Theta phase coding in a network model of the entorhinal cortex layer II with entorhinal-hippocampal loop connections

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Abstract We investigated successive firing of the stellate cells within a theta cycle, which replicates the phase coding of place information, using a network model of the entorhinal cortex layer II with loop connections. Layer II of the entorhinal cortex (ECII) sends signals to the hippocampus, and the hippocampus sends signals back to layer V of the entorhinal cortex (ECV). In addition to this major pathway, projection from ECV to ECII also exists. It is, therefore, inferred that reverberation activity readily appears if projections from ECV to ECII are potentiated. The frequency of the reverberation would be in a gamma range because it takes signals 20–30 ms to go around the entorhinal-hippocampal loop circuits. On the other hand, it has been suggested that ECII is a theta rhythm generator. If the reverberation activity appears in the entorhinal-hippocampal loop circuits, gamma oscillation would be superimposed on a theta rhythm in ECII like a gamma-theta oscillation. This is a reminiscence of the theta phase coding of place information. In this paper, first, a network model of ECII will be developed in order to reproduce a theta rhythm. Secondly, we will show that loop connections

from one stellate cell to the other one are selectively potentiated by afferent signals to ECII. Frequencies of those afferent signals are different, and transmission delay of the loop connections is 20 ms. As a result, stellate cells fire successively within one cycle of the theta rhythm. This resembles gamma-theta oscillation underlying the phase coding. Our model also replicates the phase precession of stellate cell firing within a cycle of subthreshold oscillation (theta rhythm).

Keywords Network model · Entorhinal cortex layer II · Loop connections · Stellate cell · Theta rhythm · Phase coding · Spike-timing dependent plasticity

Introduction

The entorhinal cortex and the hippocampus are crucial brain areas for space recognition and sequence learning. Place cells have been found in these areas, and it has been supposed that place information is encoded by phases of the place cell firing with respect to a theta rhythm rather than by firing rate (O'Keefe and Dostrovsky 1971; O'Keefe and Recce 1993). This is what is called “phase coding.” Place cells corresponding to a sequence of places successively fire at intervals of 20–40 ms (gamma range), and the sequence of such firings repeats at intervals of 100–200 ms (theta range) (Jensen and Lisman 1996; Lisman 1999; Lisman and Otmakhova 2001). Moreover, the phase of place cell firing advances within a theta cycle when the animal traverses a place field (Skaggs and McNaughton 1996; Mehta et al. 2002). Although most arguments about the phase coding, including firing of single neurons

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similar to the phase precession due to current injection to the dendrite or dendritic membrane potential oscillation (Kamondi et al. 1998; Magee 2001; Lengyel et al. 2003), has been restricted within the hippocampus after the finding of place cells, it has been suggested that the entorhinal cortex also plays important roles in place recognition and phase coding (Yamaguchi 2003; Jensen and Lisman 2005; Hafting et al. 2005a; O'Keefe and Burgess 2005). Recently, it has also been reported that neurons called grid cells in the medial entorhinal cortex layer II are theta-modulated and show phase precession (Hafting et al. 2005b).

The entorhinal cortex is located between the neocortex and the hippocampus. Layer II of the entorhinal cortex (ECII) receiving signals from the neocortex sends signals to the hippocampus, and layer V of the entorhinal cortex (ECV) receiving signals from the hippocampus sends signals back to the neocortex. In addition to this major pathway, projection from ECV to ECII also exists in the entorhinal cortex (Dolorfo and Amaral 1998; Richter et al. 1999; Kloosterman et al. 2003; van Haeften et al. 2003), and signals through the hippocampus may interfere with afferent signals from the neocortex in ECII. Interestingly, as the frequency of activity in afferent pathways to the entorhinal cortex is increased, activities of both deep and superficial layers of the entorhinal cortex are increased and this results in increase in activity in the hippocampus (Jones 1993). This is supposed to be a cause of the reverberation of neuronal activity observed in the entorhinal-hippocampal loop circuits *in vitro*. Besides, a neuron population in ECII activates the same or closely overlapping neurons in ECII through the hippocampal circuitry and EC layer V neurons (Buzsáki 1989; Buzsáki et al. 1990). This is also supposed to be a cause of reverberation of neuronal impulses observed in the entorhinal-hippocampal circuitry *in vivo*. On the other hand, it has been reported that long-term potentiation (LTP) is induced in deep-to-superficial layer projections in the entorhinal cortex by theta burst stimulation of the deep layers (Yang et al. 2004). Moreover, a weak stimulation of the deep layers induced a much larger magnitude of LTP in deep-to-superficial layer projections when paired with theta burst stimulation of the superficial layers. This indicates that the superficial afferent pathways cooperate with the deep-to-superficial layer projections to potentiate the synaptic weight. This is what is called associative LTP. It is therefore inferred that reverberation readily appears in the enhanced entorhinal-hippocampal loop circuits. The frequency of the reverberation would be in a gamma range because

it takes signals 20–30 ms to go around the loop circuits (Buzsáki 1989; Buzsáki et al. 1990; Bartesaghi and Gessi 2003).

Theta rhythm is observed in a wide range of the entorhinal cortex and the hippocampus (Mitchell and Rank 1980; Alonso and García-Austt 1987; Buzsáki 2002). Theta rhythm observed in the dentate gyrus is significantly affected by impairment of the entorhinal cortex (Montoya and Sainsbury 1985). Moreover, two relatively independent theta generators exist in the hippocampus, which are mediated by the entorhinal cortex and the CA3-mossy cell recurrent circuitry respectively (Kocsis et al. 1999). Therefore, it has been suggested that the entorhinal cortex is also a theta rhythm generator (Mitchell and Rank 1980). Stellate cells in ECII cause subthreshold oscillations at a theta frequency due to interactions between persistent low-threshold Na^+ current (I_{NaP}) and hyperpolarization-activated inward current (I_h) (Magistretti and Alonso 1999; Dickson et al. 2000a; Fransén et al. 2004). Since most of such rhythmic cells are located in superficial layers (Alonso and García-Austt 1987), it has been supposed that the theta rhythm results from synchronization of subthreshold oscillations in the stellate cells.

However, recurrent excitatory connections do not exist in ECII, although such excitatory connections are widespread in layers V and III of the entorhinal cortex (Dhillon and Jones 2000). In contrast, stellate cells are strongly inhibited by fast-spiking inhibitory interneurons, which axon collateral arborization widely spread in ECII (Jones and Bühl 1993). In fact, large-amplitude IPSPs, which may result from synchronous firing of interneurons, have been observed in ECII (Dickson and Alonso 1997). Moreover, membrane hyperpolarization of stellate cells caused by inhibitory input is accompanied by decrease in I_{NaP} and delayed increase in I_h . This results in rebound excitation and resets oscillatory cycle of the subthreshold oscillations (Dickson et al. 2000b). Therefore, it has been supposed that, when stellate cells receive synchronous inhibitory inputs, depolarizing phases of subthreshold oscillations initiate in synchrony. Consequently, theta rhythm appears, and firing of stellate cells tends to be correlated to the theta rhythm.

If reverberation appears in the entorhinal-hippocampal loop circuits as mentioned above, repetitive firing at a gamma frequency would be superimposed on subthreshold oscillations at a theta frequency in ECII like a gamma-theta oscillation observed experimentally. This is a reminiscence of the theta phase coding of place information; place cells successively fire at a gamma frequency within each theta cycle following the order of places.

In this paper, first, a network model of ECII consisting of 30 stellate cells and one inhibitory interneuron will be developed in order to reproduce a theta rhythm. Secondly, we will develop an ECII network model with loop connections that mimic entorhinal-hippocampal loop circuits and show that loop connections from stellate cells to the other ones are selectively potentiated by afferent signals (pulse trains) whose frequencies are properly different. This implies that if the frequency of afferent signals conveys place information and decreases with increase in the distance between the animals and the places ahead, stellate cells representing those places would be selectively linked by loop connections. As a result, stellate cells fire successively within each theta cycle. This resembles a gamma–theta oscillation underlying the phase coding. Our model also replicates the phase precession of stellate cell firing within a cycle of subthreshold oscillation (theta rhythm).

Methods

Network model of the entorhinal cortex layer II with loop connections

The present network model of the entorhinal cortex layer II consisted of 30 stellate cells and one interneuron, as shown in Fig. 1a. Since recurrent excitatory connections do not exist in ECII (Dhillon and Jones 2000), the stellate cells are not mutually connected through excitatory synapses within the present layer II network model, while the stellate cells are mutually inhibited via the interneuron. The present model has only one interneuron for simplicity because the axon collateral arborization of fast-spiking inhibitory interneurons widely spreads in ECII (Jones and Bühl 1993) and large-amplitude IPSPs, which may result from synchronous firing of inhibitory interneurons, are observed in stellate cells (Dickson and Alonso 1997). Stellate cells also receive afferent inputs through excitatory synapses. Moreover, since EPSPs occur spontaneously at a low rate in stellate cells in the entorhinal cortex layer II (Jones and Woodhall 2005), stellate cells in the present network model receive excitatory random synaptic input independently. The distribution of interpulse intervals of the random input is Gaussian; the average interval is 1 s and the standard deviation is 250 ms. The stellate cells consequently fire at about 0.73 Hz. This low-rate firing of the stellate cells activates the interneuron and is enough to synchronize subthreshold oscillations.

ECII sends signals to the hippocampus, and the hippocampus sends signals back to ECV. In addition to this major pathway, projection from ECV to ECII also exists in the entorhinal cortex, as mentioned above. Thus, as the frequency of neuronal activity in afferent pathways to the entorhinal cortex is increased, reverberation of activity may occur in the entorhinal-hippocampal loop circuits. Our model of the entorhinal cortex layer II contains loop connections that mimic the entorhinal-hippocampal loop circuits, as shown in Fig. 1a.

Although the entorhinal-hippocampal loop circuits are assumed to be simple delay lines in the present network model, the real hippocampus contains recurrent networks such as the CA3 pyramidal cell layer and several local circuits such as the CA3-DG feedback circuit, besides the major trisynaptic pathway. However, when electrical stimulation of the perforant path activates the hippocampal trisynaptic circuitry, the population discharges of CA1 pyramidal cells activate neurons in the EC layer V, and then those neurons activate the same population of EC layer II whose axons (perforant path fibers) have previously stimulated by the electrical pulse (Buzsáki 1989; Buzsáki et al. 1990). This suggests that a neuron population of EC layer II reactivates the same or closely overlapping neurons in the EC layer II through the hippocampal trisynaptic circuitry and EC layer V neurons. In other words, ECII-to-ECII projections through the hippocampus are not divergent electrophysiologically despite the divergence of the anatomical organization within the hippocampus. On the other hand, the terminal field of deep-to-superficial layer projections in EC observed anatomically covers approximately 33% of the surface area of the EC (Dolorfo and Amaral 1998), and axons of EC layer V neurons traveling superficial layers ramify in EC layer II (van Haeften et al. 2003). Based on these experimental results, the entorhinal-hippocampal loop circuits were modeled as simple delay lines connecting EC II stellate cells in all-to-all fashion, and the loop connection weights C_{LC} were modified by Eq. 4 as mentioned below. The transmission delay through the loop connections is 20 ms.

Although the signal pattern and the frequency of afferent input to the entorhinal cortex have not been well known, the firing rate of neurons in the post-rhinal cortex connected to the medial entorhinal cortex is 3–31 Hz (Fyhn et al. 2004). Regular pulse trains were therefore used to stimulate stellate cells as afferent signals to ECII. It is also assumed that the impulse rate conveys sensory information such as place information because it is known that the intensity of sensory stimuli is coded by the frequency

Fig. 1 Entorhinal cortex layer II model. **(a)** Network model of the layer II with loop connections that mimic entorhinal-hippocampal loop circuits. The network consists of 30 stellate cells (open circles) and one inhibitory interneuron (filled circle). There is no excitatory connection between stellate cells within layer II, while stellate cells are mutually inhibited via the interneuron. Stellate cells receive afferent stimuli through excitatory synapses, as indicated by arrows. Stellate cells also receive excitatory random synaptic inputs independently. Stellate cells are connected by loop connections in an all-to-all

fashion. The transmission delay through the loop connections is 20 ms. The weight of the loop connections is modified by a Mexican hat learning rule shown in Fig. 4c. **(b)** Subthreshold oscillation (~ 5.5 Hz) elicited in an isolated stellate cell. $I_{in} = 6.9 \mu\text{A}/\text{cm}^2$. The stellate cell often fires around apexes of the subthreshold oscillation (~ 3.5 Hz). **(c)** Schematic representations of the stellate cell. **(d)** Schematic representation of the interneuron. The multicompartmental structures and the dimensions of each compartment of the present neuron models are the same as those in Fransén et al. (2002)

of sensory signals at least at peripheral sensory system levels. Equations of the synaptic currents take the following form:

$$I_{\text{syn}} = g_{\text{syn}}(V_{\text{syn}} - V), \quad (1)$$

$$g_{\text{syn}} = C_{\text{syn}}(\exp(-t/\tau_{1(\text{syn})}) - \exp(-t/\tau_{2(\text{syn})})), \quad (2)$$

where g_{syn} and V_{syn} are the synaptic conductance and the equilibrium potential respectively. The subscript syn denotes the following synaptic connections: an excitatory connection from a stellate cell to the interneuron (IS), inhibitory connections from the interneuron to a stellate cell mediated by GABA_A and GABA_B (SI_A and SI_B), an excitatory loop connection from one stellate cell to another stellate cell (LC), a synaptic connection to a stellate cell for receiving afferent stimuli (AF), and a synaptic connection to a stellate cell for receiving random pulses (RAND). Parameter values are summarized in Appendix A.

Deep-to-superficial layer projections in the entorhinal cortex are potentiated by theta burst stimulation of the deep layers, and stimulation of deep layers induces LTP more efficiently in cooperation with stimulation of superficial layers (Yang et al., 2004). The loop connections in the present model are therefore modified depending on the relative timing of pre- and postsynaptic spikes. Mexican hat learning rule shown in Fig. 4c was adopted to modify the weight of the loop connections. The modification function $F(\Delta t)$ is as follows:

$$F(\Delta t) = \frac{M_1}{\sigma_1 \sqrt{2\pi}} \exp(-(\Delta t)^2 / (2\sigma_1^2)) - \frac{M_2}{\sigma_2 \sqrt{2\pi}} \exp(-(\Delta t)^2 / (2\sigma_2^2)), \quad (3)$$

where $M_1 = 1.22$, $M_2 = 1.2$, $\sigma_1 = 8$, and $\sigma_2 = 13$. Δt is the relative spike timing between pre- and postsynaptic cells, i.e. (spike time of postsynaptic cell) - (spike time of presynaptic cell). Each pair of pre- and postsynaptic spikes modifies C_{LC} by the following equation:

$$C_{LC} \rightarrow C_{LC} + C_{\max} F(\Delta t). \quad (4)$$

If $C_{LC} > C_{\max}$, C_{LC} was set equal to $C_{\max}$, and if $C_{LC} < C_{\min}$, C_{LC} was set equal to $C_{\min}$. $C_{\max} = 0.05 \mu \text{ S/cm}^2$. $C_{\min} = 0.001 \mu \text{ S/cm}^2$. The initial value of C_{LC} was $0.005 \mu \text{ S/cm}^2$.

Simulations were performed using C-language, and the fourth order Runge–Kutta algorithm was used to integrate the equations. Initial conditions of variables were random. The step size was 0.005 ms.

Models of entorhinal cortex layer II neurons

Multicompartmental models of the stellate cell and the interneuron in the entorhinal cortex layer II have been developed by Fransén et al. (2002, 2004). These models well reproduce physiological properties of those cells in the entorhinal cortex. Fransén et al. have noted that dendritic compartments are important for matching features of spike shape, afterhyperpolarization shape, and spike-frequency accommodation with those in experimental data. We therefore adopted their realistic models to develop a network model of ECII, though the stellate cell model was modified as follows.

The present stellate cell model is also composed of one compartment representing the soma, one compartment representing the initial segment, three compartments connected in succession representing a single principal dendrite, and two compartments representing remaining dendrites, as shown in Fig. 1c. Equations of the present stellate cell model are as follows:

$$\begin{aligned} C dV_4/dt = & \gamma_{3,4}(V_3 - V_4) + \gamma_{5,4}(V_5 - V_4) \\ & + \gamma_{7,4}(V_7 - V_4) - I_{\text{ionic},4} \quad (\text{for soma}), \end{aligned} \quad (5)$$

$$\begin{aligned} C dV_7/dt = & \gamma_{4,7}(V_4 - V_7) - I_{\text{ionic},7} \\ & (\text{for initial segment}), \end{aligned} \quad (5')$$

$$\begin{aligned} C dV_k/dt = & \gamma_{k-1,k}(V_{k-1} - V_k) + \gamma_{k+1,k}(V_{k+1} - V_k) \\ & - I_{\text{ionic},k} \quad (\text{for dendrites}), \end{aligned} \quad (5'')$$

$$\begin{aligned} I_{\text{ionic},k} = & g_{\text{Na},k} m_k^2 h_k (V_{\text{Na}} - V_k) + g_{\text{K(DR)},k} n_k (V_{\text{K}} - V_k) \\ & + g_{\text{Ca},k} s_k^2 (V - V_k) + g_{\text{K(AHP)},k} q_k (V_{\text{K}} - V_k) \\ & + g_{\text{K(C)},k} c_k \cdot \min(1, \chi_{\text{K(C)},k}/250) (V_{\text{K}} - V_k) \\ & + g_{\text{L}}(V_{\text{L}} - V_k) + g_{\text{KL}}(V_{\text{KL}} - V_k) \\ & + g_{\text{NaP},k} x_k \cdot y (V_{\text{NaP}} - V_k) \\ & + (g_{\text{Hf},k} H_{\text{f},k} + g_{\text{Hs},k} H_{\text{s},k}) (V_{\text{H}} - V_k) + I_{\text{in}} + I_{\text{syn}}, \end{aligned} \quad (6)$$

$$\begin{aligned} dz_k/dt = & \alpha_{z,k}(1 - z_k) - \beta_{z,k} z_k \\ & (z_k : m_k, h_k, n_k, s_k, q_k, c_k, x_k, y_k, H_{\text{f},k}, H_{\text{s},k}), \end{aligned} \quad (7)$$

$$d\chi_{\text{K(C)},k}/dt = -\phi_{\text{K(C)},k} I_{\text{Ca},k} - \beta_{\chi_{\text{K(C)},k}} (\chi_{\text{K(C)},k} - 5 \times 10^{-6}), \quad (8)$$

$$\begin{aligned} d\chi_{\text{K(AHP)},k}/dt = & -\phi_{\text{K(AHP)},k} I_{\text{Ca},k} \\ & - \beta_{\chi_{\text{K(AHP)},k}} (\chi_{\text{K(AHP)},k} - 5 \times 10^{-3}), \end{aligned} \quad (9)$$

where $\gamma_{k-1,k}$ is the conductance connecting compartments, $k-1$ and k (see Fig. 1c for the compartment numbers). $g_{\text{T},k}$ and $V_{\text{T},k}$ are the maximum conductance and the equilibrium membrane potential for an ionic channel respectively. The subscript T denotes the following ionic currents: a sodium current (Na), a delayed potassium current (K(DR)), a high-threshold calcium current (Ca), a calcium-dependent potassium current (K(AHP)), a fast calcium- and voltage-dependent potassium current (K(C)), a potassium leak current (KL), a leak current excluding the potassium leak current (L), a persistent sodium current (NaP), a fast hyperpolarization-activated inward current (Hf), and a slow hyperpolarization-activated inward current (Hs). I_{syn} is synaptic currents; excitatory synaptic currents, I_{IS} , I_{LC} , I_{AF} , and I_{RAND} , are injected to the proximal compartment of the remaining dendrite and inhibitory synaptic currents, I_{SLA} and I_{SLB} , are injected to the soma compartment. The ion-gating variable z_k stands for m_k , h_k , n_k , s_k , q_k , c_k , x_k , $H_{\text{f},k}$, and $H_{\text{s},k}$. The gating variable y is constant ($y = 0.576$) in this paper because its time constant is very large (about 6 s). I_{Ca} is the calcium current, i.e. the third term on the right-hand side of Eq. 6. $\chi_{\text{K(C)},k}$ and $\chi_{\text{K(AHP)},k}$ are the intracellular calcium concentrations that act on K(C) and K(AHP) respectively. Parameter values and voltage-dependence of the rate constants, α_z and β_z , are listed in Appendix B.

Muscarinic ion channels, which have a large time constant, exist in stellate cells in the entorhinal cortex (Klink and Alonso 1997). The current $I_{\text{in}} (= 6.9 \mu \text{ A/cm}^2)$ being constant throughout the present paper is therefore included in the present stellate cell model instead of the muscarinic current. The stellate cell is depolarized up to about -55 mV by this constant current, and cause subthreshold oscillation spontaneously at about 5.5 Hz, as shown in Fig. 1b. Although the isolated stellate cell often fires at apexes of the subthreshold oscillation at about 3.5 Hz, the firing rate reduces in the network because of recurrent inhibition; the firing rate is about 0.73 Hz even when receiving a random

synaptic input. The subthreshold oscillation is caused by the interplay between the persistent Na^+ current (I_{NaP}) and the hyperpolarization-activated inward current (I_h) (Magistretti and Alonso 1999; Dickson et al. 2000a; Fransén et al. 2004). I_h is increased at a hyperpolarized state, while I_{NaP} is increased at a depolarized state. These opposite voltage-dependent increases of I_h and I_{NaP} are responsible for subthreshold oscillations. Large I_h at a hyperpolarized state causes depolarization and then I_{NaP} increases. The increase in I_{NaP} boosts the depolarization. In turn, deactivation of I_h leads to deactivation of I_{NaP} and the membrane potential returns to the hyperpolarized state. Then, I_h increases and depolarization starts again. Moreover, the deactivation of I_h follows that of I_{NaP} with a certain delay. This delayed deactivation of I_h is also responsible for initiating the hyperpolarizing phase of the oscillations.

The interneuron model is exactly the same as that developed by Fransén et al. (2002). The equations of the model are as follows:

$$CdV_k/dt = \gamma_{k-1,k}(V_{k-1} - V_k) + \gamma_{k+1,k}(V_{k+1} - V_k) - I_{\text{ionic},k}, \quad (10)$$

$$\begin{aligned} I_{\text{ionic},k} = & g_{\text{Na},k} m_k^2 h_k (V_{\text{Na}} - V_k) + g_{\text{K(DR)},k} n_k (V_{\text{K}} - V_k) \\ & + g_{\text{Na,SO}} m_{\text{SO}}^3 h_{\text{SO}}^3 (V_{\text{Na}} - V_{\text{SO}}) \\ & + g_{\text{K(DR),SO}} n_{\text{SO}}^4 (V_{\text{K}} - V_{\text{SO}}) + g_{\text{Ca},k} s_k^2 (V_{\text{Ca}} - V_k) \\ & + g_{\text{K(AHP)},k} q_k (V_{\text{K}} - V_k) + g_{\text{L}} (V_{\text{L}} - V_k) \\ & + g_{\text{KL}} (V_{\text{KL}} - V_k) + I_{\text{IS}}, \end{aligned} \quad (11)$$

$$dz_k/dt = \alpha_z(1 - z_k) - \beta_z z_k \quad (z_k : m_k, h_k, n_k, m_{\text{SO}}, h_{\text{SO}}, n_{\text{SO}}, s_k, q_k), \quad (12)$$

$$\begin{aligned} d\chi_{\text{K(AHP)},k}/dt = & -\phi_{\text{K(AHP)},k} I_{\text{Ca},k} \\ & - \beta_{\chi_{\text{K(AHP)}}} (\chi_{\text{K(AHP)},k} - 5 \times 10^{-3}), \end{aligned} \quad (13)$$

where $g_{\text{Na,SO}}$ and $g_{\text{K(DR),SO}}$ are the maximum conductances for sodium and potassium channels in the soma compartment respectively, while g_{Na} and $g_{\text{K(DR)}}$ are for sodium and potassium channels in the dendrite compartments respectively. This interneuron model is composed of six compartments: one compartment representing the soma, three compartments representing the principal dendrite, and two compartments representing remaining dendrite, as shown in Fig. 1d. A compartment representing the initial segment does not exist, but the soma compartment where spikes are initiated has Na^+ and K^+ currents with faster kinetics. The excitatory synaptic current I_{IS} is injected to the

distal compartment of the principal dendrite. The notation for other variables and parameters is the same as that of the above stellate cell model. See Fransén et al. (2002) for parameter values and voltage-dependence of the rate constants, α_z and β_z .

Results

Synchronization of subthreshold oscillations in stellate cells and responses of the stellate cells to regular pulse trains

The present network model of ECII reproduced a theta rhythm as synchronized subthreshold oscillations. When there is no connection between the interneuron and the stellate cells, stellate cells receiving low-rate random pulses often fired (~ 3.3 Hz) and were not synchronized (Fig. 2a). However, if stellate cells were mutually inhibited via the interneuron, stellate cells occasionally fired around apexes of subthreshold oscillations due to recurrent inhibition (~ 0.73 Hz) and subthreshold oscillations were synchronized (Fig. 2b). This is because occasional firings of stellate cells due to low-rate random inputs activate the interneuron, and then stellate cells are inhibited in synchrony. Although firings of the stellate cells were sparse, as shown in the upper panel in Fig. 2b, inhibition of stellate cells by the interneuron was enough to reset the oscillatory cycle of subthreshold oscillations. In fact, the interneuron fired almost every period of synchronous subthreshold oscillations (Fig. 2c).

When regular pulse trains (afferent stimuli) that trigger synaptic currents I_{AF} are fed to stellate cells causing synchronous subthreshold oscillations, the firing phase of those stellate cells with respect to the subthreshold oscillations depends on the frequency (reciprocal of interpulse interval) of the regular pulse trains. One of the stellate cells was stimulated by a 40 Hz regular pulse train and another one by a 30 Hz regular pulse train. Since the amplitude of EPSPs evoked by a regular pulse train is suppressed by recurrent inhibition during hyperpolarized phases of subthreshold oscillation, depolarization due to the integrated EPSP is paced by synchronous subthreshold oscillations. In consequence, firings of those stellate cells were almost phase-locked in synchronized subthreshold oscillations though the stellate cells occasionally failed in firing (Fig. 3a). The probability of failure in firing increases with decrease in the frequency of the regular pulse train; the range of the firing frequency is 2–4 Hz. Although the interspike interval between the two neurons considerably

Fig. 2 Synchronization of subthreshold oscillations in stellate cells. **(a and b, upper panels)** Raster plots of firing of stellate cells. **(a, lower panel and b, middle panel)** Superimposed firing patterns of 30 stellate cells. **(b, lower panel)** Firing pattern of the inhibitory interneuron. **(a)** Subthreshold oscillations are not synchronized as there is no connection between the stellate cells and the interneuron. Firing rate of the stellate cells receiving

random synaptic input is about 3.3 Hz. **(b)** Subthreshold oscillations are synchronized when stellate cells are mutually inhibited via the interneuron. The firing rate of the stellate cells reduces due to recurrent inhibition (~ 0.73 Hz). The interneuron fires almost every period of synchronized subthreshold oscillations (~ 4.5 Hz)

fluctuates, the spikes caused by the 40 Hz pulse train almost always preceded the spikes caused by the 30 Hz pulse train in individual cycles of synchronized subthreshold oscillations except for occasional firing due to random pulses. This is because the rise in integrated EPSP induced during depolarizing phases of subthreshold oscillations by higher-frequency stimulation is faster than that induced by lower-frequency stimulation. In fact, the firing phase of one of the stellate cells with respect to synchronous subthreshold oscillations advances with increase in the frequency of the regular pulse train (Fig. 3b). Standard deviations are however relatively large because of considerably large fluctuations of the period of synchronous subthreshold oscillations.

Time differences between spikes of two stellate cells were obtained (Fig. 3c). These stellate cells are hereafter referred to as the stellate cells, A and B, so that the ordinate is the spike-time difference Δt , i.e. (spike time of the stellate cell B)-(spike time of the stellate cell A). Frequencies of the pulse train that is fed to the stellate cell A are indicated in Fig. 3c and the abscissa is the frequency of the pulse train fed to the stellate cell B. The

spike time difference increases with increase in the difference between frequencies of the pulse trains that are fed to the stellate cells, A and B. It should be noted that the spike time difference is not determined by a pair of specific stimulus frequencies but by the difference between stimulus frequencies. For example, spike time difference of 20 ms is provided by pairs of stimulus frequencies, {30, 22}, {35, 27}, or {40, 30} [Hz].

Synaptic potentiation of loop connections by afferent signals to ECII neurons

Histograms of the relative timing of spikes in the stellate cells, A and B, (Fig. 4a, b) were obtained to compare the distribution of the spike timing with the Mexican hat learning rule (Fig. 4c). It should be noted that the abscissas in Fig. 4a, b do not represent the difference between spike times of the stellate cells, but the difference between the spike time of the stellate cell A delayed by 20 ms and the spike time of the stellate cell B because the preceding spike of the cell A interacts with the following spike of the cell B after

Fig. 3 Responses of two stellate cells in the ECII network to afferent stimuli (regular pulse trains). The ECII network does not have loop connections in here. **(a)** Superimposed firings of the stellate cells, A and B. Firings of the stellate cells are almost phase-locked in synchronized subthreshold oscillations though the stellate cells occasionally failed in firing. Spike of the stellate cell A caused by a 40 Hz pulse train (solid line) almost always precedes the spike of another stellate cell B caused by a 30 Hz pulse train (dotted line) in each cycle of synchronized subthreshold oscillations. **(b)** Firing phase of one of the stellate cells with respect to synchronous subthreshold oscillations. Subthreshold oscillations of stellate cells receiving no regular pulse train were averaged and used to determine the phase at which the stellate cell fired in response to a periodic pulse train. The abscissa is the stimulus frequency. The phase of firing advances with increase in the stimulus frequency. Bars indicate standard deviation. **(c)** Mean spike timing between two stellate cells, A and B. Figures indicated in this panel are the frequencies of the pulse train fed to the stellate cell A. The abscissa is the frequency of the pulse train fed to the stellate cell B. The spike time difference increases with increase in the difference between the frequencies

20 ms through a loop connection. Enhancement of loop connections by activation of the stellate cells is not permitted here.

Fig. 4 Histograms of the relative timing of spikes in two stellate cells in the layer II network with loop connections. Enhancement of loop connections by the activity of the stellate cells is not permitted here. The ordinate shows the number of spike pairs for 90 s in **(a, b)**. **(a)** Two stellate cells, A and B, were stimulated by 40 and 30 Hz pulse trains respectively. Many of the time differences between spikes of the stellate cells fall into the LTP time window of ± 10 ms. **(b)** Stellate cell A was stimulated at 40 Hz and the stellate cell B was not stimulated. Spike timing is not concentrated within the LTP time window. **(c)** Mexican hat learning rule. Spike time of the stellate cell A stimulated by a 40 Hz pulse train is delayed by 20 ms in Fig. 4a, b

When the stellate cells, A and B, are stimulated by 40 and 30 Hz pulse trains (afferent stimuli) respectively, many of the time differences between spikes of the stellate cells fall into the time window of ± 10 ms (Fig. 4a) and enhancement of the loop connection $A \rightarrow B$ is expected. Other interspike intervals outside the LTP window would induce LTD though synaptic modification is absent outside the time window of ± 20 ms. These LTD windows is presumably responsible for increasing the selectivity of pairs of afferent signals that enhance loop connections. In other words, the LTD windows may sharpen the LTP window and

reduce the ambiguous potentiation by larger spike timing Δt . When the stellate cell A alone was stimulated by a 40 Hz pulse train, the stellate cell B fired on occasion. The number of spike pairs is small, and spike timing is not concentrated within the LTP window (Fig. 4b). Loop connections are therefore not expected to be enhanced as a whole.

The stellate cell A was stimulated by a 40 Hz pulse train and the stellate cell B was stimulated by 35, 30, 25, 20, or 15 Hz pulse train to see the dependence of the distribution of the spike timing on the difference between the stimulus frequencies (Fig. 5a–e). The abscissas represent the difference between the spike time of the stellate cell A delayed by 20 ms and the spike time of the stellate cell B. The Mexican hat learning rule is shown once again in Fig. 5f for

Fig. 5 Histograms of the relative spike timing between two stellate cells stimulated by several pairs of regular pulse trains. The ECII network has loop connections, but enhancement of loop connections is not permitted in here. (a–e) The stellate cells A was stimulated by a 40 Hz pulse train and the other stellate cell B was stimulated by 35, 30, 25, 20, or 15 Hz pulse train. Spike time of the stellate cell A stimulated at 40 Hz is delayed by 20 ms. The ordinate shows the number of spike pairs for 90 s. (f) Mexican hat learning rule is shown once again for comparison. The average spike timing shifts from negative to positive and the number of spike pairs reduces with decrease in the frequency of stimulation of the stellate cell B. A pair of pulse trains whose frequencies are appropriately different is coincidentally selected by the learning rule

comparison, but enhancement of loop connections is not yet permitted. The average spike timing shifts from negative to positive and the number of spike pairs reduces with decrease in the frequency of the stimulus pulse train fed to the stellate cell B. This is because the rise in the integrated EPSP induced in the stellate cell B becomes slower and the firing rate of the stellate cell B reduces with decrease in the stimulus frequencies. These results indicate that pairs of afferent pulse trains whose frequencies are appropriately different can be coincidentally selected by the Mexican hat learning rule. In other words, if the time difference between the firing of the stellate cell A caused by a higher-frequency pulse train and the firing of the stellate cell B caused by a lower-frequency pulse train is around 20 ms, the time difference between the reentrance spike from the stellate cell A and the spike of the stellate cell B is within a LTP time window of ± 10 ms. It is consequently expected that loop connections between stellate cells stimulated by selected pairs of afferent pulse trains are potentiated. It should be noted here that the peak of the histogram tends to move toward $\Delta t = 0$ if loop connections are enhanced, because input from the stellate cell A to the stellate cell B tends to entrain the firing of the stellate cell B through the potentiated loop connection.

Enhancement of loop connections under the Mexican hat learning rule is now permitted. The stellate cell A was stimulated by a 40 Hz pulse train again. The synaptic conductance of the loop connection increased with time when the frequency of the pulse train fed to the stellate cell B was around 30 Hz (Fig. 6a). However, when the frequency of the stimulation of the stellate cell B was 37.5 or below 20 Hz, the synaptic conductance was not enhanced. The enhanced synaptic conductance of the loop connection 30 s after the onset of the stimulation is shown in Fig. 6b as a function of the frequency of the stimuli fed to the stellate cell B. This clearly shows the remarkable synaptic enhancement by pairs of pulse trains selected by the Mexican hat learning rule. Bars in Fig. 6b indicate standard deviation.

Then, four out of 30 stellate cells were simultaneously stimulated by pulse trains to see whether specific loop connections were enhanced even when more than two stellate cells were simultaneously stimulated at different frequencies. About 40, 30, 20, 10 Hz pulse trains were fed to the stellate cells, A, B, C, and D, respectively during the first period of 40 s (period (i) indicated by the bar above Fig. 7a) and those pulse trains were in turn fed to the stellate cells, B, C, D, and E, during the next period of 40 s (period (ii)). After that, the other three pairs of four stellate cells, C–F, D–G, and E–H, were

Fig. 6 Enhancement of a loop connection. **(a)** Time courses of enhancement. The stellate cell A was stimulated by a 40 Hz pulse train. Figures indicated in this panel are the frequencies of the pulse train fed to the stellate cell B. Synaptic conductance of the loop connection $A \rightarrow B$ increases with time when the stellate

cell B is stimulated at around 30 Hz. **(b)** Enhanced synaptic conductance of the loop connection 30 s after the onset of stimulation. The synaptic conductance $A \rightarrow B$ is remarkably enhanced by pairs of pulse trains selected by the Mexican hat learning rule. Bars indicate standard deviation

successively stimulated by the above pulse trains every 40 s (periods (iii)–(v)). The loop connection from the stellate cell A to the stellate cell B was most potentiated during the first period of 40 s (Fig. 7a, $A \rightarrow B$). Enhancement of the loop connection from the stellate cell B to the stellate cell C was intermediate (Fig. 7a, $B \rightarrow C$) and the other loop connections were not enhanced in this period of time. Loop connections,

$B \rightarrow C$, $C \rightarrow D$, $D \rightarrow E$, and $E \rightarrow F$, were successively potentiated every 40 s as shown in Fig. 7a. Loop connections, $A \rightarrow C$, $A \rightarrow D$, $A \rightarrow E$, and $A \rightarrow F$, were not enhanced during the stimulation (Fig. 7b), and neither were remaining connections (data not shown). Given that the frequency of afferent stimuli conveying place information decreases with increase in the distance between the animal and places ahead, loop connections between stellate cells representing those places would be selectively potentiated by afferent stimuli whose frequencies are properly different.

Fig. 7 Time courses of enhancement of loop connections when four out of 30 stellate cells were simultaneously stimulated by pulse trains whose frequencies were different. **(a)** 40–10 Hz pulse trains were fed to the stellate cells A–D respectively during the first period of 40 s (period (i) indicated by the bar), and these pulse trains were in turn fed to the stellate cells B–E during the next period of 40 s (period (ii)), and so on. Loop connections, $A \rightarrow B$, $B \rightarrow C$, $C \rightarrow D$, $D \rightarrow E$, and $E \rightarrow F$, were successively enhanced every 40 s. **(b)** Loop connections, $A \rightarrow C$, $A \rightarrow D$, $A \rightarrow E$, and $A \rightarrow F$, were not enhanced during the stimulation and neither were remaining connections (data not shown)

Sequential firing of stellate cells due to potentiated loop connections

The stellate cell A alone was stimulated by a 40 Hz pulse train after the loop connections, $A \rightarrow B$, $B \rightarrow C$, $C \rightarrow D$, $D \rightarrow E$, and $E \rightarrow F$, were potentiated. The stellate cells A–D fired and the firing rate decreased in that order (Fig. 8a). The stellate cells, E and F, hardly fired though their loop connections were potentiated. The histogram of the intervals between the spike of the stellate cell A and the spikes of other stellate cells B–D is shown in Fig. 8b. The stellate cell A fired at $t = 0$. This reveals that the stellate cells B–D fire successively after the firing of the stellate cell A. These interspike intervals result from the transmission delay through the loop connections, and the sequence firing is induced by potentiated loop connections. Relative timing of spikes considerably fluctuates, as indicated by the distributed histogram of relative spike timing. However, the stellate cells hardly fire in reverse order excluding occasional firing caused by random input.

Fig. 8 Firing of the stellate cells whose loop connections are potentiated. **(a)** Firing patterns of four stellate cells A–D. The stellate cell A alone was stimulated by a 40 Hz pulse train. The stellate cells, E and F, hardly fired. **(b)** Histogram of the time difference between the spike of the stellate cell A and the spikes of other stellate cells B–D. The stellate cell A fired at $t = 0$. The stellate cells B–D fired successively after the firing of the stellate cell A. The ordinate shows the number of spike pairs for 90 s

We will finally replicate a phase precession phenomenon in stellate cells. When a 40 Hz pulse train was fed to the stellate cell A alone, the stellate cells, B and C, fired successively after the firing of the stellate cell A (Fig. 9a). Then, a 40 Hz pulse train was fed to the stellate cell B (C) alone. In consequence, the firing of the stellate cell B (C) was followed by the stellate cells, C and D (D and E) (Fig. 9b, c). Spikes of the stellate cells, A and B, were missing in Fig. 9b, c respectively, because those stellate cells received neither an afferent pulse stimuli nor effective reentrance spikes through loop connections. If the stellate cells A–E recognize the places A–E, a high-frequency sensory signal would be successively fed to the stellate cells A–E when the animal traverses the place field. Under these conditions, for example, the spike of the stellate cell C advances within one cycle of synchronized subthreshold oscillations, as shown in Fig. 9.

Discussion

In the network model proposed by Fransén (2005), excitatory synaptic coupling between stellate cells is necessary to replicate theta rhythmic firing in addition

Fig. 9 Sequential firing of three stellate cells within a cycle of subthreshold oscillation. Loop connections between the stellate cells A–F were potentiated in their order. In each trace in **a–c**, the first cell alone was stimulated by a 40 Hz pulse train. Given that the stellate cells A–E recognize the places A–E, a high-frequency sensory signal would be fed to the stellate cell A first, then to the stellate cell B, and to the cells C–E successively when the animal traverses the place field. In this situation, for example, the spike of the stellate cell C advances within a cycle of subthreshold oscillations, replicating the phase precession

to subthreshold oscillations in stellate cells. There is however scarcely any recurrent excitatory connections in ECII (Dhillon and Jones 2000), while stellate cells are strongly inhibited by inhibitory interneurons (Jones and Bühl 1993; Dickson and Alonso 1997). Thus, it has been supposed that recurrent inhibition plays an important role in synchronization of subthreshold oscillations (Dickson et al. 2000b). The present model of ECII, which did not contain recurrent excitatory connections between stellate cells within layer II but inhibitory connections via one interneuron, indeed showed synchronization of subthreshold oscillations.

The present network model of ECII showed synchronous subthreshold oscillations in stellate cells as reproduction of a theta rhythm. The phase of stellate cell firing with respect to the subthreshold oscillations depends on the frequency of afferent stimuli (pulse train). In other words, stellate cells fire in order of the stimulus frequencies. Moreover, using an ECII network model with loop connections that mimic entorhinal-hippocampal loop circuits, it was demonstrated that pairs of afferent pulse trains whose frequencies were properly different were selected by virtue of loop connections, and loop connections were selectively potentiated by those pairs of afferent signals. As a result, stellate cells fired successively within each theta cycle even when the first one stellate cell alone was stimulated. This is a reminiscence of gamma-theta field oscillations underlying sequence learning. If firing of these stellate cells represents a sequence of places where the animal traverses, the present model with loop connections would replicate a phase precession phenomenon after selective potentiation of loop connections.

The entorhinal-hippocampal loop circuitry was model by simple delay lines in the present model. This simplification was helpful to understand the fundamental role of the major pathway in the hippocampus that was an appendage to the entorhinal cortex having capability of causing reverberation activity. However, introduction of the architectural organization and learning capability of the hippocampus into a model of the entorhinal-hippocampal system would promote a better understanding on functional roles of the hippocampus in sequence learning. These interesting issues should be studied in future work.

It is required in the present model that frequencies of pairs of afferent pulse trains are properly different for potentiating loop connections. In fact, some pairs exist so that reentrance spikes due to stellate cell firing caused by a higher-frequency pulse train almost coincide with firings of some other stellate cells caused by lower-frequency pulse trains. Since the time differences between the reentrance spikes and the firings are within a LTP time window, reentrance spikes cooperate with afferent stimuli to potentiate loop connections selectively. The frequency of afferent stimuli is however not specified. Only appropriate difference between the frequencies is necessary. This means that stellate cells responding afferent stimuli in properly different frequencies are selectively linked by loop connections in order of the stimulus frequencies. By virtue of this property, frequencies of afferent pulse trains may change coherently when loop connections are potentiated by those signals.

It has been suggested that firing phase of the CA1 pyramidal cell with respect to a background theta depends on a ramp-like depolarization in the experiments where the CA1 pyramidal cell is stimulated by a sinusoidal current superimposed on a DC current (Kamondi et al. 1998). In the present ECII network model, stellate cells cause synchronized subthreshold oscillations (theta rhythm) and depolarization was caused by integration of EPSPs evoked in the stellate cells by regular pulse train stimulation. Since the integrated EPSP in the hyperpolarizing phases of the subthreshold oscillation is relatively suppressed by the recurrent inhibition, the amplitude of the integrated EPSP is paced by the subthreshold oscillation. Consequently, firing phase of each stellate cell depends on the stimulus frequency. In other words, stellate cells successively fire within each cycle of subthreshold oscillation in order of stimulus frequencies. The present model also demonstrated that the phase-coded sequence information was stored by selective enhancement of loop connections.

Fransén et al. (2004) have noted that dendritic compartments are important for matching features of spike shape, afterhyperpolarization shape, and spike-frequency accommodation with those in experimental data, as mentioned above. A central mechanism for phase coding in the present model is that firing phase of the stellate cell causing synchronized subthreshold oscillation depends on the frequency of an afferent pulse-train stimulation fed into the stellate cell. Although this firing phase is almost determined by the integrated EPSP paced by subthreshold oscillation, this firing phase might also be influenced by subthreshold oscillation shape, spike shape, afterhyperpolarization shape, and so on. Therefore, Fransén's multi-compartmental models (Fransén et al. 2002, 2004), which reproduced above features well, were adopted in the present paper. Our suggested mechanism could however be reproduced by simpler cell models: for example, a single compartment minimal model containing only a few ionic currents such as I_{NaP} and I_h . This interesting issue should also be studied in future work.

Synapses are potentiated in deep-to-superficial layer projections in the entorhinal cortex by theta burst stimulation of deep layers, and stimulation of the deep layers induces much larger amplitude of LTP in cooperation with stimulation of superficial layers, as mentioned above. In the present model, Mexican hat type learning rule was adopted for coincident detection of reentrance spikes and afferent stimuli in ECII, though physiological evidence for the learning rule in the deep-to-superficial layer projections has not been provided. It would also be

possible to detect coincidence of those signals by an asymmetric spike-timing dependent learning rule that has been found in many brain areas including the hippocampus (Levy and Steward 1983; Debanne et al. 1994; Bi and Poo 1998). Only slight change in the time difference between reentrance spikes and afferent stimuli would be required in order to get into the LTP time window. However, selectivity of pairs of afferent signals presumably decreases because the asymmetric spike-timing dependent learning rule does not have a LTD time window in the region of positive spike-timing where a reentrance signal precedes an afferent signal. In the case of Mexican hat learning rule, LTD time windows exist on both sides of central LTP time window. This would be effective in increasing selectivity of pairs of afferent signals that reinforce loop connections.

When the animal acquires information about a route to some destination, the animal does not seem to memorize places continuously along the route, but seems to learn a sequence of discrete places at some intervals. In general, the frequency and the duration of sensory signals code intensity and duration of sensory stimuli. It is therefore plausible that the frequency of sensory signals, which convey information about the places ahead of the animal, decreases with increase in the distance between the animal and the places, because the intensity of sensory stimuli resulting from close places would be stronger than that resulting from apart places. As a result, route information would be stored as a sequence of discrete places selected by a proper difference between the frequencies of sensory signals. The mechanism for selection of sensory signal pairs demonstrated by the present model would shed light on one aspect of the sequence learning.

Most arguments about sequence learning based on the theta phase coding have been restricted in the hippocampus after the finding of place cells. Recently, it has been suggested that spatial information is represented upstream of the hippocampus in the medial entorhinal cortex (Yamaguchi 2003; Hafting et al. 2005a; O'Keefe and Burgess 2005). Grid cells found in the medial entorhinal cortex are activated at vertexes of a grid of equilateral triangles (Hafting et al. 2005a). Such grid cells in layer II of the entorhinal cortex are theta-modulated and show phase precession (Hafting et al. 2005b). It has also been reported that phase precession is preserved after stimulus-induced theta phase reset and transiently inactivated hippocampal activity, indicating that the timing of spikes may be updated by extrahippocampal inputs. (Zugaro et al. 2005). This

suggests that position information comes from the entorhinal cortex. The present model of the entorhinal cortex with loop connections may transform afferent signals with different frequencies into metric representation. Moreover, the stellate cells show phase precession. The present model might reflect a part of properties of the grid cell though we have not reproduced a grid-like firing structure. The problems whether stellate cell acts as a grid cell, whether place cells exist in the entorhinal cortex besides grid cells and what is the relevance between grid cells and place cells still remain to be clarified.

Involvement of the entorhinal cortex in the phase coding has been suggested. Yamaguchi (2003) hypothesized that theta phase precession was generated in the entorhinal cortex by phase-locking between theta rhythm and neuronal firing, and demonstrated that an entorhinal-hippocampal model consisting of layers II and III of the entorhinal cortex in addition to the hippocampal CA3 and CA1 layers successfully learns sequential behavioral inputs and retrieve stored sequential memory. Her model also reproduced the phase precession underlying sequence learning. However, simple oscillator units, whose frequencies were the same and phases were shifted one after another, were used for all layers to describe local field theta rhythm. In other words, mechanisms for generating a theta rhythm and phase-locking of sequence neuronal firing in the theta rhythm are not included. In the present paper, we demonstrated how theta rhythm was generated in the entorhinal cortex and how afferent signals were coded in compressed form within each theta cycle using a network model of ECII with loop connections that mimic entorhinal-hippocampal loop circuits. Our model also reproduced phase precession of stellate cell firing. These gamma-theta oscillations in ECII would also be responsible for storing sequence information more precisely downstream of the entorhinal cortex in the hippocampal CA3 and CA1 subfields.

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Appendix A

Parameter values in Eqs. 1 and 2 are shown in Table 1.

Table 1 Parameter values of synaptic connections

	IS	SI_A	SI_B	LC	AF	RAND
V_{syn} (mV)	0	-70	-85	0	0	0
$\tau_{1(\text{syn})}$ (ms)	2	1	30	2	2	2
$\tau_{2(\text{syn})}$ (ms)	2	7	90	2	2	2
C_{syn} ($\mu\text{S}/\text{cm}^2$)	0.4	0.2	0.019	0.001–0.05	0.02	0.00875

Appendix B

Parameter values of the stellate cell in the entorhinal cortex layer II are shown in Table 2 and 3. Rate constants of ion-gates of the stellate cell are as follows:

$$\alpha_m = \frac{-0.32(V + 41.9)}{\exp((V + 41.9)/4.0) - 1},$$

$$\beta_m = \frac{0.28(V + 14.9)}{\exp((V + 14.9)/5) - 1},$$

$$\alpha_h = 0.128 \exp\left(\frac{-(V + 38.0)}{18.0}\right),$$

$$\beta_h = \frac{4.0}{1 + \exp(-(V + 15.0)/5.0)},$$

$$\alpha_n = 0.016 \frac{-(V + 19.9)}{\exp(-(V + 19.9)/5) - 1.0},$$

$$\beta_n = \frac{0.25}{\exp(-(V + 35.0)/40.0)},$$

$$\alpha_s = \frac{1.6}{1.0 + \exp(-0.072(V - 5))},$$

$$\beta_s = 0.10 \frac{0.02(V + 8.9)}{\exp((V + 8.9)/5.0) - 1.0},$$

$$\alpha_q = \begin{cases} 6.0\chi_{\text{K}_{\text{AHP}}} & (\chi_{\text{K}_{\text{AHP}}} < 30.0) \\ 30.0 & (\chi_{\text{K}_{\text{AHP}}} \geq 30.0) \end{cases}, \quad \beta_q = 1.0,$$

$$\alpha_c = \begin{cases} \frac{\exp(0.053872(V - 2.56397))}{18.975} & (V \leq -10) \\ 2.0 \exp(-(V + 53.5)/27.0) & (V > -10) \end{cases},$$

$$\beta_c = \begin{cases} 2.0 \exp(-(V + 53.5)/27.0) - \alpha_c & (V \leq -10) \\ 0.0 & (V > -10) \end{cases},$$

$$\alpha_x = 0.091 \frac{(V + 42.0)}{1 - \exp(-(V + 42.0)/5.0)},$$

$$\beta_x = \frac{-0.062(V + 42.0)}{1 - \exp((V + 42.0)/5.0)},$$

$$x_\infty = \frac{1.0}{1.0 + \exp(-(V + 52.7)/4.4)},$$

$$\tau_{\text{Hf}} = \frac{1}{\alpha_{\text{Hf}} + \beta_{\text{Hf}}} = \frac{0.51}{\exp((V + 2.3)/10) + \exp(-(V + 344)/52)},$$

Table 2 Conductance profile of the stellate cell in the entorhinal cortex layer II

	Initial segment	Soma	Principal dendrite			Remaining dendrite	
			Proximal	Medial	Distal	Proximal	Distal
g_{Na}	15	3.8	3.8	3.8	1.9	3.8	1.9
$g_{\text{K(DR)}}$	21.5	10.7	10.7	10.7	5.4	10.7	5.4
g_{Ca}	0	0.1	0.1	0.1	0.1	0.1	0.1
$g_{\text{K(AHP)}}$	0	0.01	0.01	0.01	0.01	0.01	0.01
$g_{\text{K(C)}}$	0	1,340	0	0	0	0	0
g_{NaP}	0	0.065	0.065	0.065	0.065	0.065	0.065
g_{Hf}	0	0.112	0.112	0.112	0.112	0.112	0.112
g_{Hs}	0	0.0605	0.0605	0.0605	0.0605	0.0605	0.0605
$\phi_{\text{K(C)}}$	0	17,400	0	0	0	0	0
$\phi_{\text{K(AHP)}}$	0	61,340	97,370	97,370	21,930	16,730	3,760

The unit of the conductance is $\mu\text{S}/\text{cm}^2$

Table 3 Conductances between neighboring compartments

γ	
Distal—medial dendrites	2.84×10^{-5} (μS)
Medial—proximal dendrites	2.84×10^{-5}
Proximal dendrite—Soma	5.65×10^{-5}
Soma—proximal remaining dendrite	2.34×10^{-4}
Proximal—distal remaining dendrites	1.19×10^{-4}
Soma—Initial segment	1.51×10^{-4}

$$H_{f\infty} = \frac{\alpha_{Hf}}{\alpha_{Hf} + \beta_{Hf}} = \frac{1.0}{(1 + \exp((V + 78.2)/9.78))^{1.36}},$$

$$\tau_{Hs} = \frac{1}{\alpha_{Hs} + \beta_{Hs}} = \frac{5.6}{\exp((V - 13.0)/14.0) + \exp(-(V + 264)/43.0)},$$

$$H_{s\infty} = \frac{\alpha_{Hs}}{\alpha_{Hs} + \beta_{Hs}} = \frac{1.0}{(1 + \exp((V - 7.87)/15.9))^{58.5}},$$

$$C = 1.0 \text{ } (\mu\text{F}/\text{cm}^2), V_{Na} = 87.0,$$

$$V_K = -83.0, V_{Ca} = 80.0,$$

$$V_L = -83.0, V_{KL} = -83.0, V_{NaP} = 55.0,$$

$$V_H = -20.0 \text{ (mV)}, g_L = 0.02, g_{KL} = 0.12 \text{ } (\mu\text{S}/\text{cm}^2),$$

$$\beta_{K(C)} = 2, \beta_{K(AHP)} = 5.0 \times 10^{-3} \text{ (ms}^{-1}\text{)}$$

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