred angle for Group 1, 120 degree angle for Group 2, and 240 degree angle for Group 3. Grid cell firing arises from the convergent spiking of the three groups of persistent firing neurons. When all three persistent firing groups fire in synchrony, the grid cell will fire (dots). B. Grid cell spiking (dots) occurs only when all of the persistent firing neurons fire at the same phase, resulting in a typical grid cell firing pattern. Gray line indicates rat trajectory from experimental data (Hafting et al., 2005).

the basis for a model of the grid cell responses of medial entorhinal neurons (Burgess, 2008; Burgess et al., 2007; Giocomo et al., 2007; Hasselmo, Giocomo, & Zilli, 2007). An example of how this phase code can result in grid cell firing is shown in Fig. 5.

6. Alternate mechanisms for phase coding

There could be many possible mechanisms for the maintenance of the phase code. The phase code could depend upon intrinsic membrane potential oscillations (Giocomo & Hasselmo, 2008a; Giocomo et al., 2007; Hasselmo et al., 2007), but the same framework can be used to describe a phase code using stable persistent spiking (Hasselmo, 2008a). An example using stable persistent spiking is shown in Fig. 5. In this example, a population of neurons all have the same baseline level of stable persistent spiking. Within this population, different neurons receive input coding the velocity of movement relative to different directions. In Fig. 5A, the response of the network to movement in one direction is shown, demonstrating how the velocity input systematically shifts the phase of spiking of one group of cells relative to the other groups. In Fig. 5B, the response of the circuit during random movements within a circular open field environment is shown. The relative phase shift caused by the different velocity signals cause patterns of interference resulting in grid cell firing properties. The pattern of activity represented by grid cells can be read out as a purely spatial code by grid cell activation of spiking in a population of hippocampal place cells, as shown in a number of models (Gorchetchnikov & Grossberg, 2007; Hasselmo, 2008c; Rolls, Stringer, & Elliot, 2006; Solstad, Moser, & Einevoll, 2006).

The same model could describe oscillatory dynamics involving feedback interactions between excitatory neurons and inhibitory cortical interneurons. Numerous studies have shown that circuits of excitatory neurons interacting with inhibitory interneurons can cause oscillatory dynamics at gamma frequency (Chow, White, Ritt, & Kopell, 1998; White, Chow, Ritt, Soto-Trevino, & Kopell, 1998). More complex dynamical interactions can cause oscillatory dynamics at theta frequency (Cutsuridis, Cobb, & Graham, 2008, 2009; Denham & Borisyuk, 2000; Kunec, Hasselmo, & Kopell, 2005; Pervouchine et al., 2006; Rotstein et al., 2005). Circuits that generate synchronous rhythmic activity of neurons have the potential for generating phasic firing of neurons at different phase relationships. Different groups of neurons with the same internal connectivity but lesser cross-connectivity could show different phases of firing. If external depolarizing input causes even a small magnitude linear shift in frequency of one oscillation, then this will cause systematic shifts in relative phase of spiking in different groups of neurons. In this case, the framework described here can be used for coding memory in these types of networks.

One problem that confronts the models of grid cells based on intrinsic mechanisms concerns the effect of phase noise. As seen in Fig. 1B, membrane potential oscillations show high variability in oscillation period, and persistent spiking activity shows variability in spiking phase. Simulations with this level of variability show a rapid loss of coding accuracy (Giocomo & Hasselmo, 2008a; Welinder, Burak, & Fiete, 2008; Zilli, Yoshida, Tahvildari, Giocomo, & Hasselmo, in review). However, these effects of noise could be reduced by network interactions. For example, analysis of the spike time response curves (STRC) in entorhinal stellate cells shows that the *h* current results in excitatory synaptic potentials causing phase shifts that drive neurons toward synchrony (Acker et al., 2003; Pervouchine et al., 2006). Experimental data shows that individual stellate cells receiving input from a dynamic clamp replicating excitatory interactions with other stellate cells will synchronize (Netoff, Acker, Bettencourt, & White, 2005a; Netoff et al., 2005b). Thus, stellate cells firing rhythmically in response to external input will shift into phase with each other due to recurrent excitatory coupling. This synchronization on the population level should be able to overcome the independent variability of the intrinsic mechanisms for membrane potential oscillations or persistent spiking. Simulations have demonstrated that network dynamics can maintain synchrony despite noise within individual neurons (Zilli and Hasselmo, unpublished work).

Thus, the grid cell firing properties of entorhinal cortex could involve the interaction of different populations of neurons. There are a number of different possible configurations. One possible network configuration could involve an interaction of persistent firing cells and cells showing membrane potential oscillations. Persistent firing cells can change frequency with depolarization and maintain activity without synaptic input. Studies of synchronization due to membrane potential oscillations commonly use a steady applied current to ensure a stable background firing frequency (Acker et al., 2003; Rotstein et al., 2006). However, excitatory recurrent connectivity sufficient to maintain spiking activity would tend to drive the neurons to higher frequencies. In contrast, intrinsic persistent spiking cells in medial entorhinal cortex layer III (Yoshida et al., 2008) or postsubiculum (Yoshida & Hasselmo, 2009) can maintain stable