

# Efficient Control of Theta Traveling Waves by Synchronized Inhibition through Gap Junctions and GABAergic Connections in a Hippocampal CA3 Model

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## Abstract—

Inhibitions play an important role in organizing directional theta traveling waves of neuronal activities in a hippocampal CA3 recurrent network model. In the hippocampus, gap junctions and GABAergic connections exist between interneurons. We analyzed the role of the coexistent connections in the network and found that the coexistent connections suppress the activity of interneurons but keep the capability of the organization of directional theta traveling waves. In the network, the synchronization of interneurons was enhanced and sufficient inhibitions to control directional traveling waves occurred. These results suggest that the interaction between interneurons through gap junctions and GABAergic connections contribute to the efficient control of theta traveling waves in the hippocampus by increasing the effect of a few inhibitory activities.

## 1. Introduction

In the hippocampus, theta (4 – 12 Hz) oscillations travel along the longitudinal axis of the hippocampus [1]. It has been suggested that propagation of neuronal activities through recurrent connections of the hippocampal CA3 is a possible mechanism of the traveling waves. Although the propagation of neuronal activities in the hippocampal CA3 remains unclear *in vivo*, previous studies demonstrated that waves of neuronal activities traveling radially at theta frequency are spontaneously and input-dependently organized in a hippocampal CA3 recurrent network model composed of pyramidal cells and inhibitory interneurons [2]. Furthermore, a CA3 recurrent network model with an anisotropic inhibitory structure organize directional theta traveling wave [3]. Inhibitions play an important role in organizing the directional traveling waves in the network.

In the hippocampus, interneurons form not only gap junctions but also GABAergic connections on other interneurons [5]. The previous study focused only on the role of gap junctions during the organization of traveling waves [3]. It demonstrated that gap junctions enhance inhi-

bitations and contribute to organizing directional theta traveling waves. In this study, we analyzed the role of coexistence of both the types of connections in the network. By emphasizing the coexistent connections, the activities of interneurons were suppressed but the directional theta traveling waves were still organized. We show that sufficient inhibitions to control directional traveling waves occurred by enhancing the synchronization of interneurons in the network. In other words, theta traveling waves were controlled by a few inhibitory activities. These results suggest that the interaction between interneurons through gap junctions and GABAergic connections contribute to the efficient control of theta traveling waves in the hippocampus.

## 2. Methods

### 2.1. Hippocampal CA3 Model

We modified a biophysical CA3 recurrent network model developed by Yoshida and Hayashi [2]. The present CA3 network model was composed of 2,304 pyramidal cells and 288 inhibitory interneurons. Pyramidal cells were placed on  $48 \times 48$  lattice points. Inhibitory interneurons were placed on the points at regular intervals (Fig.1). All neurons were locally contacted with other neurons. A pyramidal cell formed excitatory chemical synapses on 20 pyramidal cells in its surrounding  $7 \times 7$  region (e.g. gray thin lines in Fig.1(a)) and on all interneurons in  $11 \times 11$  region (e.g. gray thick lines in Fig.1(a)). An interneuron formed inhibitory chemical synapses (GABAergic connections) on 60 pyramidal cells (e.g. gray solid lines in Fig.1(b)) and with 8 interneurons in  $13 \times 9$  off-center region (e.g. gray bold lines in Fig.1(b)). Interneurons have slightly long chemical connections in the downward direction. Furthermore, an interneuron formed gap junctions mutually on up to 8 interneurons in its surrounding  $9 \times 9$  region (e.g. black lines in Fig.1(b)). Neurons around edge receive connections in a different manner from majority of the neurons. The irregular connectivity causes different activity. Here,

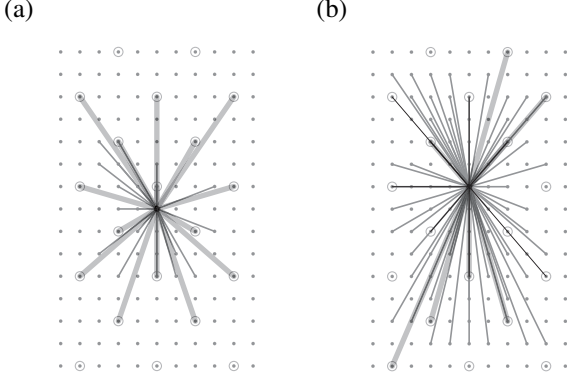


Figure 1: Synaptic connections from a pyramidal cell (a) and an interneuron (b) in the hippocampal CA3 recurrent network. Pyramidal cells (dot) and interneurons (open circle) were positioned at each lattice point. Both types of neurons were connected through chemical synapses to pyramidal cells (gray thin lines) and to interneurons (gray thick lines). Interneurons were also connected with other interneurons through gap junctions (black lines).

we assumed a torus structure to remove the ununiformity of connections around the edge. Edge neurons were connected also to other neurons on the opposite side. All neurons in the network cause uniform activity on the assumption. Thus, neuronal activities organized in the network are not caused by the different activities of edge neurons.

The membrane potential  $V_i$  of the  $i$ -th pyramidal cell was updated as follows:

$$\begin{aligned}
 CdV_i/dt = & g_{Na}m^2h(V_{Na} - V_i) + g_{Ca}s^2r(V_{Ca} - V_i) \quad (1) \\
 & + g_{Ca(low)}s_{low}^2r_{low}(V_{Ca} - V_i) + g_{K(DR)}n(V_K - V_i) \\
 & + g_{K(A)}ab(V_K - V_i) + g_{K(AHP)}q(V_K - V_i) \\
 & + g_{K(C)}c \min(1, \chi/250)(V_K - V_i) + g_L(V_L - V_i) \\
 & + g_{af}(V_{syn(e)} - V_i) + I_{syn},
 \end{aligned}$$

where  $g_x$  and  $V_x$  of the 1st–7th terms are the conductance and the equilibrium potential for the respective ion channels (x): Na, Ca, Ca(low), K(DR), K(A), K(AHP), K(C).  $g_L$  and  $V_L$  are the conductance and the equilibrium potential for leakage, respectively.  $g_{af}$  and  $V_{af}$  are the conductance and the equilibrium potential for the afferent excitatory synapse, respectively.  $I_{syn}$  is total synaptic currents from postsynaptic neurons. We introduced gap junctions [6] into interneurons. The membrane potential of the  $i$ -th interneuron was updated as follows:

$$\begin{aligned}
 CdV_i/dt = & g_{Na}m^3h(V_{Na} - V_i) + g_{K(DR)}n^4(V_K - V_i)(2) \\
 & + g_L(V_L - V_i) + I_{syn} + \sum_j^{N_{gap}} g_{gap}(V_j - V_i),
 \end{aligned}$$

where  $g_{gap}(= 0.0016 \mu S)$  is the coupling conductance through a gap junction between interneurons.  $N_i^{gap}$  is the number of gap junctions with other interneurons. Other parameters are described in ref.[2]; however part of the parameters were changed as follows:  $g_{af} = 0.004 \mu S$ ,

$V_{ip} = -75$  mV. The synaptic conductance between pyramidal cells was updated by asymmetric STDP [2]. We set the synaptic conductance for each synapse and maximum modification rates for LTP and LTD as follows:  $C_{pp} = 0.0004 - 0.001 \mu S$ ,  $C_{pi} = 0.002 \mu S$ ,  $C_{ip} = 0.001 \mu S$ ,  $C_{ii} = 0.001 \mu S$ ,  $M_{LTP} = 0.05$ ,  $M_{LTD} = 0.0525$ .

## 2.2. Simulation Conditions

We used the network model with gap junctions between interneurons as a control (control condition). Additionally, we defined a different network model. Each interneuron formed gap junctions and inhibitory chemical synapses on the same targets within  $9 \times 9$  region (coexistent condition). Although gap junctions do not always coexist with inhibitory chemical synapses between interneurons in the hippocampus, we assumed that all pairs of interneurons have both types of connections in order to evaluate the effect of the coexistent connections clearly.

We ran ten times simulations in each condition. In a simulation trial, we updated the membrane potential of all neurons for 110 s. Synaptic inputs and synaptic weights were updated from 1 s and 10 s, respectively. We evaluated neuronal activities emerged in the networks at 9 s and 109 s.

## 2.3. Evaluation for Organized Traveling Waves

Traveling waves with horizontal wavefronts propagate upwardly in the network where interneurons downwardly elongate their axons [3]. To confirm whether obvious horizontal wavefronts emerge in the network, we evaluated synchronization of pyramidal cells at a location on the vertical axis by calculating the ratio of co-firing neurons to the total number of neurons at the same location on the vertical axis for each 20 ms bin. Stripes indicate that traveling waves with horizontal wavefronts propagate in the vertical direction (Fig.3, 4(a) (b)).

We evaluated the direction of weights in which a pyramidal cell acquired strong connections across trials. The weight direction of the  $j$ -th pyramidal cell at time  $t$  is calculated as follows:

$$R_j(t) = \frac{1}{N_{trial}N_{post}} \sum_k^{N_{trial}} \sum_l^{N_{post}} (w_{lj}^k(t) - w_{lj}^k(0))e^{i\theta_{lj}^k}, \quad (3)$$

where  $N_{trial}$  and  $N_{post}$  are the number of trials and the number of postsynaptic pyramidal cells, respectively.  $w_{lj}^k(t)$  is a synaptic weight to the  $l$ -th postsynaptic pyramidal cell from the  $j$ -th pyramidal cell at time  $t$  in the  $k$ -th trial.  $\theta_{lj}^k$  indicates the angle between the  $j$ -th pyramidal cell and the  $l$ -th postsynaptic pyramidal cell in the  $k$ -th trial. Large  $R_j(t)$  indicates that traveling waves passing through the  $j$ -th neuron in a particular direction are organized across trials (e.g. long arrows in Fig.3, 4 (c) (d)).

It has been suggested that the timing of inhibition relative to the firings of a pyramidal cell plays an important role in controlling the neuronal activities in a recurrent network [3]. In each trial, 100 neurons (pyramidal cells or

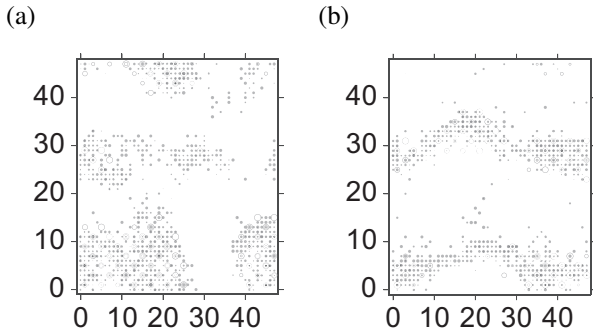


Figure 2: Neuronal activities (pyramidal cells (dot) and interneurons (open circle)) emerged in the network for 20 ms at 9 s (a) and 109 s (b) under the control condition.

interneurons) were randomly selected. We evaluated the population firing rates of all interneurons connecting to the selected neurons around the first firings of the selected neurons within wavefront (Fig.5).

### 3. Results

Directional traveling waves were spontaneously organized in the network model under the control condition. Figs.2(a), 3(a) show neuronal activities at 9 s. The neural activities did not propagate in a particular direction. A certain structure was not embedded initially in the network of pyramidal cells (Fig.3(c)). After 100 s, neural activities upwardly propagated in the network (Fig.2(b)). Neurons at the same location on the vertical axis tend to fire simultaneously. Traveling waves with obvious horizontal wave fronts were organized in the network. As shown in Fig.3(b), upward traveling waves with obvious horizontal wave fronts were organized frequently in the networks. Synaptic connections from a pyramidal cell to upper pyramidal cells were strengthened through synaptic plasticity (Fig.3(d)). Traveling waves always propagating upwardly were spontaneously organized in the network.

Under the coexistent condition, a certain structure was not embedded initially in the network of pyramidal cells (Fig.4(c)). Thus, neural activities did not propagate always in a particular direction initially (Fig.4(a)). Traveling waves were gradually organized in the network through the update of synaptic weights. Finally, upward traveling waves with obvious horizontal wave fronts were organized frequently in the network (Figs.4(b), (d)).

There are no clear differences in the organization of traveling waves between both conditions (Figs.3, 4). Indeed, the activities of presynaptic interneurons around the activities of pyramidal cells were not clearly different (Fig.5(a)). Thus, pyramidal cells received almost the same inhibitions from interneurons in the two conditions. Conversely, the activities of presynaptic interneurons around that of other interneurons were clearly different (Fig.5(b)). Under the coexistent condition, presynaptic interneurons tend to fire

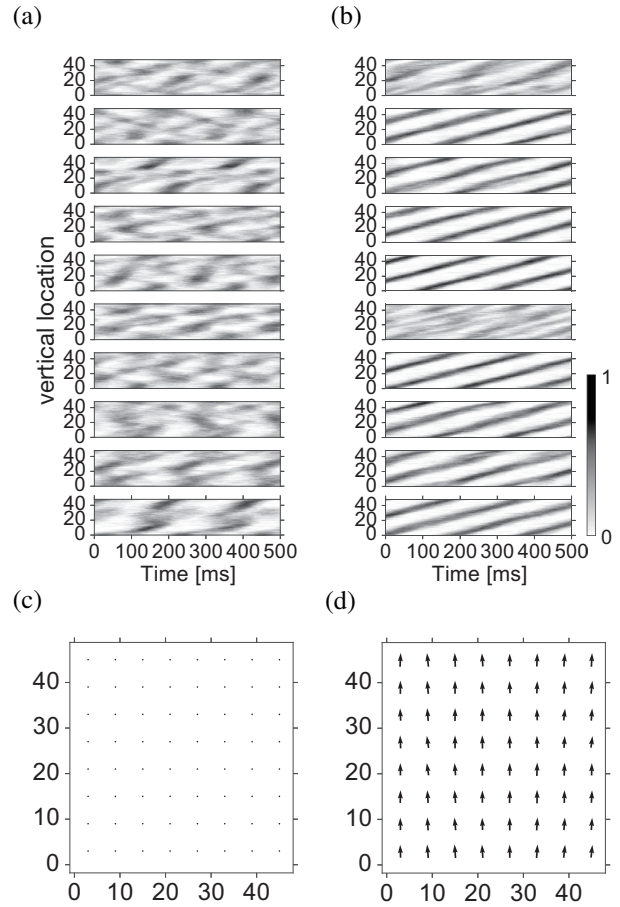


Figure 3: Neuronal activities and synaptic weights organized in the networks at 9 s (a,c) and 109 s (b,d) under the control condition. (a,b) Each panel shows neuronal activity in each trial. Gray scale indicates cofiring ratio at each location on the vertical axis for every 20 ms time window. (c,d) Network was divided into 64 blocks. Each arrow indicates the averaged weight direction in each block.

simultaneously with postsynaptic neurons. The co-firings of interneurons caused synchronized inhibition. Furthermore, on-going activities of interneurons at 109 s in the coexistent condition were significantly lower than that in the control condition ( $18.5 \pm 3.19$  Hz (mean  $\pm$  SD) in the control condition;  $17.6 \pm 3.31$  Hz in the coexistent condition;  $p < 0.001$ ,  $t$ -test).

### 4. Conclusion

We demonstrated that the CA3 recurrent network model organize traveling waves with horizontal wave fronts in both the conditions. There are no clear differences between them in organization of traveling waves. The effect of inhibitions on pyramidal cells does not depend on the differences between both conditions. Under the coexistent condition, the firings of interneurons were suppressed. On the other hand, the synchronization of interneurons was en-

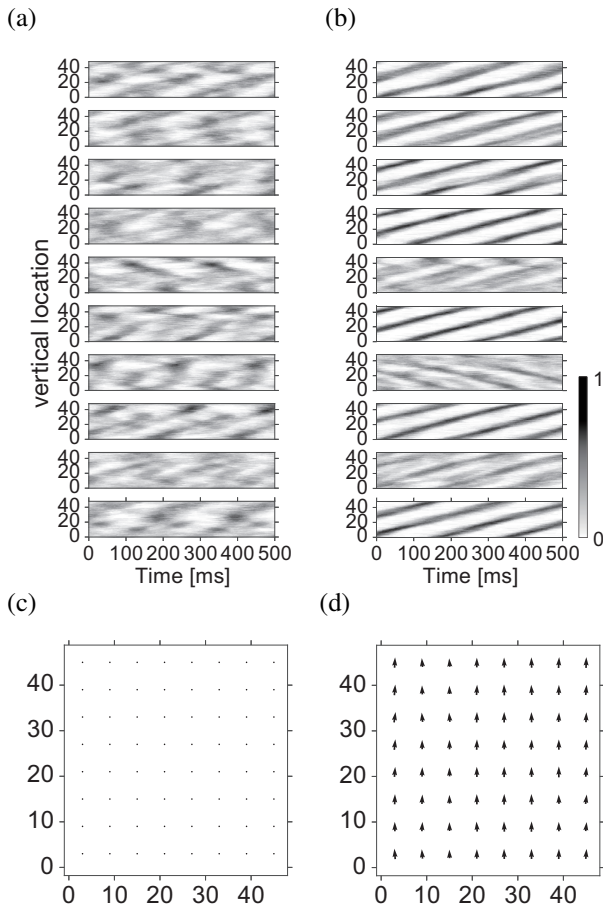


Figure 4: Neuronal activities and synaptic weights organized in the networks at 9 s (a,c) and 109 s (b,d) under the coexistent condition. (a,b) Each panel shows neuronal activity in each trial. Gray scale indicates cofiring ratio at each location on the vertical axis for every 20 ms time window. (c,d) Network was divided into 64 blocks. Each arrows indicates the averaged weight direction in each block.

hanced.

It has been suggested that a network of interneurons connected through two types of connections works as a synchrony detector [7]. The wavefront of traveling waves is composed of the synchronized activities of pyramidal cells. Interneurons may increase their activities simultaneously with others by detecting the synchronized activities in wavefronts. Conversely, interneurons may reduce their activities by no response to unsynchronized activities of pyramidal cells out of wavefronts.

Consequently, a few inhibitory activities efficiently inhibit the activities of pyramidal cells. These results suggest that the coexistence of gap connections and GABAergic chemical synapses contributes to the efficient control of directional traveling waves with saving the activities of interneurons.

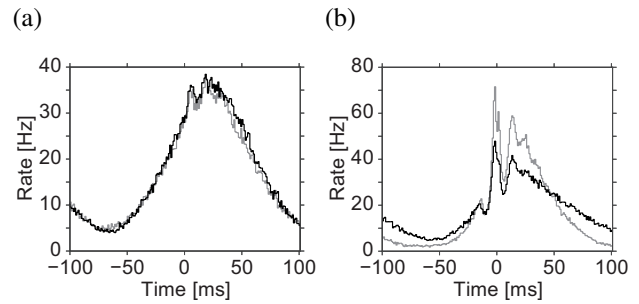


Figure 5: The population firing rates of presynaptic interneurons around the firings of selected pyramidal cells (a) and interneurons (b) at 109 sec under the control (black line) and coexistent condition (gray line).

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### References

- [1] E.V. Lubenov and A.G. Siapas, “Hippocampal Theta Oscillations Are Travelling Waves,” *Nature*, vol.459, no.7246, pp.534–539, 2009.
- [2] M. Yoshida and H. Hayashi, “Regulation of Spontaneous Rhythmic Activity and Organization of Pacemakers as Memory Traces by Spike-Timing-Dependent Synaptic Plasticity in a Hippocampal Model,” *Phys. Rev. E*, vol.69, no.1, pp.011910:1–011910:15, 2004.
- [3] T. Samura, Y. Sakai, H. Hayashi, and T. Aihara, “Roles of Gap Junctions in Organizing Traveling Waves in a Hippocampal CA3 Network Model,” *Neural Inf. Process.*, pp.384–392, 2016.
- [4] Q. Yang and H.B. Michelson, “Gap Junctions Synchronize the Firing of Inhibitory Interneurons in Guinea Pig Hippocampus,” *Brain Res.*, vol.907, pp.139–143, 2001.
- [5] T. Fukuda and T. Kosaka, “Gap Junctions Linking the Dendritic Network of GABAergic Interneurons in the Hippocampus,” *J. Neurosci.*, vol.20, no.4, pp.1519–1528, 2000.
- [6] T. Shinozaki, Y. Naruse, and H. Cateau, “Gap Junctions Facilitate Propagation of Synchronous Firing in the Cortical Neural Population: A Numerical Simulation Study,” *Neural Netw*, vol.46, pp.91–98, 2013.
- [7] M. Galarreta and S. Hestrin, “Spike Transmission and Synchrony Detection in Networks of GABAergic Interneurons,” *Science*, vol.292, no.5525, pp.2295–2299, 2001.