A Model of Intracellular Theta Phase Precession Dependent on Intrinsic Subthreshold Membrane Currents

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A hippocampal place cell fires at an increasingly earlier phase in relation to the extracellular theta rhythm as a rodent moves through the place field. The present report presents a compartment model of a CA1 pyramidal cell that explains the increase in amplitude and the phase precession of intracellular theta oscillations, with the assumption that the cell receives an asymmetric ramp depolarization (<10 mV) in the place field and rhythmic inhibitory and/or excitatory synaptic driving. Intracellular subthreshold membrane potential oscillations (MPOs) increase in amplitude and frequency, and show phase precession within the place field. Theta phase precession and MPO power and frequency increase in the place field are caused by a shift in excitatory–inhibitory response, intrinsic theta-frequency resonance, and intrinsic oscillations that depend on voltage-dependent persistent Na⁺ and slowly inactivating K⁺ currents, but not on \( I_{Na} \). Phase precession is diminished when theta-frequency resonance is decreased. Simulated spikes fire near the peak of MPOs and precess similarly as the MPOs. The phase of the MPOs/spikes codes for distance in a one-dimensional place field, and phase precession is only weakly dependent on firing rate, running speed, or the duration needed to cross the place field. In addition, phase precession within the place field resumes quickly after disruption by maximal afferent pulse stimulation.

Introduction
A place cell fires at a high rate when an animal runs through a particular location in the environment (O’Keefe and Nadel, 1978; Muller, 1996), with action potentials occurring progressively earlier in the theta-frequency cycle (O’Keefe and Recce, 1993; Skaggs et al., 1996). Theta (4–10 Hz) rhythm in the hippocampus and related structures (Vanderwolf, 1988; Stewart and Fox, 1990; Bland and Colom, 1993; Buzsáki, 2002) serves as a reference for a phase code (Hopfield, 1995) of an animal’s location at different running velocities (Huxter et al., 2003).

Harvey et al. (2009) showed three main “subthreshold signatures” of place cells by whole-cell recording of hippocampal neurons in head-fixed mice running through a virtual reality track: (1) an asymmetric ramp-like depolarization, (2) an increase in the amplitude of intracellular theta oscillations, and (3) a phase precession of the peaks of the membrane potential oscillations (MPOs) with the extracellularly recorded theta rhythm. Since spikes fire near the peak of the MPOs (Harvey et al., 2009), spike precession in the place field is determined by MPO precession. Furthermore, the increase in amplitude of the MPOs constrains the participation of the rhythmic EPSPs in intracellular theta generation, since rhythmic EPSPs decrease with depolarization while rhythmic IPSPs increase (Leung and Yim, 1986; Fox, 1989; Ylinen et al., 1995; Bland et al., 2002).

Various models have been proposed for phase precession of place cell firing. Linear interference models propose MPOs of higher frequency at the dendrites compared with the soma (Burgess and O’Keefe, 1996; Lengyel et al., 2003). Other models are not explicit as to the increase in MPO frequency but propose that increasing dendritic excitation over somatic inhibition fires somatic spikes earlier in each theta cycle (Kamondi et al., 1998; Magee, 2001; Harris et al., 2002; Losonczy et al., 2010). In addition, a slow ramp–like depolarization would decrease the latency of spike onset (Harris et al., 2002; Mehta et al., 2002; McClelland and Paulsen, 2009). Some models emphasize that a neural network is critical for phase precession (Jensen and Lisman, 1996; Tsodyks et al., 1996; Wallenstein and Hasselmo, 1997; Bose and Recce, 2001; Hasselmo and Eichenbaum, 2005; Geisler et al., 2007, 2010), but few models address fully the intrinsic properties of single neurons.

Intrinsic theta-frequency MPOs were induced by a small depolarization in entorhinal cortex stellate cells (Alonso and Llinás, 1989) and hippocampal CA1/CA3 pyramidal cells (Leung and Yim, 1991). In hippocampal pyramidal cells, a persistent Na⁺ current \( I_{NaP} \) and a slowly inactivating K⁺ current \( I_{KS} \) or \( I_{M} \) are required for generating low-threshold MPOs (Leung and Yim, 1991) and somatic resonance at theta frequency (Leung and Yu, 1998; Hu et al., 2002, 2007, 2009).

In the present report, electrophysiological responses of a CA1 pyramidal cell are simulated by a compartment model with \( I_{NaP} \) and \( I_{KS} \) in addition to other intrinsic currents. When a depolarization ramp and rhythmic synaptic driving are assumed, the model shows phase precession, and frequency and amplitude increase of the subthreshold MPOs.
Materials and Methods

Compartment neuron model. Electrophysiological responses of a CA1 pyramidal cell were simulated using a compartment model represented by first-order differential equations. The main model consists of 38 compartments (Fig. 1). Each compartment is assumed to be a cylindrical cable, and the $i$th compartment is described by the following:

$$G_{L,i+1} (V_{i+1} - V_i) + \frac{G_{L,i} (V_{i-1} - V_i)}{C_i} = \frac{dV_i}{dt} + \frac{G_m (V_i - E_i)}{C_i} + (I_{Na} + I_A + I_D + I_h + I_{IIa} + I_{III} + I_{m} + I_{out})_i,$$

where $V_{i-1}, V_{i+1}$ and $V_{i+1}$ are membrane potential of the $(i-1)$th, $i$th, and $(i+1)$th compartments, respectively; $G_m$ and $C_i$ are membrane conductance and capacitance of the $i$th compartments, respectively; $G_{L,i+1}$ is longitudinal conductance between the $i$th and the $(i+1)$th compartments; and $E_i$ is leak current reversal potential, normally $-70$ mV but adjusted to keep resting membrane potential near $-66$ mV.

Specific membrane capacitance ($C_m$) of $1 \, \mu F/cm^2$, specific membrane resistance ($R_m$) of $30,000 \, \Omega cm^2$ ($G_m = 0.033 \, mS/cm^2$), and longitudinal resistivity $R_l$ of $200 \, \Omega cm$ are assumed. All compartments are assumed to have the same electronic length of $0.03A$, and $G = G_{Na}(0.03)^2 = 1111 \, G_{Na}$ $G_m/C_i = 0.033 \, mS^{-1}$ is the same for all compartments, but coupling strengths between compartments, or $G/G_m$ (Eq. 1) may differ because of different $C_i$ (Table 1). Division by $C_i$ in Equation 1 converts all currents and conductances as per area since $C_i = C_m$ area of the compartment, where $C_m$ is specific membrane conductance. Units used are $C_m$ (microfarads), voltage (millivolts), time (milliseconds), conductance (millisiemens per square centimeter), and current density (microamperes per square centimeter).

The intrinsic currents $I_{Na}$, fast Na$^+$ transient current, and $I_{DR}$ (delayed rectifier current), assumed for thick-circle compartments (14–23, 37, 38) in Figure 1, follow the description of Hoffman et al. (1997) as follows. $I_{Na} = G_{Na} m^3 h (V - E_{Na})$, where $G_{Na}$ is maximal Na$^+$ conductance, and $E_{Na} = 58$ mV. Parameters $m$ and $h$ are originally defined by Hodgkin and Huxley, and referred to specifically as $I_{Na}, m$ and $I_{Na}, h$, respectively. Each parameter ($m$ or $h$) is defined by voltage-dependent rate constants $\alpha$ and $\beta$ that determine the time constant $\tau$ and steady-state (subscript ss) value.

$$\frac{dm}{dt} = (- m + \alpha_m(V)) / \tau_m$$

and similar equations for other parameters,

$$\alpha_m(V) = \alpha_m(V)/(\alpha_m(V) + \beta_m(V))$$

$I_{Na}(V) = 0.364(V - V_{NaD})/(1 - \exp(- (V - V_{NaD})/4.5))$

$$\beta_m(V) = -0.248(V - V_{NaD})/(1 - \exp(-(V - V_{NaD})/4.5))$$

$$\tau_m = 0.8/(\alpha_m(V) + \beta_m(V))$$

$$h_m(V) = 1/(1 + \exp((V + 58)/5))$$

$I_{DR} = \text{delayed rectifier K}^+ \text{ current} = G_K \ n^4 (V - E_K)$,

$$\alpha_n(V) = \alpha_n(V)/(\alpha_n(V) + \beta_n(V))$$

$$\alpha_n(V) = 0.08(V + 40)/(1 - \exp(-(V - 40)/3))$$

$$\beta_n(V) = -0.005(V + 10)/(1 - \exp(-(V + 10)/5))$$

$$\tau_n = 1/(\alpha_n(V) + \beta_n(V))$$

For axonal compartments 18, 37, and 38, VNaD is replaced by VNaA (Table 1) and no $I_{Na}$ is assumed, but $G_K$ is eightfold that of the other compartments. The voltage for half-maximal activation of $I_{Na}$ at the axon and dendrites are named VNaA and VNaD, respectively, and will be referred to as the axonal (VNaA) and dendritic (VNaD) spike threshold. $I_A$ (A current) and $I_h$ (H current) follow the properties described by Leung and Peloquin (2006) as follows:

$$I_A = K^+ A \text{-channel current} = G_A \cdot f_{Ka} \cdot m^4 h^2 (V - E_k),$$

$$G_A = I_A \text{ maximal conductance, } E_k = -85 \text{ mV},$$

where $f_{Ka}$ is a gain factor (channel density) that increases 1.57-fold for every 100 $\mu m$ increase in depth from the soma toward the apical dendrites, as used by Hoffman et al. (1997), and 2.57-fold for every 100 $\mu m$ increase from the soma toward the basal dendrite. Depths of the dendritic compartments and $f_{Ka}$ are listed in Table 1. $I_A$ parameters are defined as follows:

$$m_{na}(V) = \alpha_{na}(V)/(\alpha_{na}(V) + \beta_{na}(V))$$

$$\alpha_{na}(V) = -0.01(V + 34.4)/(\exp(V + 34.4) - 21) - 1)$$
The proximal compartments (Table 1) have higher voltage threshold for
From left: Compartment number, depth from alvear surface, diameter (Diam) of compartment, angle (°) of long axis of soma-dendritic compartment with the vertical, coupling strength of VHS in units of 18.3 ms−1 with compartment in brackets, hA can have dendritic (VHS) of axonal (VNA) threshold, VH can be distal (D) or proximal (P), hA and hNA, gain factor for VD and VHA, respectively; relative strengths of VHA (GABA), VHA (GABA), and Exc (excitation) during afferent stimulation.

\[
\beta_{\text{max}}(V) = 0.01 \times (V + 34.4) / (\exp((V + 34.4)/21) - 1)
\]

\[
\tau_{m A} = 0.2 \text{ ms}
\]

\[
\alpha_{\text{max}}(V) = -0.01 \times (V + 58) / (\exp((V + 58)/8.2) - 1)
\]

\[
\beta_{\text{max}}(V) = 0.01 \times (V + 58) / (\exp((V + 58)/8.2) - 1)
\]

\[
h_{\text{max}}(V) = \alpha(V) / \alpha_{\text{max}}(V) + \beta(V)
\]

\[
\tau_n = 5 \text{ ms for } V < -20 \text{ mV, and } (5 + 0.26 \times (V + 20))
\]

\[
\tau_n = 5 \text{ ms for } V > -20 \text{ mV}
\]

The proximal compartments (Table 1) have higher voltage threshold for
I_{Na} activation, as defined by the \( \alpha_{\text{max}}(V) \) and \( \beta_{\text{max}}(V) \) parameters below (Hoffman et al., 1997):

\[
\alpha_{\text{max}}(V) = -0.01 \times (V + 21.3) / (\exp((V + 21.3)/35) - 1)
\]

\[
\beta_{\text{max}}(V) = 0.01 \times (V + 21.3) / (\exp((V + 21.3)/35) - 1)
\]

The hyperpolarization-induced cation current \( I_n \) is described by a single parameter \( \kappa \) (Gasparini et al., 2004) such that

\[
I_n = G_n \times f_a \times \kappa \times (V + 30), \quad \text{with reversal potential of } -30 \text{ mV and } G_{\text{max}} = 0.2 \text{ mS/cm}^2
\]

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\]

\[
\alpha_n(V) = \exp(0.08316 \times (V + 75))
\]

\[
\beta_n(V) = \exp(0.03326 \times (V + 75)) \]

\[
\tau_n = 49.8 \times \beta_n(V) / (1 + \alpha_n(V))
\]

\[
\kappa_n(V) = 1 / (1 + \exp((V + 81)/8))
\]

\[
f_a \text{ is a gain factor (channel density) that is 1 at the soma, increases twofold from 0 to 100 } \mu \text{m, and another twofold from 100 to 200 } \mu \text{m (Magee, 1998), as listed for the compartments in Table 1.}
\]

With an electrotonic length constant \( \lambda = 1375 \mu \text{m, the soma compartment 17 is assumed to be a cylinder of } 8 \mu \text{m diameter and 51 } \mu \text{m length (0.03A), and the unbranched apical dendritic shaft (compartments 19 and 20) of 5 } \mu \text{m diameter and 82 } \mu \text{m length is equivalent to 0.06A. Two primary basal dendritic branches are assumed to be 3.2 } \mu \text{m diameter. The actual depths of the dendritic compartments with respect to the alvear surface (Table 1) are relevant for field potential generation and not for intracellular voltage simulations. These compartment depths assume that (1) bifurcation of the primary and secondary dendrites occurs every 80–100 } \mu \text{m and satisfies the } \Sigma d^{1/2} \text{ rule of Rall (1964), and (2) the two basal dendritic branches are angled at 30° from the vertical, while}
two apical dendritic branches angled at 15° come from the apical dendritic shaft represented by compartment 20. The two daughter apical branches are not shown in Figure 1 but are lumped into a single compartment 21, since the two compartments together behave electrophysiologically as a cable of uniform diameter with the mother branch (compartment 20). Similar assumptions are made for further bifurcations along the apical and basal dendritic branches.
ramp is applied with peak conductance RpG at the distal dendrites (compartments 35 and 36), or at the middle dendrites (compartments 22 and 23), or as an injected current (peak RPI at the soma); the ramp amplitude is adjusted to yield $15 \text{ mV}$ depolarization at the soma. Noise inputs are added to most simulations. For a distal ramp, Poisson-distributed impulses (mean interval, 5 ms) are applied to excite the distal dendrites with a peak conductance of ExG and single decay rate constant of 0.35 ms$^{-1}$. For a proximal current ramp, current noise is added with Poisson distribution (with a mean interval of 5 ms), amplitude ExI and decay rate constant 0.35 ms$^{-1}$. Typical noise magnitudes are ExG = 0.05 to 0.4, and ExI = 3 (for somatic ramp), or ExI = 0.2$\mathrm{SA}$ (for ZAP function input).

A rhythmic inhibitory conductance $Si \cdot \sin(2\pi f t + \phi)$ is applied to the proximal compartments, and an excitatory conductance driving function $Se \cdot \sin(2\pi f t)$ is applied to the dendrites (Fig. 1), where $f = 5$–12 Hz. Si is peak inhibitory conductance, and Se is peak excitatory conductance. The driving functions are sinusoidal, assuming increase and decrease from a tonic level. Proximal-inhibitory and distal-excitatory driving functions are consistent with models of generation of extracellular theta rhythm (Leung, 1984; Kamondi et al., 1998). The excitatory drive is assumed to be 60° ($= \phi$) advanced of the inhibitory drive (Leung, 1984). This results in firing of pyramidal cells at $250^\circ$ phase during baseline (see Fig. 5B), while maximal inhibition occurs at 0 or 360°. For display in the figures below, the rhythmic inhibitory driving is reversed in polarity [i.e., shown as $-Si \cdot \sin(2\pi f t)$] to facilitate a direct comparison with the membrane potential response (since positive or high inhibition results in negative membrane potential response).

The MATLAB differential equation solver [ODE23 using Runge–Kutta (2,3) formula] uses variable time steps ($<0.09$ ms), and the resulting membrane voltages are linearly extrapolated and sampled at 1 ms interval. If spikes are not present, the MPO signal is the soma voltage after low-pass ($<16$ Hz) digital filtering that does not shift the phase. In the presence of spikes, defined as sharp transients above $-30 \text{ mV}$ in the wide band simulated soma voltage, the spike peaks are first identified. A MPO signal without spikes is derived from the 1 ms resampled voltage data, after each spike peak and two adjacent points (total of 3 ms duration) are removed and replaced by the average voltage before and after the removed points. The latter procedure removes the spike peaks but spike afterpotentials may remain. The peaks of the inhibitory driving function are used as the reference (zero phase) for measuring phase shift of the MPO or spike peaks. Power of the MPOs at the soma is estimated by Fourier transform during baseline (called base power) and for the whole duration of the depolarizing ramp (called place power); the same duration (typically 1024 ms) is used to construct the power spectra for baseline and place.

To study whether phase precession is disrupted by evoked inhibition and excitation of CA3 afferents, single-pulse stimulation (impulse function) of the associational and commissural afferents is assumed to activate excitatory conductance in the midapical dendrites (Fig. 1, inset; Table 1) with maximal conductance of 1.13 mS/cm$^2$ at compartments 21, 22, 25, and 26, and 2.27 mS/cm$^2$ at compartments 23 and 24. Single-pulse evoked GABA$_A$ and GABA$_B$ inhibitory conductances are described by the function $(r - t_d) \cdot \exp(-t / t_d)$; $t_d = 2, r = 33.3$ ms for GABA$_A$ conductance function acting on proximal compartments (Fig. 1, inset) that peaks at 2.11 mS/cm$^2$. For GABA$_B$ conductance, $t_d = 20$ and $r = 192$ ms, and it peaks at 0.18 mS/cm$^2$ in dendritic compartments with standard strength and 0.36 mS/cm$^2$ in dendritic compartments with double strength; GABA$_B$ conductance strengths are listed in Table 1.

Results
Phase code of place location
To clearly visualize the dynamics of the subthreshold MPOs, simulations using a high spike threshold ($V_{\text{NaA}} = 80 \text{ mV}$) are first presented. During baseline, before an animal moves into...
the place field of the simulated neuron (Fig. 2A), combined excitatory and inhibitory rhythmic inputs result in MPO peaks of $-290^\circ$ phase with respect to the inhibitory conductance driving function. In the place field, a distal-dendritic excitatory ramp is assumed. Phase precession of the MPO peaks starts approximately one theta cycle after ramp onset and continues after the peak of the ramp (Fig. 2A). In addition, the amplitude of the MPOs gradually increases during the ramp (Fig. 2A). After the place field is traversed, rapid restoration of the baseline phase occurs. If the duration of running through the field is longer (Fig. 2B, 1024 ms; C, 2048 ms), the decrease of phase with time becomes more gradual (Table 2). When MPO phase is plotted as a fraction of the animal’s distance in a one-dimensional place field, assuming constant speed, a similar phase precession function with distance is found for different running speeds (Fig. 2D). The phase decrease with distance is approximately linear with time for the initial 85% of the place field, and then the phase may increase slightly during the last 15% of the field (Fig. 2C,D, open arrow). For a 512 ms run duration, no phase increase is found; this relates to the observation that the phase decrease appears to persist for one more theta cycle, regardless of ramp duration, after the peak of the ramp at 75% of the field. The slope of the linear regression line changes slowly with duration (run speed)—it decreases 27% from 238° to 174° per place field while the duration changes fourfold (Fig. 2E).

**Evoked inhibition only transiently disrupts phase precession**

To test whether phase precession is disrupted by a strong afferent stimulation (Zugaro et al., 2005), the subthreshold model is subjected to an afferent stimulation pulse that generates an EPSP followed by an IPSP$_A$ mediated by GABA$_A$ receptors, with or without a GABA$_B$ receptor-mediated IPSP$_B$. During the strong IPSP$_A$, all synaptic responses are shunted and phase could not be estimated from the MPO peaks for approximately two theta cycles. In experimental situation, spikes were silent for 200–250 ms (Zugaro et al., 2005). As the IPSP$_A$ subsides, the simulated MPO amplitudes increase and phase precession continues, as if no IPSP$_B$ had occurred (Fig. 3A). If a prolonged IPSP$_B$ is evoked, the MPO phase is disrupted for approximately seven theta cycles ($-0.8$ s) after the stimulus and then the phase and its precession resume at the normal magnitude and rate (Fig. 3B,D). Disruption of phase coding by an IPSP$_B$ has not been shown experimentally. The effect of the evoked inhibition does not depend on the timing of the inhibition in relation to the ramp. At all onset times, an evoked IPSP$_A$ disrupted the phase precession for approximately two theta cycles, and an evoked IPSP$_B$ disrupted the phase for approximately seven theta cycles.

**Phase precession of spike follows that of MPOs**

When spiking occurs, they show a gradual phase precession in the place field, with each spike generally firing near an MPO peak (Fig. 4B), and thus, spikes and the filtered MPO peaks precess at similar rates (Fig. 4B, C; Table 3). When spikes are suppressed by setting a high spike threshold (Fig. 4A), subthreshold MPOs (sub MPO) still precess at a similar rate as the filtered MPOs during normal spiking (Fig. 4, compare A, B, and group data plotted in C). Despite the asymmetric depolarization ramp, the average spike rate within the field is symmetric (Fig. 4C, inset), as was observed experimentally (O’Keefe and Recce, 1993). As shown for subthreshold MPOs (Fig. 2D), MPOs and spike precession during normal spiking condition show a small dependence on run duration (Fig. 4D). Phase precession of spikes is generally similar to that of MPOs for run duration of 1–2 s, but it is more

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**Figure 4.** Spike precession resembles MPO peak precession in spiking model ($S_e = 0.2, S_l = 0.4$), during 512 ms baseline and 1024 ms place field (red line on time axis). A. From top to bottom traces, depolarizing ramp with distal apical dendritic noise, excitatory (exc) and reversed inhibition (–inh) drive, phase at MPO peaks (filled blue circles) or spikes (filled red circles), continuous traces (bottom) of unfiltered (green) and filtered (0–16 Hz) somatic potentials. Spiking suppressed with high axon spike threshold ($V_{NaA} = V_{NaD} = -34$ mV). B. MPO traces and phase with normal spike thresholds ($V_{NaA} = -39$ mV; $V_{NaD} = -34$ mV), and single or double spikes fire near the peak of the MPOs. C. Phase plot, showing the average phase of the subthreshold MPO peaks (sub MPO) with high axon spike threshold (12 trials, X symbols linked by a dash line), and scatter plot of the phase of MPO (open circles) and spike peaks (solid square symbols) with normal axon spike threshold (12 trials). Note high and low spike threshold simulations yield a similar linear regression slope of the phase precession for MPO peaks (dotted line; $-146^\circ/\text{s}; R^2 = 0.55$) and spike peaks (thick line; $-138^\circ/\text{s}; R^2 = 0.51$) with the latter line displaced downward from the former. The inset shows the firing rate running average (in spikes/second, integrated every 0.2 s). D. Magnitude of linear regression slope of phase of the MPO peaks or spikes during the initial 75% of place field (units of degree/field) for different run duration. E. Regression slopes for a fixed (1024 ms) duration run plotted versus different average firing rate within the place field simulated by varying spike thresholds. Thresholds from low to high firing rate are, respectively, $V_{NaA} = -36.5, -37.5, -39$ (above with $V_{NaD} = -34$), then $V_{NaA} = -39$ and $-40$ (both with $V_{NaD} = -36$); units are in millivolts.
variable (Fig. 4D, Table 3) as expected from the addition of spike threshold noise (see Materials and Methods).

The relationship between spike rate and phase precession in the place field is investigated by varying spike thresholds at the axon and/or dendrites (VNaA and VNaD do not vary in time in the simulations). Varying spike thresholds changes the mean firing rate, but theta phase precession of the spikes and MPOs in the place field is found with all firing rates, except spike phase precession is minimal at a firing rate of ∼2/s (Fig. 4E). There is a small increase of precession per field with firing rate change from 3 to 13 Hz, but the simulated data are consistent with the presence of spike phase precession during runs with low and high firing rates (Huxter et al., 2003).

A small phase precession reversal after the peak of the depolarizing ramp is also found for the simulated spikes during long-duration runs (Figs. 4C, 5B, D, open arrow). However, experimentally, spike phase precession within the place field was reported to continue after spike firing decreased (O’Keefe and Recce, 1993; Huxter et al., 2003), and some cells even showed steeper phase precession near the end of the place field (Skaggs et al. (1996), their Fig. 7). In the present model, continuous spike phase precession without reversal can be achieved if inhibitory driving is terminated, for example, at a time near the peak of the depolarizing ramp [Fig. 5C, asterisk (*)]. The latter results in earlier cessation of firing (Fig. 5, compare C with B; D, inset), but for the few spikes that fire after the ramp peak (Fig. 5C,D, solid arrow), they fire near the peak of a membrane potential that oscillates at ∼12 Hz. These ∼12 Hz oscillations are near the natural frequency of MPOs induced by the depolarization ramp (Fig. 5A); and the oscillations are there whether excitatory driving is present or not. A fast phase precession at a rate of 0.85°/ms (Fig. 5D, dashed line at 2000–2200 ms) is caused by the difference between the driving frequency (9 Hz) and the natural frequency.

**Rhythmic inhibition and depolarization result in power increase and precession of MPOs**

As described above, when combined rhythmic excitation and inhibition are given during the depolarizing ramp, there is a gradual phase precession of the MPOs and spikes (Fig. 6A1). The amplitude of the MPOs increases in the place field, as shown by the power spectrum in the place field (place) compared with that during baseline (base) (Fig. 6A2). In the place field compared with baseline, the peak frequency of the MPOs is increased [Fig. 6A2, asterisk (*)], together with a clear second harmonic of the theta driving frequency (Fig. 6A2, arrow).

When driven by rhythmic excitation only, phase precession of MPOs during the depolarizing ramp is small (Fig. 6B1), com-

![Figure 5. Early termination of inhibitory driving results in intrinsic oscillations and accelerated spike phase precession. A, Membrane potential shows ∼13 Hz oscillations in response to 2048 ms duration depolarizing ramp alone, after a baseline of 512 ms. B, Depolarizing ramp with inhibitory and excitatory driving induce spike precession, which reverses (open arrow) at ramp repolarization. C, Early termination of inhibitory driving (*) at the peak of the depolarization ramp (time, 2048 ms) allows natural oscillations (∼12 Hz) to emerge immediately after the asterisk (*), with spikes arising from the MPO peak (solid arrow). D, Group data for spike phase versus time with “full” duration (filled square symbols) and “short” (early terminated) inhibitory driving (unfilled circle symbols). Spike firing rates for both conditions are shown in inset; 10 simulations for each condition. Base phase indicates average phase of MPO peaks during baseline. Linear phase precession of spikes occur for both conditions during the rising phase of the depolarization ramp (solid red line; −80°/s; R² = 0.61). After the depolarization peak, reversed phase precession for full duration driving (open arrow) does not happen with short duration driving which results in a faster phase precession (solid arrow) after the ramp peak at ∼2048 ms (dotted red line; −852°/s; R² = 0.44).](image-url)
pared with combined excitatory and inhibitory driving (Fig. 6A, Table 3). Rhythmic excitation results in MPOs with decreased power/amplitude during the ramp depolarization (Fig. 6B2) compared with baseline. The latter is caused by a decrease in electromotive force of excitation (reversal potential, 0 mV; baseline resting potential, −66 mV). Few spikes fire within the place field, and there is no significant spike phase precession when multiple simulations are grouped, or even when spike thresholds are decreased to allow for a higher firing rate.

When driven only by rhythmic inhibition, phase precession of MPOs and spikes in the place field is modest but consistently observed (Fig. 6CI, Table 3). The MPO amplitude and power increase during the depolarizing ramp (Fig. 6C2) because of an increase in the electromotive force of inhibition (reversal potential assumed for Cl− is −72 mV) and intrinsic resonance (see below).

The phase precession of MPOs decreases slightly when the rhythmic modulation strength increases (Table 2). Driving frequency within 5–11 Hz results in similar theta phase precession in the place field, while driving at 13–15 Hz gives maximal MPO amplitudes but relatively lower phase precession during the second half of the place field (data not shown). The 9 Hz data presented are representative of the 5–11 Hz frequency range.

### Nature of the depolarizing ramp and rhythmic excitatory driving

With a distal dendritic depolarizing ramp, which has been assumed for the above simulations, an increase in MPO frequency and power does not occur with rhythmic excitatory driving alone (Figs. 6A, 7A). Since both rhythmic excitatory driving and ramp act on the distal dendrites (compartments 35 and 36; Fig. 7A1), and the excitatory electromotive force decreases with depolarization, a decreased response to rhythmic excitatory driving (Fig. 7A2, A3) during the ramp is observed. If the ramp inputs are shifted to excite the midapical dendrites (compartments 22 and 23), while keeping the average ramp depolarization at the soma the same, decreased response to rhythmic distal-dendritic driving in the place field is still apparent at the midapical compartments, but it is compensated by proximal resonant response such that the somatic MPOs are mainly unchanged in amplitude in the place field (Fig. 7B).

More robust increase in somatic MPO amplitude in the place field occurs if the ramp is moved proximally, either becoming a depolarizing current at the soma (Fig. 7C) or a basal-dendritic excitation (data not shown). Voltage-dependent resonance in the place field is evidenced by a large increase in somatic MPO amplitude [Fig. 7C2, asterisk (*)] and an increase in MPO frequency and power (Fig. 7C3). The somatic ramp alone, without rhythmic driving, induced intrinsic oscillations of ~12 Hz (Fig. 7C2).

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**Figure 6.** Inhibitory or excitatory rhythmic synaptic driving induces weak phase precession of the MPOs in the spiking model. Left column 1, Phase measures at the MPO peaks (filled circles) are plotted with the intracellular potential (lowest trace) and ramp/sinusoidal driving. Right column 2, Power spectrum of the MPOs in simulated place field (“place”; solid red trace), compared with that during baseline (“base”; dashed blue trace). A, MPO and spike precession are observed after combined excitatory and inhibitory driving, but much weaker after only excitatory (exc) driving (B), or only inhibitory (inh) driving (C). D, Same as A after combined excitatory and inhibitory driving but with Ih = 0; MPO power is increased, particularly during baseline. Column 1 shows an increase in power and frequency of MPOs in the place field in A and D (*), and an increase in second harmonic of theta (arrow) in A, C, and D.
High resonance models show MPO power increase and large phase precession

Since $I_{NaP}$ and $I_{KS}$ have been implicated in theta-frequency resonance and MPOs (Introduction), different peak conductances of $I_{NaP}$ and $I_{KS}$, $G_{NaP}$ and $G_{KS}$, respectively, are simulated in subthreshold models. With the parameters presented for the normal $G_{NaP}$ model above ($G_{NaP} = 0.8$; $G_{KS} = 8$), step current depolarization of the membrane to approximately $-59$ mV evoked a damped oscillation (Fig. 8A1), characterized by a relatively sharp MPO power peak at 12 Hz (Fig. 8A2). The half-peak bandwidth (HBW) of the MPO power spectrum measures 7.5 Hz, within the range of HBW determined experimentally by step or ZAP currents in CA1 pyramidal cells in vitro (Leung and Yim, 1991; Leung and Yu, 1998). Applying a swept-frequency sinusoidal current (ZAP 1991; Leung and Yu, 1998). Applying a swept-frequency sinusoidal current (ZAP current) at a mean membrane potential (Fig. 8A2) at a mean membrane potential of $-59$ mV also yields a maximal impedance magnitude at $-12$ Hz (Fig. 8A). Both magnitude and phase shift of the impedance are larger at $-59$ mV compared with $-67$ mV resting membrane potential (Fig. 8A2, rest).

In a model with half normal $G_{NaP}$ ($G_{NaP} = 0.4$; $G_{KS} = 8$; Fig. 8B), step depolarization or ZAP current driving results in less rhythmic MPOs and low resonance, with a broad power peak at $\sim 16$ Hz. A model with zero $G_{NaP}$ and $G_{KS}$ shows no rhythmic response and no clear power peaks, with step or ZAP currents (Fig. 8C, zero $G_{NaP}$ model). A high $G_{KS}$ model ($G_{KS} = 24$; $G_{NaP} = 0.8$; Fig. 8D) results in a broad response peak at $20-25$ Hz, using a step or ZAP current.

Somatic current-induced depolarizing ramp and proximal rhythmic inhibitory driving are used to study phase precession in the above models. Only subthreshold MPOs are illustrated. In a high-resonance model, strong phase precession occurs during the ramp, and a clear increase in MPO power and frequency is observed in the place field compared with baseline (Fig. 9A). Reducing $G_{NaP}$ decreases resonance and the slope of phase precession in the place field (Fig. 9A–C, dashed linear regression line; Table 4, Inhibitory driving alone). However, MPO power in the place field is still higher than baseline in the zero $G_{NaP}$ model (Fig. 9C2). The model with high $G_{KS}$ shows a higher phase precession and only a small MPO power increase in the place field (Fig. 9D). In the same models, driving by a rhythmic excitatory input generally yields a smaller phase precession than inhibitory drive, but a similar result that phase precession in the place field decreases with resonance of the model (Table 4, Excitatory driving alone). No phase precession is found with purely excitatory driving in the zero $G_{NaP}$ (and zero $G_{KS}$) model.

When normal spike thresholds are assumed in the above models, a brief 5 ms current induces a spike followed by afterpotentials of different shapes in different models (Fig. 8, column 1, spike trace). The normal $G_{NaP}$ model (Fig. 8A1) has the largest depolarizing afterpotential (DAP), while the high $G_{KS}$ model (Fig. 8D1) has the largest afterhyperpolarization (AHP) of medium duration.

In separate simulations, it is shown that reduction or abolition of $I_{h}$ has no effect on the phase precession of MPOs (Fig. 6D, Table 3), when a similar resting membrane potential is kept. Reduction of $I_{h}$ increases input resistance and enhances dendritic inputs preferentially, giving larger MPO amplitudes, more so during baseline than in the place field (Fig. 6, compare D with normal $I_{h}$ responses in A). Similarly, 50% reduction of $I_{A}$ or $I_{K}$ increases input resistance but does not affect phase precession. The small phase precession found with inhibitory driving in the zero $G_{NaP}$ model (Fig. 9C) can be partly attributed to voltage-dependent conductance of the Na$^{+}$ transient current. A small increase in MPO phase precession rate is shown with increasing spike rate, or decreasing spike threshold (Fig. 4E).
Phase precession explained by passive and active (voltage-dependent) processes

Phase precession in the place field is attributed to both passive and active mechanisms. The passive mechanism occurs as a change in balance between excitatory and inhibitory drives (e.g., simulated in Figs. 2 and 6). During the baseline, the phase in response to a pure inhibitory drive (with respect to the peak of the inhibitory conductance) is $\approx 180^\circ$ (hyperpolarization is a negative response; Fig. 6C), and the phase in response to a pure excitatory drive is $\approx 300^\circ$ (Fig. 6B). The resultant vector ($R_1$), at resting membrane potential of $-67$ mV, is approximated by the vector sum of the inhibitory response (vector $E_1$) and the excitatory response (vector $E_2$). In the place field, where the depolarizing ramp is assumed to peak at $-52.7$ mV, the excitatory response ($E_2$) decreases by approximately one-half, because of a decrease in electromotive force and nonlinear shunting (Fig. 7A2), while the inhibitory response ($I_2$) increases approximately sevenfold because of an increase in electromotive force. The resultant vector $R_2$ in the place field thus shifts toward $I_2$, a decrease in phase by $87^\circ$ from $R_1$.

Phase and amplitude change also occurs because of active resonance, contributed by a voltage-dependent intrinsic mechanism. The steady-state phase lag in response to a constant 9 Hz driving current is $\approx 6.3^\circ$ during baseline ($-67$ mV), and $\approx 50.7^\circ$ at the peak of the depolarization ramp (Fig. 10B, inset), as determined using sweep-frequency current (Fig. 8A). This voltage-dependent phase shift occurs with an excitatory drive, resulting in a negative $44^\circ$ phase shift of $E_2$ with respect to $E_1$ (Fig. 10B). Similarly, $I_2$ is shifted $-44^\circ$ from $I_1$ (Fig. 10B), and the resultant vector (sum of $E$ and $I$ vectors) is also $-44^\circ$ shifted from that during baseline (data not shown). The active resonance contributes an additional $44^\circ$ to the passive condition (which gives $87^\circ$), resulting in a $132^\circ$ shift of $R_2$ with respect to $R_1$ (Fig. 10C). Phase change because of self-sustaining intrinsic oscillations (Figs. 5A, C, 7C2) has not been included in Figure 10. The latter phase precession is caused by having an intrinsic oscillation of higher frequency than the reference theta signal (9 Hz assumed above).

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**Figure 8.** Subthreshold membrane potentials are induced by a step depolarizing current, or with current swept from 1 to 40 Hz ($I_{step}$, green trace) simulated in models with different conductances for persistent Na$^+$ current ($G_{NaP}$) and slowly inactivating K$^+$ current ($G_{KS}$). For all simulations, resting membrane potential ranges from $-65$ to $-66.5$ mV. Column 1, The soma ($V_{soma}$, red traces) is depolarized $-8$ mV by a step current (onset at red dot; horizontal dotted red line is $-60$ mV), or induced to spike (black trace) by a 5 ms current (red line underneath spike trace). In another simulation, during the step current depolarization, a zap current ($I_{zap}$, shown only in A) is applied, giving soma potential ($V_{soma}$, blue traces). Poisson’s noise $E_{ex}$ $= 0.2*SA$ is added to the step and ZAP currents. Column 2, Logarithmic power spectrum of $V_{soma}$ or impedance (Imp) spectrum estimated by $I_{step}$. A, Model with normal $G_{NaP} = 0.8, G_{KS} = 8$, in units of millisiemens per square centimeter, shows damped oscillation with current step, spike with depolarizing afterpotential (DAP), and a spectral peak at $\approx 12$ Hz in both power and impedance; zap current amplitude $SA = 2 \mu A/cm^2$. Imp and phase function estimated in column 2 during rest ($-65.5$ mV) and steady depolarization ($-59$ mV). B, Model with one-half $G_{NaP} = 0.4, G_{KS} = 8$ shows poorly rhythmic $V_{soma}$ spike with small DAP, and broad power and impedance peaks; $SA = 9$. C, Model with zero $G_{NaP}$ (also $G_{KS} = 0$) shows no detectable rhythm, no spike DAP, power or impedance peaks, $SA = 5$. D, Model of high $G_{NaP}$ ($= 24$) and $G_{NaP} = 0.8$ shows no theta-frequency rhythms, spike with large afterhyperpolarization (AHP), and broad power/impedance peaks at $20-25$ Hz, $SA = 18$. 
The single-compartment model with no $G_{NaP}$ conductance ($G_{NaP} = G_{KS} = 0$) shows no subthreshold resonance when driven by a ZAP function at a steady-state resting membrane potential of −58.7 mV (Fig. 11A3,B). Adding $G_{NaP} = 0.1$ (and $G_{KS} = 1$) conductance bestows a peak response at −11 Hz and half-peak bandwidth of 16 Hz (Fig. 11B). When combined rhythmic excitatory and inhibitory inputs are given to the $G_{NaP} = 0.1$ model with a high spike threshold ($V_{NaD} = −32$) assumed, gradual phase precession appears soon after the onset of an excitatory ramp (Fig. 11C), and the phase decreases during the depolarizing phase of the ramp. The phase precession of the MPOs remains similar when a normal spike threshold ($V_{NaD} = −35$) is assumed (Fig. 11C2). The phase decrease within the place field occurs with different run durations, as shown in the plot of phase versus normalized field duration (Fig. 11D). Similar to the 38-compartment model, the magnitude of the average phase precession slope for the MPO peaks is only weakly dependent on duration (Fig. 11E). Spikes ride on top of the MPO peaks, and the linearly fitted phase precession slope of spikes is larger than that for MPO peaks (Fig. 11E; also apparent in C2).

The one-compartment model (Fig. 11C) shows a large increase in MPO amplitude with ramp depolarization in the place field, similar to that during a somatic ramp in the 38-compartment model (Fig. 7C). Impedance spectrum of a single compartment (Fig. 11B) is similar to that of the 38-compartment model (Fig. 8A). However, the single-compartment model shows a smaller rate of MPO phase precession, and a smaller total phase decrease in the place field compared with the 38-compartment model (Fig. 11D).

**Discussion**

**Space coding and theta-frequency oscillation**

This report illustrates how oscillations can be used to generate neural coding of absolute space (Figs. 2D, 4D, 11D). A spatial signal is coded by a depolarization ramp, and the transduction of this depolarization into a phase code depends on an external oscillator serving as a phase reference as well as a driving input and intrinsic membrane properties. A phase code for MPO is directly related to a phase code for spiking, since spikes tend to fire at the MPO peaks, in support of the notion that precession of MPOs is the cause of spike precession (Harvey et al., 2009).

Like most reliable coding, the present phase code has a considerable safety margin. Phase precession of the MPO peaks is only briefly affected by single-pulse afferent-evoked excitation.

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**Table 4. Phase precession of subthreshold MPOs during a somatic injected depolarizing current ramp of 1024 ms, driven by either rhythmic excitatory or rhythmic inhibitory input at 9 Hz**

<table>
<thead>
<tr>
<th>$G_{NaP}$</th>
<th>$G_{S}$</th>
<th>$S_{i}$</th>
<th>$S_{e}$</th>
<th>Reg line slope (°/s)</th>
<th>$R^2$</th>
<th>Base power</th>
<th>Place power</th>
<th>Power ratio</th>
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<td>17</td>
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<tr>
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<td>0.4</td>
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<td>0</td>
<td>0</td>
<td>−25</td>
<td>0.36</td>
<td>462</td>
<td>1694</td>
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<td>0.78</td>
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<tr>
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<td>1335</td>
<td>615</td>
<td>0.46</td>
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</table>

For all models, resting membrane potential is −65 to −66 mV, and average depolarization during ramp is −59 to −60 mV. Driving amplitude is adjusted to give similar baseline power across models. All parameters are defined as in Table 2.
and inhibition (Fig. 3). It can occur with rhythmic excitatory or/and inhibitory driving of different modulation depths. Phase precession results from different mechanisms induced by the depolarization ramp. The first is a passive phase change caused by a shift in the relative strengths of the excitatory and inhibitory responses (Fig. 10A). The second is an active theta-frequency resonance that mainly depends on the interaction between slow voltage-dependent Na\(^+\) and K\(^+\) currents (Fig. 10B). The third is a nonlinear interaction of driven and intrinsic oscillations; intrinsic oscillations can be induced by a moderate depolarization of approximately −60 mV alone (Figs. 5A, 7C2). Other than generating phase precession, the active voltage-dependent mechanisms are critical to MPO frequency increase and a second harmonic in the place field (Figs. 6, 9A).

Phase precession of the order of 180°, consistent with the spike phase precession after a single run through the place field (Schmidt et al., 2009), are simulated by passive and resonance mechanisms in the present report. Larger phase precession of 180°–360° (O’Keefe and Recce, 1993; Skaggs et al., 1996) may require activation of intrinsic oscillations (Figs. 5C,D, 7C2). A small reversal of phase precession is found at the end of a long-duration simulated run through the place field (Figs. 2 D, 5B; but see Figs. 2A, 7A2). Whether this small phase reversal of the MPOs occurs \textit{in vivo} is not known, but spikes were reported to continue their phase precession despite decreasing firing rate (Huxter et al., 2003). Factors such as spike accommodation will suppress spiking during ramp repolarization (Harris et al., 2002), and cessation of inhibitory driving and release of intrinsic oscillations will maintain continuous spike phase precession (Fig. 5C).

Either excitatory or inhibitory rhythmic driving can result in phase precession in the place field during a depolarizing ramp. With a distal dendritic depolarization ramp, a rhythmic inhibitory drive typically gives stronger phase precession than a rhythmic excitatory drive. This is explained by a depolarization-induced increase in driving current for an inhibitory, but not an excitatory drive. An increase in rhythmic driving increases peak depolarization and gives stronger phase precession via a voltage-dependent mechanism.

Two membrane currents—\(I_{NaP}\) and \(I_{KS}\)—particular contribute to intrinsic phase precession. Interaction between \(I_{NaP}\) and \(I_{KS}\) has been shown to result in oscillatory response in other studies (Gutfreund et al., 1995; White et al., 1995; Golomb et al., 2006; Prescott and Sejnowski, 2008). In CA1 pyramidal cells \textit{in vitro}, theta-frequency resonance at a depolarized voltage depended on both \(I_{NaP}\) and \(I_{KS}\) (Hu et al., 2002, 2007), and low-threshold subthreshold theta-frequency MPOs were suppressed when \(I_{NaP}\) was blocked (Leung and Yim, 1991). \(I_{NaP}\) contributes to the depolarizing afterpotential (Yue et al., 2005), as shown by the simulated action potential (Fig. 8), and the present study suggests that neurons with different \(I_{NaP}\) to \(I_{KS}\) ratio may show different phase precession rate (Fig. 9). The present report further predicts that phase precession of theta-frequency MPOs will be reduced when \(I_{NaP}\) or \(I_{KS}\) is blocked. Blockade of \(I_{NaP}\) in CA1 pyramidal cells did not affect MPOs (Leung and Yim, 1991) or proximal resonance (Hu et al., 2002), and the present model suggests that \(I_{NaP}\) blockade increases MPO amplitudes but does not affect phase precession (Fig. 6D). Nolan et al. (2004) reported larger theta field potentials in \(I_{NaP}\)-knock-out mice, but theta phase precession was not studied.

**Properties of the external inputs**

Two types of external inputs—a depolarization ramp and a rhythmic synaptic input—are assumed. The simulations here do not predict a location for the depolarizing ramp, but they elucidate the consequences of proximal versus distal ramp depolarization. A distal dendritic ramp would suppress rhythmic excitation and increase passive phase precession during combined excitatory–inhibitory driving, since a decrease of excitatory strength will shift the resultant phase more toward the inhibitory vector (Fig. 10A). However, for a fixed current, proximal rather than distal ramp causes a larger depolarization that activates stronger active currents, including \(I_{NaP}\) and \(I_{KS}\), thus giving stronger voltage-dependent phase precession (Fig. 7). As distinct from models in which a depolarizing ramp serves to decrease spike latency (Magee, 2001; Harris et al., 2002; Mehta et al., 2002), the ramp in the present model decreases the period of the MPOs. Since the entorhinal cortex codes for spatial information (Hafting et al., 2005), a distal apical dendritic ramp excitation of CA1 from the entorhinal cortex (Witter, 2007) appears to be more realistic for place coding. Furthermore, other studies suggest that place coding does not require the integrity of CA3 (Brun et al., 2002, 2008). However, during recall, CA3 may be necessary (Wallenstein and
and CA3 pyramidal cells may provide a ramp excitation of CA1 pyramidal cells at the midapical dendritic synapses (Amaral and Lavenex, 2007; Witter, 2007).

In studies in vivo, injection of current at the soma did not induce MPOs in CA1 neurons of awake mice (Harvey et al., 2009) or affect the phase of MPOs of CA1 neurons during a theta rhythm (of ~4 Hz) in urethane-anesthetized rats (Bland et al., 2002). It is possible that the conditions during which currents were injected are different from those present within the place field [e.g., lack of I_{m} modulation (below) or nonoptimal theta frequency].

Comparison with previous models
Phase precession, frequency, and power increase of the subthreshold MPOs were intracellular signatures of place cells (Harvey et al., 2009). The present report emphasizes that an intrinsic voltage-dependent mechanism contributes to these signatures. Two recent reports suggest that network models can also account for the intracellular MPO results, as shown in a CA3 network model (Romani et al., 2010) and a nonlinear recurrent network of CA1 neurons (Jayet Bray et al., 2010). Given the different types of neurons that demonstrate theta activity (Bland and Colom, 1993; Buzsáki, 2002) and phase precession (Moser et al., 2008) in the hippocampal formation, including neurons in the dentate gyrus, CA3, and entorhinal cortex, it is likely that more than one mechanism contributes to phase precession. The strength of the present model lies in its close ties with physiological data, and the ability to experimentally test the model by manipulating intrinsic membrane properties of a single CA1 cell.

Interference among two or more independent frequency sources can result in phase precession in hippocampal place cells (Burgess and O’Keefe, 1996; Lengyel et al., 2003) and entorhinal grid cells (Burgess et al., 2007; Hasselmo, 2008). In particular, phase precession in place cells is proposed to result from interference of independent somatic and dendritic oscillations of different frequencies. In the present model, an independent somatic oscillation may be generated by an intrinsic voltage-dependent mechanism involving slowly inactivating, proximal Na⁺ and K⁺ currents that are activated by a small depolarization (Leung and Yim, 1991; Hu et al., 2002, 2007). No dendritic oscillations have been included in the present model because they require large depolarization (greater than ~50 mV) to activate in vitro (Leung and Yim, 1991) or in vivo (Kamondi et al., 1998). A crucial difference between the present model and previous linear interference models is that intrinsic resonance/oscillations are voltage dependent and not manifested outside of the place field. Thus, there are no off-field oscillations as in a linear interference model (Burgess and O’Keefe, 1996). The contribution of intrinsic resonance/oscillations to MPO phase precession is not included in another somatic-dendritic interaction model (Losonczy et al., 2010).

Hippocampal activation may be needed for optimal coding of space through phase precession. A movement-related theta rhythm indicates hippocampal activation by the medial septum and brainstem (Vanderwolf, 1988; Lee et al., 1994; Leung, 1998; Bland, 2000; Buzsáki, 2002), which involves cholinergic, GABAergic, and glutamatergic afferents (Amaral and Lavenex, 2007). Septal inputs may increase excitability and spiking, as well as modulate subsequent response through intracellular signaling (Krniević, 1993; Leung and...
Peloquin, 2010). In particular, muscarinic cholinergic modulation may decrease various K⁺ conductances in the hippocampus (Krnjevic, 1993), including Iᵥ, and increase theta-frequency resonance. It is known that place field firing was disrupted by blockade of muscarinic cholinergic receptors (Brazhnik et al., 2004).

In conclusion, it is shown that rhythmic synaptic driving, with the appropriate intrinsic membrane properties, results in robust phase precession of the subthreshold MPOs. An increase in the amplitude (power) and frequency of the subthreshold MPOs in the place field is simulated.

References
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