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Hippocampal place cells and the generation of a temporal code

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Abstract

Pyramidal cells in the hippocampus of freely moving rats have a spatially specific activity pattern which provides information to downstream in the phase of cell activity. We present a minimal biophysical model for the generation of the phase information from a combination of two inputs: a short duration spatial trigger and the animal's running speed. This single input is shown to determine the start and end of the spatial firing, and a transient phase code for location. Three different simple networks are shown to produce this behavior, without changes in synaptic conductance or connectivity. © 2000 Elsevier Science B.V. All rights reserved.

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1. Background

There is considerable current interest in the ways in which the temporal firing pattern of neurons may provide information that is not conveyed by changes in the averaged firing rate. The biophysical mechanisms underlying the generation and detection of firing rate changes are well established. If the central nervous systems use alternate coding schemes, there must be neuronal mechanisms for generating and detecting them. A robust temporal code has been found in the firing pattern of

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pyramidal cells in the hippocampus of freely moving rats [11]. Firing of these pyramidal cells, called place cells, is correlated with the animal's location in an environment [10]. The preferred firing location of a place cell is called its place field, which has been shown to be a useful population firing rate code for the animal's position in an environment [16,17]. In addition to this firing rate code, the timing of place cell activity provides additional information on the animal's location. During locomotor activity, the hippocampal EEG has a characteristic 6–12 Hz sinusoidal form called the theta rhythm [5], and the phase and frequency of this rhythm is highly correlated throughout the CA1 region of the hippocampus [2].

O'Keefe and Recce found that as the rat runs through a place field, on a linear track, the phase of the theta rhythm at which a place cell fires systematically precesses [11]. Furthermore, each time the animal enters the place field, the firing begins at the same phase. Over the next five to ten cycles of the theta rhythm, the firing phase undergoes up to 360° of phase precession [11,12] and then stops firing. Most place cells fire in only one of the directions of movement along the linear track [8,11]. In addition, the phase of hippocampal place cell firing is more correlated with the animal's location within the place field than with the time that has passed since it entered the place field [11]. This suggests that the phase of place cell activity provides more information on the location than is available from the firing rate of the cell alone. Place cells in both the CA1 region and the upstream CA3 region are found to undergo phase precession [11]. Place cells also show evidence of phase precession in two-dimensional environments [3], but the properties of phase precession in two dimensions are less well understood.

We previously described a minimal biophysical model for the generation of the phase precession that is correlated with the animal's spatial location, but is the result of a temporal process [1]. This is in contrast to previous models of phase precession, which have relied on explicit and external spatial inputs to achieve the correlation between location and phase of firing [6,13,14,7]. These models thus duplicate the temporal code embodied in phase precession, but do not address how these codes may be generated by neuronal mechanisms. We have developed a minimal network model of the CA3 region that identifies possible neural mechanisms that can generate phase precession [1]. The model relies on temporal relationships to obtain phase precession and accounts for spatial correlation through a speed correction mechanism.

In this paper we present several different network models to support the claim that pyramidal cell firing is temporally correlated. In particular, we show how these networks produce two different firing patterns corresponding to the animal being in the place field, or outside of the place field. These two firing patterns of the networks occur through a change in the functional role of the neurons, not changes in network parameters or synaptic conductivity. The change in roles can be understood by identifying the neurons in the network that control the network dynamics. The essential common features in these networks are that the inter-burst frequency of pyramidal cells increases linearly with running speed, and the presence of at least one slowly decaying current which persists for at least one theta cycle (100 ms). This current can either be intrinsic to a particular cell, or may represent the summed

activity of a large number of neurons, which each provide short lasting inhibition at different points in time. For simplicity we model this as a single slow current.

2. Model

The pyramidal cell **P** is assumed to be a bursting oscillator, corresponding to a cell assembly of co-active place cells, which together encode a single spatial location. The pacemaker input **T** represents the underlying theta rhythm, which is paced by the medial septum. It can either be taken as a projected input, or as an intrinsic input within the CA3 region. The dentate granule cell **G** is also modeled as an oscillator, but its synaptic pathway to **P** is active only at the beginning of a place field. Skaggs and co-workers [12] have shown that granule cells phase precess over a small number of cycles of theta; we simplify this here and treat **G** as a phase locked input. The interneuron(s) lie(s) at a subthreshold resting value, but is excitable in response to external input, either excitatory from **P** or inhibitory from **T**.

All of the models that we consider produce two distinct firing patterns. One of these patterns is stable out-of-place field activity and the other is transient firing in the place field, as an animal moves along a linear track. The out-of-place field behavior is characterized by **T** controlling the network, making the interneurons fire via post-inhibitory rebound. When this occurs, the pyramidal cell does not fire. The transient in-place field behavior is characterized by **P** controlling the network, which makes a subset of the interneurons fire by excitation. The in-place field behavior is initiated by a one-time dose of excitation from **G** to **P**. The statement that some interneurons fire due to the excitation from the phase precessing **P** implies that these interneurons also phase precess. In each of the networks, there is an intrinsic property that detects when the pyramidal cell and the interneuron have phase precessed through 360° . When this occurs the control of the network is recaptured by **T** and the dynamics return to a stable steady state. The time at which this change of control occurs is determined by the model without any further external input. Thus, the model also determines the end of the place field.

Each of the network elements is described by sets of voltage-gated conductance equations [9]. The membrane voltages are determined by an inward, instantaneously activating conductance that does not inactivate and an outward current with time-dependent activation. All cells contain a passive leak current as well as a constant, external applied current that maintains the intrinsic, qualitative behaviors of the cells. Activation of the synaptic currents depends on the pre-synaptic voltage and is governed by a single equation with constant rise and decay rates as in [15].

This work focuses on the interaction properties between overly simple network components. We claim that the specific details of the models are less important than the suggestion that there is a correspondence between the change from stable to transient dynamics and the phase precession phenomenon. These networks may not undergo this change in dynamics in the physiologically accurate manner, but they provide a simple way to understand this change.

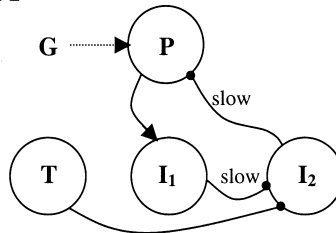
3. Results

All three of the networks described below demonstrate the basic properties of the phase precession of hippocampal place cells. The key properties are described in the context of Network 1, followed by the corresponding behaviors of Networks 2 and 3. Fig. 1 shows connections between the elements of three different networks.

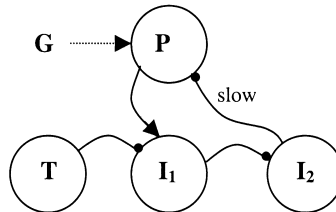
3.1. Network 1

The Network 1 model consists of one bursting pyramidal cell, **P**, an interneuron network composed of two excitable interneurons, **I**₁ and **I**₂, and an oscillatory

Network 1



Network 2



Network 3

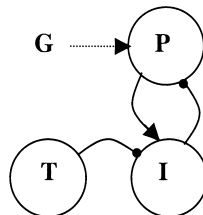


Fig. 1. Three different simple networks which reproduce the phase precession phenomenon observed in hippocampal place cells. **P** is a single cell that represents a cell assembly for a single spatial location, **I**₁ and **I**₂ are interneurons and **T** is a generic theta frequency rhythm provided to the network. **G** is a momentary excitatory trigger input to the place cell (**P**) from the fascia dentata granule cells. Excitatory synapses are illustrated with an arrow and inhibitory synapses with a filled circle. A subset of the connections have a slow duration (approx. 100 ms or one theta cycle). The details of the functional interactions within the networks is presented in the text.

pacemaker input **T**, that models the drive of the network theta rhythm. The synaptic interactions are consistent with the anatomy of the CA3 region of the hippocampus. Specifically, **P** projects to **I₁** via fast, glutamergic excitation and receives slow inhibitory input from **I₂**. The pacemaker **T** projects to **I₂** through fast inhibition. Within the interneuron network, **I₁** projects to **I₂** through a slow inhibitory input.

The model network accounts for the experimentally observed activity of a place cell as a rat runs through the corresponding place field on a linear track. The out-of-place-field and phase precession activity patterns correspond to two dynamic states of the network that differ in the input that controls the firing of the two interneurons. Experimentally, when the animal is running on a linear track, but is out of the associated place field, place cells have a very low firing rate. The corresponding model behavior is a stable, attracting state in which the interneuron **I₂** fires at the theta frequency in response to the pacemaker drive **T** but **P** and **I₁** do not fire. In this stable state, **T** controls interneuron firing and thus the network behavior. Entrance to the place field is signaled by a brief, excitatory input to **P** that represents the seed from the dentate granule cells (**G**).

As a result of the **G** input, the network enters a transient dynamic state in which **P** now controls interneuron firing. In this state, the firing phase of **P** precesses over 5–7 theta cycles. When the phase of **P** firing has advanced through up to 360°, the network returns to the stable state. The duration of phase precession is determined by the duration of the transient dynamics as the network returns to the stable state. The time length of phase precession defines the space length (extent) of the place field. In the present study we assume that the animal is running at a constant running speed, but elsewhere [1] we show that the phenomenon occurs as long as there is a linear correlation between running speed and the frequency of the theta rhythm.

Fig. 2 shows the activity patterns of Network 1 before the animal enters the place field, during the place field, and after the place field. As shown in the figure, before the animal enters the place field **I₂** fires via post-inhibitory rebound after being released from **T**. Once active, **I₂** provides slow inhibition to **P**, thus stopping it from firing. The decay rate of the inhibition is chosen such that the inhibition lasts roughly one theta period. Each time **T** fires **I₂**, the inhibition to **P** is renewed, and as a result **P** never fires. Since **P** never fires the interneuron **I₁** does not fire. In this case, the pacemaker **T** controls the activity of **I₁** and **I₂** and thus, network behavior. This firing pattern represents a stable dynamic state of our minimal network, and we denote it the **TIP** orbit.

Within the place field, the firing phase of **P** systematically precesses through up to 360° and then **P** stops firing. This occurs when **P**, instead of **T**, controls the activity of **I₁** and **I₂**. This switch in control is initiated by the burst of excitation from **G**. The **G** input provides enough excitation to **P** to allow it to fire, even in the presence of the prolonged inhibition from **I₂** (see Fig. 2). Once **P** fires, it causes **I₁** to fire. As a result, the projection from **I₁** to **I₂** becomes functional, and provides a slowly decaying inhibition that inactivates **I₂**. This implies that the inhibition from **I₂** to **P** is not renewed, i.e. the firing of **P** has the effect of functionally removing the inhibition that it receives from **I₂**. As a result, **P** can now freely oscillate due to its intrinsic mechanisms. As long as **P** controls **I₁**, **P** is capable of oscillating and fires during each theta cycle. We call this the **PIT** orbit.

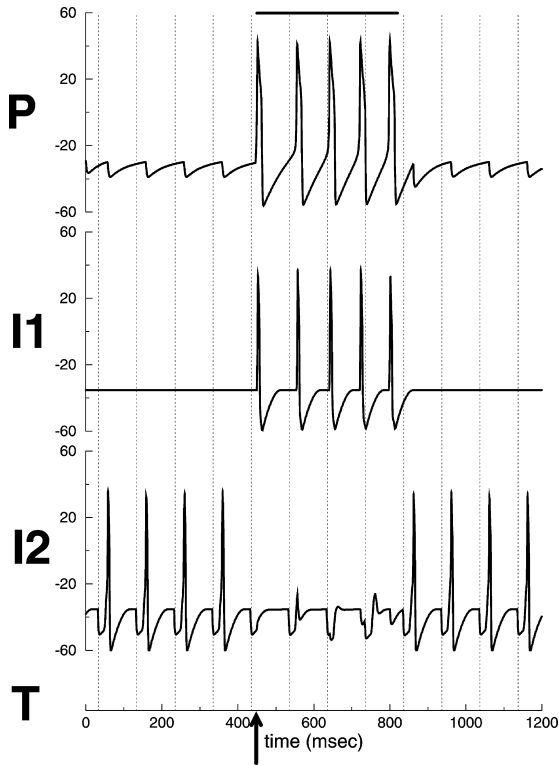


Fig. 2. Simulation of the activity of the neurons in Network 1 for a place cell in a rat that is running at a fixed speed along a linear track. The animal enters the place field and gets trigger input from the dentate granule cell at the time indicated by the arrow. The solid line at the top of the figure shows the duration of the place cell firing. The simulated intracellular voltage in each of the three cells is shown on the vertical axis. The vertical dotted lines indicate the individual theta cycles or T cell input. During the first 400 ms this input fires the I_2 cell through release from inhibition. Note that in the place field both the P cell and the I_1 cell phase precess with respect to the theta rhythm (dotted lines). The spatial nature of the I_1 cell activity may not occur in a larger network in which several P cells share it.

A sufficient condition for phase precession is that the intrinsic period of P is less than the theta period. Once P has taken control of I_1 , it is capable of oscillating at its intrinsic period. Fig. 2 shows a simulation of this phase precession. In [1] precise conditions for the phase relationship between G and T , the amount of phase precession per cycle, the expected number of cycles of phase precession as a function of relevant parameters in the network, the total amount of phase precession and other detailed mathematical formulae are presented. Since P is phase precessing and since I_1 fires each time P does, I_1 also phase precesses. In fact, one of the main predictions of the present work is that some interneurons phase precess. Specifically, P and I_1 phase precess within the associated place field. Notice also that within the place field, P fires before I_1 does.

The experimental results [11] show that place cells precess through up to 360° . In this model some interneurons also phase precess, which provides a mechanism to stop

place cell firing. When the animal is outside the place field, I_2 lies near its rest state and in a position to respond to the inhibitory input from T . When the animal is inside the place field, however, I_2 does not fire, because it receives appropriately timed inhibition from I_1 , making it unresponsive to the input from T . This timing changes from one cycle to the next because I_1 is phase precessing. Eventually, I_1 has phase precessed sufficiently so that the inhibition from I_1 to I_2 has decayed at the arrival of the inhibition from T . Once this has occurred the input from T regains control of the firing of the interneurons. This re-initiates the slower decaying inhibition from I_2 to P , thereby suppressing the firing of P , and ending the precession. Thus, the precession of the interneuron provides the network with mechanisms to end phase precession. Moreover, since the end of phase precession also means the end of place cell firing, the mechanisms also provide a means to determine the spatial extent of the place field. The initial change in control of I_2 from T to P , which is externally imposed by the dentate gyrus, provides the opportunity for precession to occur. A change in control, which is internally determined by the network, signals the end of the place field.

The temporal process described above is clearly correlated to spatial location since we fixed the running speed of the animal. In general, we can maintain the correlation of the time, space and phase if we allow the inter-burst frequency of the pyramidal cell to be dependent on the running speed of the animal. See [1] for the details.

3.2. Network 2

As before, P is a bursting oscillator which excites I_1 . T sends fast inhibition only to I_1 , and I_1 sends fast inhibition to I_2 . As before, I_2 continues to send slowly decaying inhibition to P . The parameters are chosen such that I_1 has a wider action potential if it fires via post inhibitory rebound from T as opposed to by excitation from P . Additionally, the synaptic parameters associated with I_2 are chosen to detect this difference such that I_2 fires if and only if I_1 fires by T . In **TIP**, T fires I_1 which then fires I_2 . The slowly decaying inhibition from I_2 to P prohibits P from firing and is renewed at each cycle. During **PIT**, P fires I_1 , which does not fire I_2 . Thus, as before, the slow inhibition to P has been functionally removed. As with Network 1, T regains control of I_1 after 360° of precession.

The return of control to T is different than in Network 1. At the start of the place field I_2 's first firing due to P moves it away from a state where it can respond to T ; the inhibitory input from T is no longer correctly timed to initiate a rebound spike. During the first few cycles of the precession the inhibition from T to I_1 occurs when I_1 is in its active phase and is largely insensitive to the inhibition. At later cycles of the precession the T inhibition arrives during I_1 's refractory state. Eventually, T input occurs at a phase at which I_1 reacts to it, allowing T to regain control. An advantage of Network 2 is that I_1 no longer has a spatially specific firing pattern.

3.3. Network 3

The P cell is now an excitable cell, rather than oscillatory, and has a high-threshold inward current. We require that this inward current be long lasting and persist for at

least one theta cycle. Next suppose there is only one interneuron *I* which receives fast inhibition from **T**, fast excitation from **P** and provides fast inhibition to **P**. Notice here that the slow current is no longer synaptic, but rather intrinsic to **P**. Outside the place field during **TIP**, **P** does not fire since it is excitable. At the beginning of the place field, the high threshold current is activated when **P** fires due to input from **G**. If this current persists for at least one theta cycle, then it can provide enough depolarization to allow **P** to fire again at the next cycle and allowing the **PIT** orbit to occur. As in Network 2, the process continues until **I** is fired by **T**, which will provide a time window of inhibition during which **P** cannot fire. This time window may then be suitably long to allow **P**'s inward current to decay below the oscillatory level. When this happens phase precession will end signaling the end of the place field.

4. Discussion

We presented several minimal biophysical networks, which use speed modulated temporal dynamics, to reproduce the firing patterns of hippocampal place cells. The different rhythmic states occurred through a change in the cells that control the network dynamics. We have identified a biologically plausible mechanism for the change in control, and have shown a role for transient dynamics in modeling networks of neurons. Less reduced models may use a different strategy to bring about the desired changes in control. The models we consider have minimal requirements and thus should be representative of a large class of possible models. The primary requirements are modulation in theta and pyramidal cell frequencies, due to changes in running speed, and the existence of at least one long time constant. Our models do not require complex external inputs, multi-compartment descriptions nor large networks of coupled pyramidal cells.

One of the main advantages of the present approach is that it shows how networks of neurons combine information from two sources, and develops a spatial representation. Namely, the network is able to take a limited amount of spatial information and return precise information about the location of the animal over a larger spatial extent. The network is given two pieces of external information, the beginning of the place field and the speed of the animal. With these inputs, the network is able to accurately determine the end of the place field, as well as the animal's position within this place field. The network is given no a priori information about the length of the place field. Instead, it is the internal dynamics of the network determines that the place field has ended when the pacemaker recaptures control of the interneurons after 360° of precession.

The first prediction of this model is that pyramidal cell firing can accurately be described as a speed modulated temporal process. There are several ways to test this prediction. For instance, if a rat is running on a linear track and turns around in the middle of a directional place field, then we predict the pyramidal cell will continue firing even though the animal is no longer in the place field of that cell.

The second prediction is that a subset of interneurons may also phase precess when the rat is in the place field of a place cell. The firing patterns of these interneurons in

general may not be phase correlated, but may display a transient behavior in which their firing contains phase information Csicsvari and co-workers [4] have found place cell–interneuron pairs in which the firing of the place cell precedes the firing of the interneuron by 10's of milliseconds. This finding is consistent with our prediction that interneurons may phase precess in the place field as this is precisely where the firing of the interneurons is controlled by and is preceded by the place cell.

Changes in the dynamical state of each of the networks presented in this study occurred through changes in the component controlling the network. In particular, both changes in the state of the network were initiated by a single short lasting external input, at a single point in the environment. This input can be considered a trigger signal that produces a long lasting, but transient, temporal phenomena. The trigger initiates a set of activity patterns that contain useful information about the location of the animal for downstream neurons. With speed corrections, the trigger produces a temporal code for a range of locations, which contains information that was not provided in either the speed or external input signal alone. Thus, this mechanism is a candidate for understanding the generation of temporal codes in the central nervous system.

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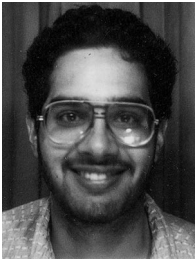
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