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Population Dynamics and Theta Rhythm Phase Precession of Hippocampal Place Cell Firing: A Spiking Neuron Model

Misha V. Tsodyks,[1,2] William E. Skaggs,[1]
Terrence J. Sejnowski,[2,3] and Bruce L. McNaughton[1]

[1]*Division of Neural Systems, Memory and Aging, University of Arizona, Tucson, Arizona;* [2]*Howard Hughes Medical Institute, The Salk Institute for Biological Studies, and* [3]*Department of Biology, University of California, San Diego, La Jolla, California*

ABSTRACT: O'Keefe and Recce ([1993] Hippocampus 68:317–330) have observed that the spatially selective firing of pyramidal cells in the CA1 field of the rat hippocampus tends to advance to earlier phases of the electroencephalogram theta rhythm as a rat passes through the place field of a cell. We present here a neural network model based on integrate-and-fire neurons that accounts for this effect. In this model, place selectivity in the hippocampus is a consequence of synaptic interactions between pyramidal neurons together with weakly selective external input. The phase shift of neuronal spiking arises in the model as a result of asymmetric spread of activation through the network, caused by asymmetry in the synaptic interactions. Several experimentally observed properties of the phase shift effect follow naturally from the model, including 1) the observation that the first spikes a cell fires appear near the theta phase corresponding to minimal population activity, 2) the overall advance is less than 360°, and 3) the location of the rat within the place field of the cell is the primary correlate of the firing phase, not the time the rat has been in the field. The model makes several predictions concerning the emergence of place fields during the earliest stages of exploration in a novel environment. It also suggests new experiments that could provide further constraints on a possible explanation of the phase precession effect.

KEY WORDS: attractor, cell assembly, oscillation, neural computation, population code

INTRODUCTION

The firing patterns of pyramidal cells in the CA1 and CA3 regions of the rat hippocampus are related to both the location of the animal in the environment and the theta rhythm, which dominates the hippocampal electroencephalogram (EEG) during exploratory movements (Vanderwolf, 1969). These cells usually fire several bursts of spikes as the rat runs through one or more limited portions of the environment, called place fields of the cell (O'Keefe and Dostrovsky, 1971). It is often assumed that this place-related firing constitutes a population code for the current location of the rat: Wilson and McNaughton (1993), for example, demonstrated that the simple spike counts in 500- to 1000-ms time intervals from about 100 simultaneously recorded cells contain sufficient information to reconstruct the rat's location with an accuracy of a few centimeters.

O'Keefe and Recce (1993) have observed that at each location within the place field of a cell, there is a tendency for the cell to fire preferentially at a particular phase of the theta rhythm, and the preferred phase of firing advances as the rat passes through the field (see also Skaggs et al., 1996). Thus, the precise timing of the cell's firing relative to the theta rhythm provides information about whether the rat is moving into or out of the cell's place field. This observation may have far-reaching implications for the general problem of temporal coding in spike trains (Richmond and Optican, 1990; Bialek et al., 1991; Tovee et al., 1993).

The neuronal mechanisms underlying this phase precession effect are unknown. As the rat passes through the place field of a cell, the number of spikes in each theta cycle typically increases through the first part of the place field and then falls off, even though the phase of firing continues to advance. If the place cell is driven by external excitation that waxes and wanes within the place field, one might expect first a phase lead and then a phase lag as the rat passes through the place field, as a consequence of changes in the timing at which the cell reaches threshold. In most cases, however, no clear phase lag can be observed.

O'Keefe and Recce (1993) proposed that the phase precession they observed could be accounted for by an interaction between two oscillators with slightly different frequencies. One, deriving from the medial septum,

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Address correspondence and reprint requests to B.L. McNaughton, ARL Division of Neural Systems, Memory and Aging, 384 Life Sciences North Building, Tucson, AZ 85724.
Dr. M.V. Tsodyks is now at the Weizmann Institute of Science, Rehovot, Israel.

would provide global modulation of pyramidal cell activity. The second, higher-frequency oscillator would be intrinsic to pyramidal cells. The two oscillators would initially be synchronized by the first spikes the cell fires as the rat enters the place field. Thereafter, the higher frequency would cause spikes to advance gradually to earlier phases. This mechanism, however, cannot account for the apparently stronger correlation of firing phase with space than with time, unless one of the frequencies depends on the running speed of the rat (O'Keefe and Recce, 1993). A dependence of theta frequency on running speed has in fact been observed, but it is quite weak (McFarland et al., 1975; Arnolds et al., 1979).

We offer here an alternative explanation based on cooperative dynamics within a population of interconnected place cells in the hippocampal formation. The basic operation of the model is as follows: Each place cell receives external input corresponding to its preferred location in space and *recurrent* input from other neurons whose place fields are located nearby in space, as well as inhibitory input from interneurons. The strength of the recurrent connections is assumed to be greater from a neuron to another further along in the direction of motion than in the reverse direction. At the beginning of each theta cycle, the first cells to fire are those with the strongest external input at the current location. These cells then excite neurons with place fields ahead of the rat, due to the asymmetry. The resulting wave of activity terminates at the end of the cycle, when the overall population activity becomes too small to sustain it further, and the new wave is initiated at the beginning of the next cycle starting from neurons corresponding to the new location of the rat. The very first firing of a neuron occurs therefore at the end of the first wave that manages to reach it, i.e., at the end of the theta cycle. Subsequent firing advances to earlier phases as the rat moves through the place field. Because the activity waves propagate only in one direction, the cell's firing does not lag to later phases as the external input wanes while the rat leaves the place field. In the present report, this proposed explanation of the phase precession effect is illustrated with computer simulations of a network of integrate-and-fire neurons.

EXPERIMENTAL CONSTRAINTS ON THE MODEL

Figure 1 shows the response of a typical CA1 pyramidal cell recorded from a rat running for food reward on a small triangular track. This cell illustrates several phenomena that have been observed in a large number of cells by O'Keefe and Recce (1993) and Skaggs and McNaughton (1996), which need to be accounted for in any model of the precession effect:

1. The overall activity of the population of pyramidal cells is strongly modulated by the theta rhythm and synchronized throughout the dorsal hippocampus.

2. The first spikes after the rat enters the place field occur about 90–120° after the peak of the CA1 pyramidal cell population activity, and spikes from subsequent cycles advance gradually to earlier phases.

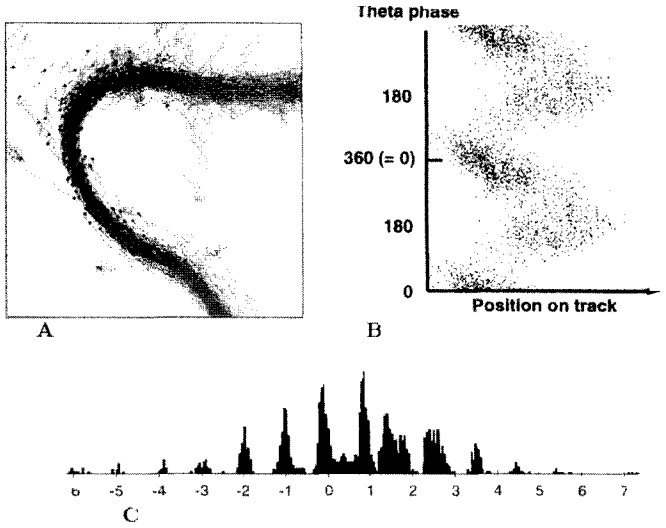

FIGURE 1. Recording of a CA1 pyramidal cell from a rat running for food reward on a triangular track, demonstrating the phase precession effect. Spike activity from the cell was recorded extracellularly using a four-channel microelectrode positioned in the dorsal CA1 cell body layer; see Skaggs et al. (1996) for details. The task of the rat was to circumnavigate a small triangular track repeatedly, always in the same direction, stopping at the center of each arm to eat a small food reward. The data for this figure encompass 55 min, and 131 laps. Hippocampal EEG was recorded from an electrode positioned near the CA1–dentate fissure and digitally filtered with a bandpass of 6–10 Hz; the theta phase of a spike was defined as its fractional distance between consecutive peaks of the filtered EEG. A: Spatial pattern of spike activity for the cell. Irregular gray lines represent the rat's trajectory, and black dots indicate the position of the rat at times when the cell emitted action potentials. This cell fired as the rat traversed one of the three corners of the triangular track; during this recording session the rat was always moving in the counterclockwise direction. The region illustrated is 25 × 25 cm. B: Plot of theta phase versus location for the cell shown in A, illustrating precession of spike activity to earlier theta phases as the rat passes through the place field. The horizontal axis indicates the rat's position on the track "straightened out" for purposes of this plot, and the vertical axis represents the phase of the theta cycle at the moment the spike was emitted. Each point represents a single spike. Phase zero is the point in the theta cycle corresponding to maximal CA1 pyramidal cell *population* activity. Two cycles of the theta rhythm are plotted for clarity. C: Plot of activity versus time, as the rat passes through the place field. To construct this histogram, a point was selected on the track, near the center of the cell's place field. The horizontal axis represents the sum of theta phase and the number of theta cycles before or after the rat passes the selected point. The height of the bars represents firing rate. As the rat enters the place field, the first spikes are aligned with the tick marks; thereafter the spikes shift to earlier phases, and by the time the rat leaves the place field, the activity is centered midway between the tick marks.

3. The overall advance in phase is always less than 360° but approaches 360° for strong place fields.

4. The location of the rat within the field, and not time after entering the field, appears to be the primary correlate of the firing phase.

5. The phase dispersion of cell spiking is minimal at the beginning and end of the place field, and largest at the time of maximal activity in the center of the field.

6. Phase shifting occurs in both one- and two-dimensional environments, but is more robust on linear tracks.

A model of these phenomena requires an analysis that includes the timing of individual spikes. However, place fields were originally defined by the average firing rate of hippocampal neurons, and much can be learned about the dynamics of the network by first considering a model in which the number of spikes averaged over several hundred milliseconds is the primary variable. In the subsequent section we extend this model to a network of explicitly spiking neurons.

AVERAGE FIRING RATE MODEL OF HIPPOCAMPAL PLACE SELECTIVITY

The main excitatory inputs to a place cell are generally thought to arise from highly preprocessed sensory information originating outside the hippocampus, and several different models have been proposed for how this input, together with intrahippocampal inhibition, could lead to place-specific firing (Zipser, 1985; Sharp, 1991). Some of the experimental facts, however, cannot easily be reconciled with such models, particularly the persistence of place fields following the removal of spatial cues or in total darkness (O'Keefe and Speakman, 1987; McNaughton et al., 1989; Quirk et al., 1990; Markus et al., 1994), the sensitivity of place fields to changes in the task being performed (Markus et al., 1995), the appearance of asymmetric fields in a symmetric environment (Sharp et al., 1990), the dependence of firing within the place field on head orientation within some but not all environments (McNaughton et al., 1983; Muller et al., 1994; Markus et al., 1995), and the strong dependence of firing on "motor set" (Foster et al., 1989). The phase precession effect can be added to this list.

Alternative models for place selectivity put the main emphasis on cooperative interactions among hippocampal neurons (Tsodyks and Sejnowski, 1995a; McNaughton et al., 1996). For example, McNaughton et al. (1996) suggested that the hippocampus contains a mechanism for updating the representation of position solely on the basis of self-motion information (path integration). The synaptic matrix is assumed to represent a set of abstract, two-dimensional surfaces or reference frames. A reference frame consists of a configuration of place cells whose interactions define a two-dimensional metric space. Locations within this space are represented by a group of neurons with interconnections that are decremental functions of distance within this space. (Note that this "distance" may bear no relation to the physical distance between the cells in hippocampus measured with anatomical methods). The only stable configurations of activity are localized peaks of activation among cells that are neighbors within the current reference frame. Linear self-motion and head-direction information causes corresponding shifts of the focus of activity within the current frame. Learned associations between the active cells of a particular frame and external input enable frame selection and correction for drift error, but otherwise external input is not required for updating the representation of position. The same population of neurons can encode a large number of different reference frames in a manner that makes spurious transitions between reference frames improbable. In the Tsodyks and Sejnowski model (1995a), each cell is "labeled" by the location where it receives the strongest external input. The external input, however, is only weakly spatially selective. Hebbian learning between cells whose labels are close to one another results in a network whose internal connections reflect the geometry of the environment. This synaptic matrix, along with global, inhibitory feedback (Marr, 1969, 1971; McNaughton and Morris, 1987), can produce robust place selectivity of neuronal firing even if the external activation is highly noisy and only slightly place-selective, because the main excitation of a place cell results from cooperative interactions with neighboring cells in the net whose external inputs are also only weakly spatially selective. In the present study, we use the Tsodyks and Sejnowski formulation to develop the model for precession of firing relative to the theta rhythm phase; however, the principles developed apply generally to models in which the neural dynamics are dominated by internal rather than external inputs.

Consider a linear environment, as shown in Figure 2. In the first model, the average firing rates of the neurons will be considered the primary variables, an assumption that leads to a valid description of the network on a time scale large compared to the theta cycle. The coordinate x_i of each model neuron is taken to be the center of its place field, as described above. Let the synaptic strengths between the neurons with coordinates x_i and x_j be

$$J_{ij} = J_1 \exp\left(-\frac{|x_i - x_j|}{l}\right) - J_0 \qquad (1)$$

where J_1 is the maximum excitatory strength, l is the decay constant of excitatory interactions, and J_0 is the global inhibitory strength.

Let the dynamics of the average membrane potential of each neuron V_i be governed by

$$\tau \frac{dV_i}{dt} = -V_i + \sum_j J_{ij} r_j + I_i^{ext}$$

$$r_j = F(V_j) \qquad (2)$$

where τ is the integration time constant of the model neuron, I_i^{ext} is the external input, and $F(V)$ is a sigmoidal function that is normalized so that the average firing rate r_j lies between 0 and 1. For further details, see Tsodyks and Sejnowski (1995a).

As shown in Figure 2, this network has sharply tuned, stable states of activity localized around the peak of the external input, even if the input is noisy and broadly tuned. As the peak of the input moves from one end of the linear apparatus to the other end, simulating the movement of a rat, the peak in the state of activity moves correspondingly.

This simple average-firing-rate model illustrates a fundamental aspect of attractor dynamics, the existence of localized states of the network that are selected by weak inputs (see Amit, 1995), but it does not address issues concerning spike timing. In the next section, the problem of the phase relationship between the theta rhythm and neuronal spiking is examined in a model comprising *spiking* neurons.

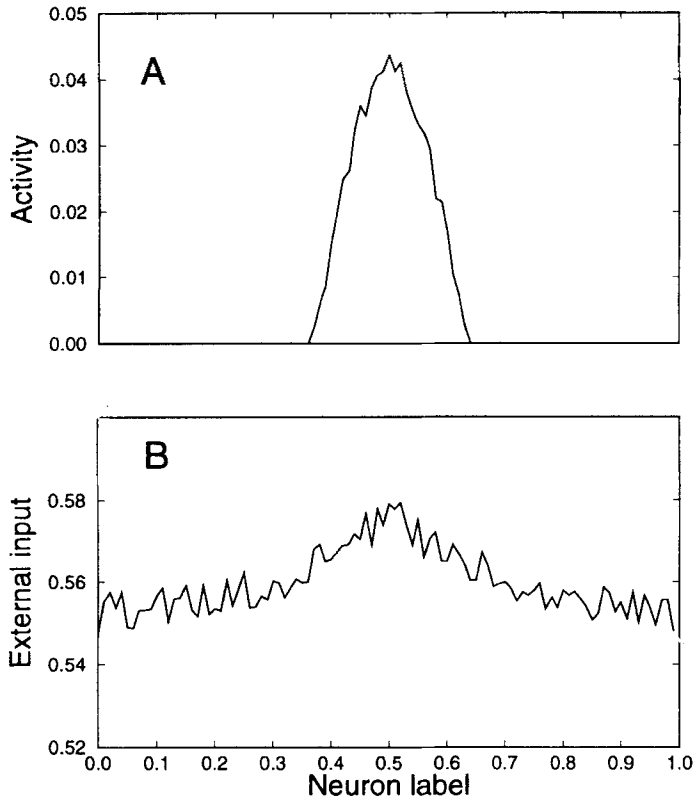

FIGURE 2. Example of a typical activity pattern for a one-dimensional network model based on average firing rates, with stable attractors. Each model neuron i is labeled by the position x_i of its place field on the horizontal axis. A: Activities of all the neurons in a network of 100 neurons in one of the stable states. Each neuron has an activity level r_i corresponding to its average firing rate, normalized to the range from 0 and 1. B: External input to the network. Parameters are $J_0 = 0.3$, $J_1 = 0.4$, $l = 0.2$. See Tsodyks and Sejnowski (1995a) for more details.

NETWORK OF INTEGRATE-AND-FIRE NEURONS AND THETA RHYTHM

In a simple integrate-and-fire model of a spiking neuron, the active conductances responsible for spike generation are replaced with the time of threshold crossing, and only passive leakage of the potential is allowed between consecutive spikes. We consider a network of such neurons, in which the potential of neuron i evolves according to the equation,

$$\tau \frac{dV_i}{dt} = -V_i + I_i^s(t) + I_i^{ext}(t) \tag{3}$$

where V_i is the membrane potential in a model neuron with a single compartment, measured in units rescaled such that the net input resistance $R_m = 1$; $I^s(t)$ and $I^{ext}(t)$ are synaptic currents mediated by intrinsic and external inputs respectively, as specified later. Whenever the potential reaches a threshold value θ, the neuron emits a spike, and its potential is instantaneously reset to some predetermined subthreshold value, V_{res}.

The total synaptic current from intrinsic inputs

$$I^s(t) = I^{ex}(t) - I^{in}(t) \tag{4}$$

is the difference between the overall excitatory current and the overall inhibitory current, which are linear sums from the corresponding populations of neurons. For simplicity, we neglect the ionic driving forces for the synaptic currents and assume that the size of the currents does not depend on the postsynaptic membrane potential. When a spike arrives at a presynaptic terminal, the postsynaptic current is instantaneously increased according to the strength of the synapse, and decays with a time constant τ^{ex} for excitatory synapses (τ^{in} for inhibitory synapses). The rise time of the postsynaptic current is assumed to be much smaller than the decay constant (Stern et al., 1992). Thus, the excitatory synaptic current of the ith neuron evolves according to the following equation:

$$\frac{dI_i^{ex}(t)}{dt} = -\frac{I_i^{ex}(t)}{\tau^{ex}} + s^{ex}(t) \sum_j J_{ij}^{ex} \delta(t - t_j^{ex}) \tag{5}$$

where J_{ij}^{ex} is the strength of the excitatory synapse between neurons j and i, and a spike in neuron j occurs at time t_j. The synapses are probabilistic (McNaughton et al., 1981), and the binary random variables $s^{ex}(t)$ representing the reliability of synaptic transmission equal 1 with probability p^{ex}, and zero otherwise. The equation for inhibitory currents is identical in form,

$$\frac{dI_i^{in}(t)}{dt} = -\frac{I_i^{in}(t)}{\tau^{in}} + s^{in}(t) \sum_j J_{ij}^{in} \delta(t - t_j^{in}) \tag{6}$$

but the parameters may be different. We should emphasize that excitatory and inhibitory components of the synaptic current, resulting from the corresponding populations of neurons, converge on the same postsynaptic targets; thus all populations are interconnected in the network.

The synaptic interactions between the pyramidal neurons have a form analogous to the first term in Equation 1:

$$J_{ij}^{ex} = \sigma_{ij} J_1 \exp\left(-\frac{|x_i - x_j|}{l}\right) \tag{7}$$

where x_i is the label of neuron i: that is, the position of the rat in the linear apparatus where the neuron receives the strongest external excitation while the rat moves in a specific direction. A synaptic structure of this form may arise during the exploratory phase as a result of associative long-term potentiation (Bliss and Lømo, 1973; McNaughton et al., 1978). Alternatively, it could arise as a consequence of some developmental process. An additional feature, which is important for explaining the phase shift, is the asymmetry of the synaptic contacts: synaptic strengths in the direction of motion are stronger than those in the opposite direction. This is captured by the factor σ_{ij}, which is

$$\begin{aligned} \sigma_{ij} &= 1, \quad i < j \\ &= \sigma, \quad i > j \end{aligned} \tag{8}$$

It is assumed that $\sigma > 1$; thus, the larger the value of σ, the stronger the asymmetry in the network. We consider possible causes for such asymmetry in the Discussion.

The firing pattern of inhibitory hippocampal neurons, also called theta cells, carries relatively little place-specific information (McNaughton et al., 1983; Kubie et al., 1990). Accordingly, we assume that their connections with each other and with the excitatory neurons are uniform, and specific labels are not assigned to each neuron as in the case of the excitatory neurons.

The term $I_i^{ext}(t)$ in Equation 3 denotes currents arising from inputs from outside the network. We assign different roles to inputs onto the excitatory and inhibitory neurons. For excitatory pyramidal cells, we assume that their input, deriving preferentially from entorhinal cortex, represents a preprocessed sensory input, and thus carries information about the rat's location in the apparatus. We assume a simple dependence, as illustrated in Figure 2B, of the form

$$I_i^{ext}(t) = I_0(1 + \lambda_e \exp(-\frac{|x_i - x_0(t)|}{l})), \quad (9)$$

where $x_0(t)$ is the rat's coordinate at time t, I_0 gives a baseline excitation for the neuron, and λ controls the degree of place-specific input modulation. For simplicity, these parameters (as well as all the others) are assumed to be uniform across the population of pyramidal neurons. Theta cells in the model do not receive place-specific external input.

The hippocampus receives inhibitory GABAergic input from the medial septum, which preferentially targets inhibitory interneurons (Freund and Antal, 1988). This input is modulated at a frequency of 6–9 Hz and is included in the model as an oscillatory input to the inhibitory population:

$$I_i^{ext}(t) = I_0(1 + \lambda_i \cos(2\pi t/\Gamma)) \quad (10)$$

where λ_i is the strength of the oscillatory component.

RESULTS

Before presenting simulations of the model specified above, we first give an intuitive description of the network behavior. As the rat runs along the track (as its position $x_0(t)$ advances from 0 to 1), the peak of external excitation shifts through successive groups of neurons. Aided by cooperative internal dynamics, the network tends to build up an activity pattern sharply peaked around the neuron whose label is closest to the current coordinate of the rat, as in Figure 2. An important new feature of the model is that, due to the asymmetry of the interactions, the activity propagates spontaneously through the network toward the neurons with higher x_i, corresponding to the direction of the rat's movement. Thus, at any given time, the neurons with the strongest direct activation by the external input tend to activate neurons in attractors along the direction of motion of the rat. Note that in this scenario, the actual center of a neuron's place field, as it would be observed experimentally, is ahead of the label assigned to the neuron, as in the model of Burgess et al. (1994).

The speed of activity-propagation during a single cycle of the theta rhythm is determined by the internal dynamics of the network. In particular, it depends on the ratio of the strengths of the external and internal connections. Over a wide range of parameters, the speed of the propagation is much faster than the actual speed of the rat. Because the intrinsic synaptic drive becomes stronger as the population activity increases, propagation tends to occur on the phase of the theta rhythm with the highest population activity. As the population activity decreases, intrinsic synaptic interactions become weaker, and the focus of activity in the network reverts to the group of neurons corresponding to the actual location of the rat.

A network of 800 excitatory and 200 inhibitory integrate-and-fire neurons was simulated using the connection scheme given above (Equation 7); see Figure 3 for parameter values. The external inputs to the pyramidal neurons are given by Equation 9 with $x_0(t) = t/4{,}000$, corresponding to traversal of the apparatus in 4000 ms by the rat moving with a constant speed. The inhibitory cells receive oscillatory input given by Equation 10. As a consequence of these two inputs, during each theta cycle activity is initiated at the group of cells with labels corresponding to the position of the rat, propagates rapidly forward, and then is extinguished (Fig. 3). On the next cycle, the same pattern occurs, but shifted slightly in the rat's direction of motion. The amount of shift is determined by the rat's velocity. The resulting phase shift of neuronal firing relative to the theta rhythm is shown in Figure 4. Because a neuron fires first as a result of activity propagated from previous place fields, the first spikes that occur upon entry into the place field appear at the latest possible phase of theta. Subsequent spikes advance gradually in phase and are more spread over the cycle at the middle of the place field, where activity of the cell is maximal.

Several observed features of the phase precession effect, which are particularly difficult to explain on the basis of single neuron dynamics, naturally follow from the dynamics of this network model:

1. For each cycle, activity in the network is initiated in the group of neurons with labels corresponding to the location of the rat, and then spreads with a speed that is independent of the speed of the rat. The preferential phase of firing of a neuron with the label x_i at a certain location of the rat x is determined by the ratio of the difference $x_i - x$ and this propagation speed, and therefore it is primarily a function of place, and not of the time after entering the place field. This is illustrated in Figure 4, where the phase is plotted as a function of position (A) and time (B), averaged over a set of 20 neurons, taken from several simulations of the rat running through the field with different speeds. As shown in Table 1, the correlation of phase with position is higher than the correlation of phase with time-in-field for these 20 neurons (cf. Table 1 of O'Keefe and Recce, 1993).

2. Because the propagation of activity in the network due to the intrinsic connections depends critically on the overall activity level, it ceases at the end of each theta cycle. As a result, the magnitude of the phase shift is always confined within 360°, as observed experimentally (O'Keefe and Recce, 1993; Skaggs et al., 1996).

3. The typical distance over which the network activity spreads during each theta cycle is of the order of the initial size of the place field (that is, the size which would have been found with-

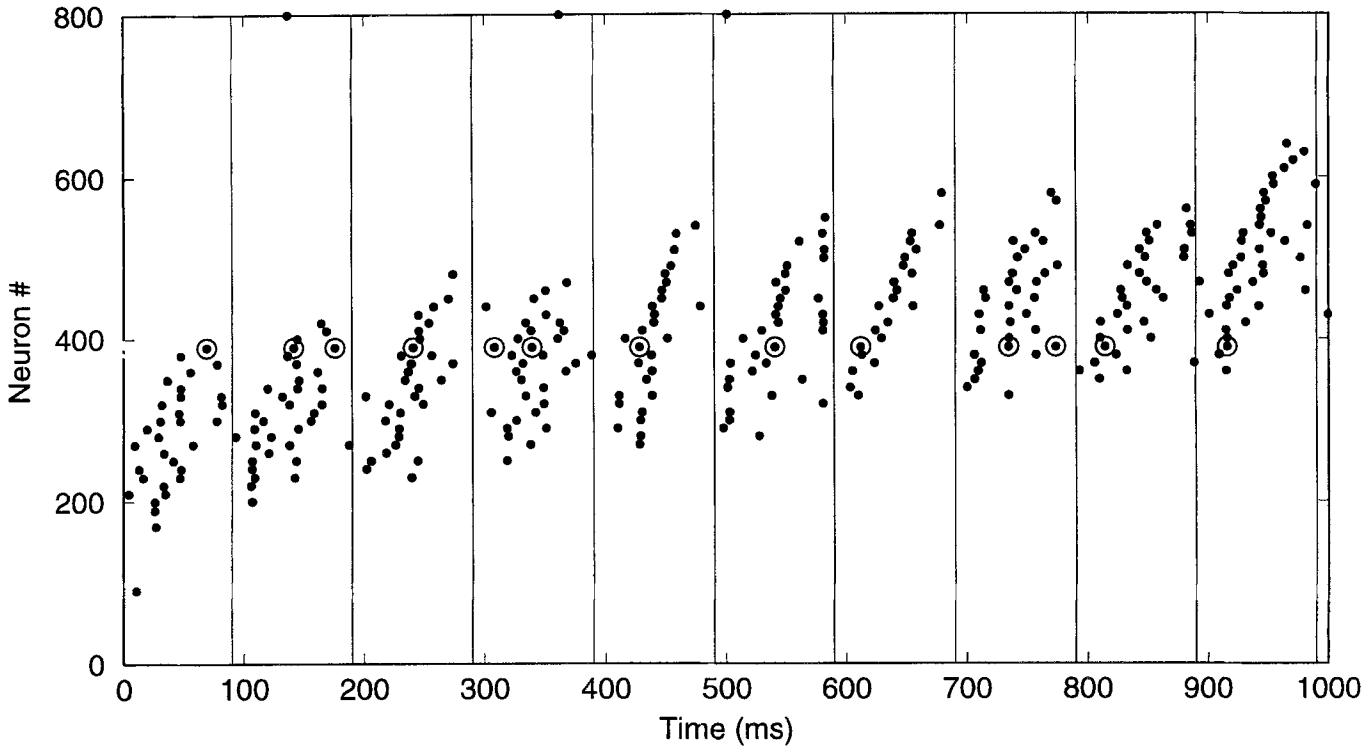

FIGURE 3. Spiking activity in a network model composed of integrate-and-fire neurons, during a simulated run of a rat through a linear apparatus. The hippocampus was modeled as an interconnected network of 800 excitatory and 200 inhibitory neurons. For each spike of an excitatory neuron i, the position label x_i of the neuron is plotted on the vertical axis, against the time at which the spike was emitted (horizontal axis). Vertical lines mark the phase of the theta cycle at which the activity of the network is minimal. The shallow overall slope is determined by the velocity of the rat; the steep slope within each theta cycle is determined by the internal dynamics of the network. The spikes of one of the neurons are surrounded by circles for purposes of illustration. Note that these spikes shift gradually from the end to the beginning of the theta cycle, with considerable dispersion near the center. The parameters of the simulation were $\tau = 20$ ms $\tau_{ex} = 6$ ms, $\tau_{in} = 4$ ms, $V_{res} = 0.85$, $\theta = 1$, $J_1 = 0.015$, $J_2 = 0.02$, $\sigma = 1.8$, $s^{ex} = 0.2$, $s^{in} = 0.7$, $I_0 = 1.02$, $l = 0.15$, $\lambda_e = 0.03$, $\lambda_i = 0.02$.

out assymmetric interconnections) (Fig. 2). The reason for this is that both the size of the place field and the distance the activity spreads in the network are determined by a common cause—the structure of the matrix of intrinsic connections (Equation 1). Thus, if the position of the rat is reconstructed from the activity of the neurons on the basis of brief samples of population activity (as described by Wilson and McNaughton, 1993), the estimate of location shifts forward during each theta cycle for a distance roughly the size of a field, which is consistent with the data of Skaggs et al. (1996). This behavior is illustrated in Figure 5, which gives the reconstructed position of the rat, as determined from the place fields using the formula,

$$x_{rec}(t) = \frac{\sum_i x_i^* n_i}{\sum_i n_i}, \qquad (11)$$

where n_i is the spike count of neuron i over 10-ms bins.

4. Detailed inspection of Figures 3 and 4 shows that the onset of firing in each cycle advances in phase more rapidly than the offset, leading to a spread of spiking over most of the cycle at the middle of the field, as observed in recordings from the hippocampus by Skaggs et al. (1996). This occurs because, after a silent period, the initial spikes in the population are more synchronized than the subsequent spikes; this is a common feature of inhibition-induced synchrony in this type of network model (Tsodyks and Sejnowski, 1995b).

DISCUSSION

The model of hippocampal place fields proposed here explains many of the observed properties of the O'Keefe–Recce phase precession effect, which are difficult to explain on the basis of dynamics intrinsic to single neurons. The phase drift of pyramidal cell firing relative to the theta rhythm is explained in the model by the spread of activity through the network on each theta cycle caused by asymmetric weights of intrinsic connections.

We should note, however, that the model fails to reproduce some of the fine details of place cell firing patterns. O'Keefe and Recce (1993) reported a mean value of 0.66 for the correlation between position and theta phase, whereas the model produces a mean correlation of 0.51. Skaggs et al. (1996) did not measure these correlations, but a comparison of Figure 4 of this study with Figure 7 of Skaggs et al. (1996) suggests again that real CA1 neu-

TABLE 1.

Correlation Coefficients of Phase With Location on the Track (Left Column), and Phase With Time After Entering the Place Field (Right Column), for the Sample of 20 Cells Shown in Figure 4*

Phase vs. position	Phase vs. time in the field
−0.55	−0.50
−0.40	−0.38
−0.54	−0.46
−0.50	−0.41
−0.52	−0.47
−0.59	−0.48
−0.48	−0.41
−0.55	−0.49
−0.56	−0.51
−0.53	−0.42
−0.55	−0.43
−0.60	−0.50
−0.51	−0.45
−0.45	−0.36
−0.57	−0.50
−0.36	−0.28
−0.47	−0.42
−0.55	−0.54
−0.43	−0.36
−0.40	−0.33

*The mean correlation with location was 0.51, versus 0.44 for correlation with time. As pointed out in the legend to Figure 4, the difference between these values would be increased if the variability in running speed were made larger.

rons show a stronger position–phase relationship than the neurons in the model do. Also, the number of spikes fired by a cell per cycle in the model only rarely exceeds 2, but in real CA1 neurons it can occasionally be as high as 8. These comparisons may well be beside the point, however, because much of the experimental data were recorded in CA1, whereas (as discussed below) the model applies either to CA3 or an area further upstream. Correlation and firing rate values could easily change as the phase precession effect is passed from one area to another, but properties such as the amount and direction of phase shift, and the dependence of phase on position rather than time, are likely to be conserved.

The asymmetric weights required by the model could be formed through a long-term potentiation (LTP)–like mechanism, during repeated stereotyped traverses through the environment, such that there are consistent sequences of cellular activation. This would require the synaptic plasticity to be asymmetric in time, so that when the rat goes sequentially through the fields of cells A and B, the connections from A to B are enhanced more than those from B to A. There is evidence for such asymmetry in the induction of LTP (Levy and Steward, 1983; Gustaffson and Wigström, 1986; Markram and Sakmann, 1995).

The model implies that the phase shift originates in an area with strong reciprocal connectivity between excitatory cells. CA3 is a natural candidate; however, recent data (Skaggs and McNaughton, 1995) indicate that a strong phase precession effect can also be seen in granule cells of the dentate gyrus, which lie upstream from CA3. The model proposed here may well be applicable to the dentate gyrus, which contains an extensive system of modifiable excitatory feedback connections, although, in contrast to CA3, these are disynaptic connections mediated by the mossy cells of the hilus (Berger et al., 1980; Ribak et al., 1985; Buckmaster et al., 1992; Buckmaster and Schwartzkroin, 1994; Hetherington et al., 1994). The model may also be general enough to apply to the entorhinal cortex, about which insufficient relevant data are available.

The synaptic structure proposed in the model explains both the formation of place fields and the phase precession effect. It thus implies that the same mechanism may be responsible for population and temporal coding in the hippocampus. Regarding a possible functional role of the phase precession, the model suggests that it could serve as a tool for anticipation of the future location of the rat on the time scale of about 1 s, based on previous experience (Muller and Kubie, 1989; Blum and Abbott, 1995). For this, the neural system has to separate the spikes occurring at different phases of theta rhythm. Whether this anticipation actually takes place is an important question for future work.

The model assumes that periodic theta modulation is provided to the hippocampus via septal inhibition of hippocampal inhibitory interneurons. Medial septal inputs to the hippocampal formation are both GABAergic and cholinergic, but the cholinergic input acts through a muscarinic second-messenger system, which has a time constant considerably longer than the period of theta (Cole and Nicoll, 1984), so the cholinergic input is unlikely to be a source of *periodic* modulation. In contrast, the majority of the GABAergic septal inputs project to GABAergic interneurons in the hippocampus (Freund and Antal, 1988), as assumed in the model, and have effects over short time scales (Bilkey and Goddard, 1985).

The network model of the phase shift was only formulated for the case of a linear environment. In rats that are exposed to linear mazes, the place fields of most neurons are highly unidirectional (McNaughton et al., 1983; Muller et al., 1994; Markus et al., 1995), and, as a consequence, different neurons are activated in a given location for opposite directions of movement. As mentioned in the Introduction, the phase precession effect also occurs in two-dimensional environments, although the pattern of phase shifting is much less obvious in this case. In cases in which the animal's movement is not constrained to stereotyped trajectories, as in two-dimensional environments, place fields are typically multidirectional (Muller et al., 1987, 1994). Thus, the same groups of cells are activated at a given location when the rat passes through it running in different directions, albeit possibly with slightly unequal rates.

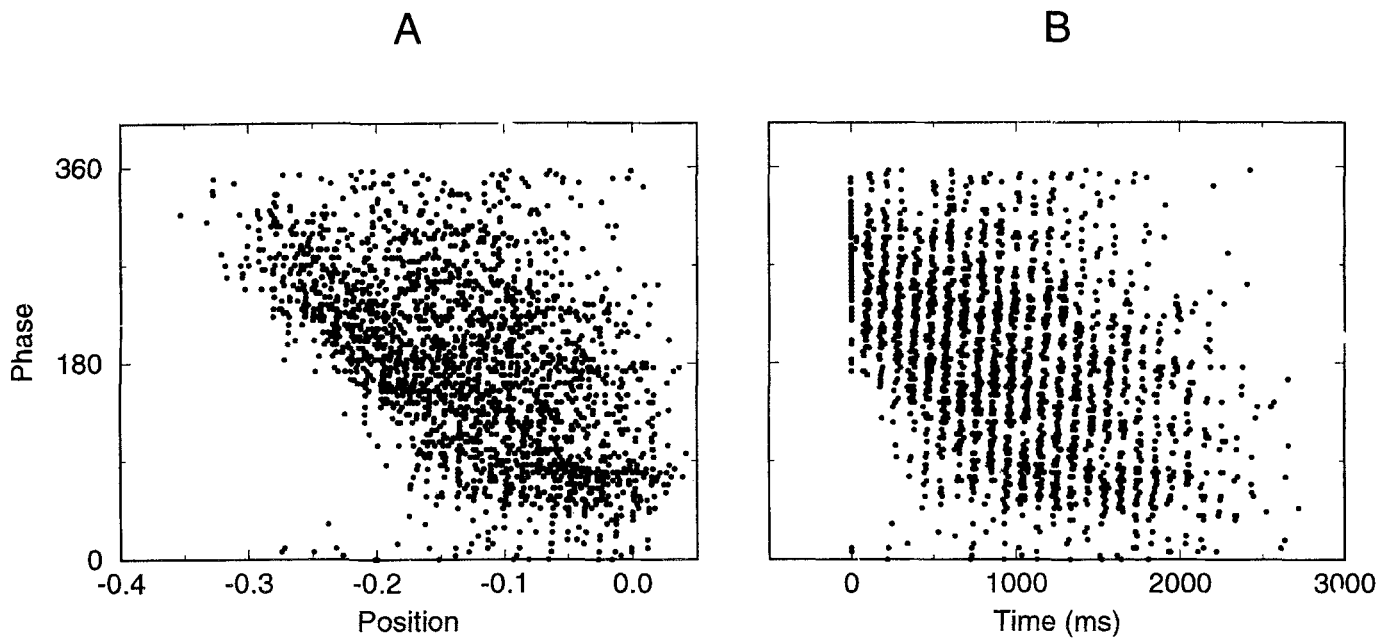

FIGURE 4. Relations of firing phase to position and time, in the integrate-and-fire network model. A: Plot of theta phase at the time of each spike, versus the position of the rat relative to the position label of the neuron, for a random sample of 20 excitatory neurons. The spikes shift steadily earlier in phase as the rat approaches the index location. B: Plot of theta phase at the time of each spike, versus the time after entering the place field of the neuron. The spikes again shift steadily earlier, but the correlation with time is weaker than the correlation with position. The vertical streaks are a simulation artifact resulting from an absence of variability in the theta cycle timing. Five runs along the track with different velocities in the range 1/4000 ms^{-1} to 1/2000 ms^{-} were simulated. If the variability in running speed is increased, the correlation of phase with position is hardly affected, but the correlation with time becomes weaker in proportion to the amount of variability. The same parameters were used as in Figure 3.

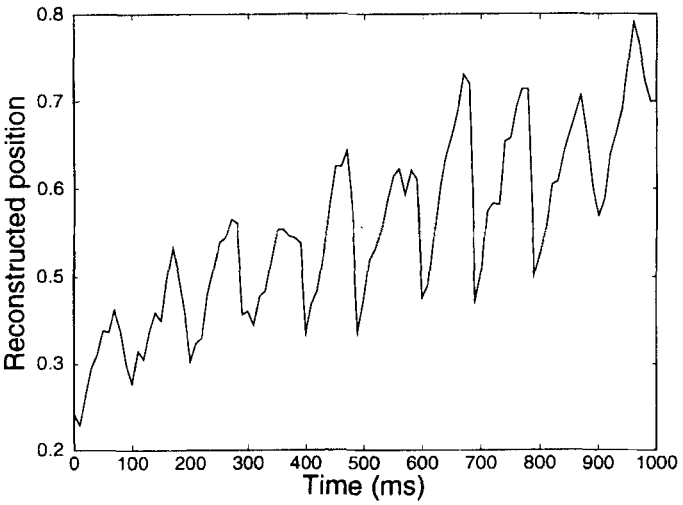

FIGURE 5. Reconstructed position of the rat, computed from the results of simulations shown in Figure 3 with the use of Equation 11. The reconstruction was computed using the whole excitatory population. The rat's actual position fell along a perfect line, but the reconstructed position shifted forward during each theta cycle and then abruptly back at the end of the theta cycle.

The generation of phase precession in our model requires some degree of directional tuning of the place cells in their place fields. This directional tuning leads to an asymmetry in the synaptic matrix, which in turn causes phase precession. For this paper we have simulated the case of linear trajectories in which the directional tuning is absolute. This assumption could be relaxed without losing the essential effect, although it remains to be determined how much directional selectivity would be necessary in two-dimensional environments to account for the magnitude of the phase precession observed under these conditions.

The hippocampus is likely to receive inputs from head-direction cells (Ranck, 1984; Taube et al., 1990), and the place representations in the hippocampus are strongly coupled to the head direction system (Knierim et al., 1995). An alternative explanation for the phase precession effect, both for one- and two-dimensional environments, could be that these head-direction inputs facilitate the intrinsically symmetric synaptic interaction between place cells in their preferred directions. In this scenario, the effective asymmetry of the interactions is not a result of long-term synaptic plasticity, but is mediated by head-directional cells, whose firing is selective for the current direction of motion. This would be a form of dynamical symmetry breaking. These possibilities require further experimental and theoretical study.

Some contingent predictions can be made from the model regarding the effects of experience on hippocampal activity. The asymmetry of the weights of the intrinsic connections, on which

the model's phase precession effect depends, could be learned through LTP-like mechanisms that are rapid in onset, asymmetric in time, and long-lasting. This would imply that the asymmetries would not be present during the first experience of an animal in a place field, and hence that no phase precession should be seen under these conditions. Failure to observe these would not disprove the model itself, but rather would suggest that the symmetry is broken by some other means, such as the influence of head direction cells as suggested above. By the same reasoning, the model also predicts that the apparent location of place fields should shift opposite to the direction of rat as a function of experience. Such an effect has recently been described (Mehta and McNaughton, 1996).

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