



# Self-organized two-state membrane potential transitions in a network of realistically modeled cortical neurons

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## Abstract

Recent studies have revealed that in vivo cortical neurons show spontaneous transitions between two subthreshold levels of the membrane potentials, ‘up’ and ‘down’ states. The neural mechanism of generating those spontaneous states transitions, however, remains unclear. Recent electrophysiological studies have suggested that those state transitions may occur through activation of a hyperpolarization-activated cation current (H-current), possibly by inhibitory synaptic inputs. Here, we demonstrate that two-state membrane potential fluctuations similar to those exhibited by in vivo neurons can be generated through a spike-timing-dependent self-organizing process in a network of inhibitory neurons and excitatory neurons expressing the H-current.

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## 1. Introduction

Subthreshold membrane potential fluctuations are considered to play active roles in the computations by cortical and subcortical neural networks. In vivo intracellular recording study has revealed that the rat striatal spiny neurons show spontaneous transitions typically at a frequency of 1 Hz between the ‘up’ state, which is about a few mV below spike threshold, and the ‘down’ state representing cell’s resting state (Stern, Jaeger, & Wilson, 1998). Furthermore, results of a combined computational and extracellular recording study have strongly indicated that the striatal neurons in awaking monkeys also exhibit spontaneous transitions between the two subthreshold states (Kitano et al., 2002b). Since the striatal neurons receive convergent cortical inputs, these ‘up’ and ‘down’ transitions in the striatal neurons may reflect similar activity transitions of cortical neurons. In fact, recent in vitro and in vivo electrophysiological experiments revealed that cortical neurons have ‘up’ and ‘down’ states and exhibit

spontaneous transitions between the two states. In a two-photon  $\text{Ca}^{2+}$  imaging study of a mouse slice preparation, it was found that many visual cortical neurons show stereotypical spontaneous state transitions (Cossart, Aronov, & Yuste, 2003). In in vivo intracellular recording study, the cat visual cortical neurons exhibited spontaneous ‘up’ and ‘down’ transitions not only during stimulus presentation, but also during the whole recording periods (Lampl, Reichova, & Ferster, 1999). In addition, the state transitions in the cat visual cortical neurons were shown to be selective to specific visual stimuli (Anderson, 2000).

From these studies, it is likely that the ‘up’ and ‘down’ transitions appear in activity of cortical neurons and constitute an elementary process in cortical computations. However, the cortical mechanism to generate such transitions largely remains unknown. In a possible mechanism, a reverberating excitation in local cortical networks may generate the transitions. In fact, it was recently suggested that the ‘up’ transition is induced by activation of hyperpolarization-activated cation current (H-current,  $I_h$ ) following interneuron-to-pyramidal inhibitory inputs (Cossart, Arnov, Portera-calliau, & Yuste, 2002). On the other hand, some of the present authors have reported that

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spike-timing-dependent plasticity (STDP) can self-organize persistent activity of low rate in a recurrent network of Hodgkin–Huxley neurons (Kitano, Câteau, & Fukai, 2002a). Here, we investigate whether the spontaneous bistable state transitions can be self-organized in a network of excitatory and inhibitory neurons in the case that the H-current is abundant in excitatory neurons.

## 2. Method

### 2.1. Neuron model

Neuronal dynamics is described by the Hodgkin–Huxley-type formulation. Our single-compartment model of excitatory neurons involves the sodium and delayed-rectifier potassium currents for spike generation (Traub, Wong, Miles, & Michelson, 1993), leak currents, transient potassium current (A-current) (Huguenard & McCormick, 1992), slowly activating potassium current (M-current) (Yamada, Koch, & Adams, 1989), and hyperpolarization-activated cation current (H-current) (Wang, 1994, see Section 2.2). An inhibitory neuron consists of the sodium and delayed-rectifier potassium currents for spike generation. Thus

$$C_{\text{pyr}} \frac{dV}{dt} = -I_{\text{Na}} - I_{\text{DR}} - I_{\text{A}} - I_{\text{M}} - I_{\text{h}} - I_{\text{L}} - I_{\text{syn}} + I_{\text{app}} + I_{\text{noise}},$$

$$C_{\text{inter}} \frac{dV}{dt} = -I_{\text{Na}} - I_{\text{DR}} - I_{\text{L}} - I_{\text{syn}} + I_{\text{app}} + I_{\text{noise}},$$

where  $I_{\text{syn}}$ ,  $I_{\text{app}}$  and  $I_{\text{noise}}$  represent synaptic inputs, an external driving input and input from a noise source, respectively. Values of maximum conductance of these ionic currents are given in Appendix A. The gating kinetics of the ionic currents follow those defined in the references. This parameter setting gives rise to the resting membrane potentials of about  $-62$  mV.

### 2.2. Hyperpolarization-activated cation current

In this study, the H-current plays a crucial role. The H-channel in pyramidal cells shows a characteristic site-dependence: the current is strongly expressed at the distal dendritic sites of the hippocampal CA1 and neocortical pyramidal neurons (Destexhe, Rudolph, & Denis Paré, 2003). The dynamics of the H-current is described by the formulation given in Wang (1994). Namely, the current is activated by hyperpolarization (the half-activation potential is about  $-69$  mV), and has a slow time constant (1000 ms at  $-74.5$  mV) and the reversal potential of about  $-40$  mV (Wang, 1994). The H-current is known to play an active role in generating a rhythmic activity in thalamocortical relay neurons (Lüthi & McCormick, 1998). The role of the H-current in cortical neurons is relatively unknown. It has,

however, been suggested that this current and the persistent sodium current may contribute significantly to the spontaneous activity of cortical neurons (Mao, Hamzei-Sichani, Aronov, Fromke, & Yuste, 2001).

### 2.3. Network organization

Our network model consists of 200 excitatory pyramidal neurons and 50 inhibitory interneurons. The pyramidal-to-pyramidal and the pyramidal-to-interneuron synapses are mediated by the AMPA glutamate receptors, and the interneuron-to-pyramidal and the interneuron-to-interneuron synapses by the GABA<sub>A</sub> receptors. The synaptic currents are described by the first-order kinetics for a gating variable. We employed the small network size to reduce a computational load to a tractable level in simulating the activity-dependent changes of many synapses. The reversal potentials of the synaptic currents as  $E_{\text{AMPA}} = 0$  mV,  $E_{\text{GABA}} = -70$  mV, and the maximum conductance is set at 0.04 (AMPA) and 0.2 (GABA) in the unit of the leakage conductance. All the neurons in the network are innervated by an external noise current that is represented by Gaussian white noise. The noise intensity is determined such that a spontaneous firing of 1 Hz appears in the absence of synaptic inputs. The excitatory-to-excitatory synapses are modifiable according to STDP: a synapse is potentiated or depressed if an interval from an EPSP to a postsynaptic action potential is positive or negative (additive rule):  $g \rightarrow g + G(\Delta t)$

$$G(\Delta t) = \begin{cases} A_+ \exp(-\Delta t/\tau_+), & \Delta t = t_{\text{post}} - t_{\text{pre}} > 0 \\ -A_- \exp(-|\Delta t|/\tau_-), & \Delta t < 0 \end{cases}$$

Parameters are set as  $A_+ = 0.01$ ,  $A_- = 0.0105$  and  $\tau_+ = \tau_- = 20$  ms such that the area law ( $A_+\tau_+ < A_-\tau_-$ ) follows and competition may occur between synapses (Song, Miller, & Abbott, 2000).

Initially, the excitatory-to-excitatory synapses have an all-to-all connectivity, but many of them are significantly suppressed in STDP learning. Other types of synaptic connections are not modifiable and have a fixed connectivity of 10%.

## 3. Results

### 3.1. Synaptic distribution

As in the previous study (Kitano et al., 2002a), the average weight of the excitatory synapses was rapidly reduced at an initial stage of STDP learning, since neurons fired at high frequencies and the average effect of LTD dominates over that of LTP in the present parameter choice (Song et al., 2000). After this short initial phase, the average

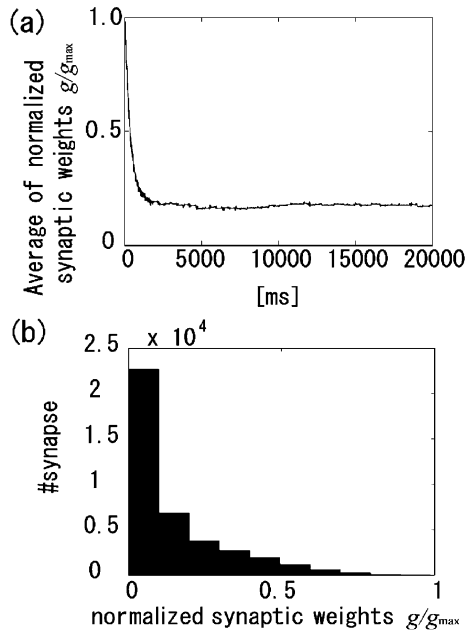


Fig. 1. The reorganization of synaptic weights during the self-organizing process. (a) The average synaptic conductance rapidly decreases at an initial stage of the STDP learning. The equilibrium is reached in about 5000 ms after the onset of learning. (b) The equilibrium weight distribution shows no apparent peak corresponding to winners.

synaptic weight and the mean firing rate of the network showed moderate decreases until the self-organizing process entered an almost stationary stage (Fig. 1a). A typical distribution of the self-organized synaptic weights is presented in Fig. 1b.

### 3.2. Spontaneous 'up' and 'down' transitions

Fig. 2a shows a typical example of the spontaneous activity of 200 excitatory neurons which was obtained by the self-organizing procedure. It is found that the individual excitatory neurons discharge high-frequency spikes in 200–300-ms long epochs separated by silent intervals equal to or longer than the active epochs. The active epochs appear almost synchronously over the ensemble of pyramidal cells and are repeated at a frequency of about 1.5 Hz. The spike raster of the neuronal ensemble and the membrane potential of a single neuron are shown in Fig. 2b for a 1.5-s long interval. We find that spikes of the individual neurons are asynchronous during each active epoch. In addition, spikes are elicited during 'up' state (around  $-55$  mV) and the membrane potential exhibits repetitive transitions between the 'up' state and the 'down' state (around  $-65$  mV). It is noted that the time necessary for the transitions is much shorter than the time spent in either state, as in experimental observations (Shu, Hasenstaub, & McCormick, 2003).

The results have clearly demonstrated that spontaneous 'up' and 'down' transitions can be self-organized by STDP in a network of pyramidal neurons expressing the H-current and inhibitory interneurons. Fig. 2c displays the average firing rates of excitatory neurons and inhibitory neurons in the course of learning. During the initial 2000 ms, both neurons show very high-frequency firing and no bi-stable transitions appear. After this initial stage, the neurons exhibit the spontaneous 'up' and 'down' transitions and this

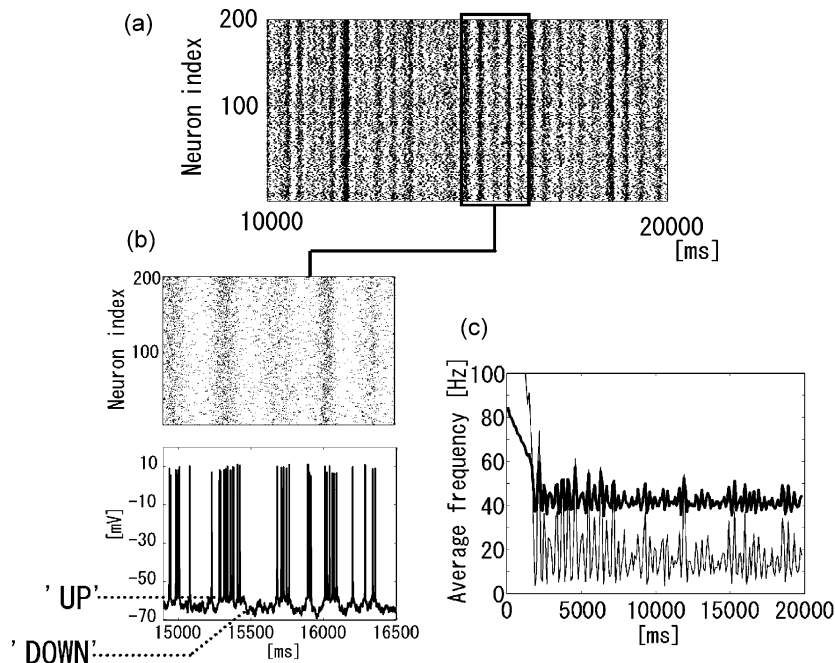


Fig. 2. The typical activity pattern exhibited by the self-organized neural circuit. (a) Spike raster of 200 excitatory neurons show alternating active and silent epochs. (b) Part of spike raster is magnified and the membrane potential fluctuations are shown for an excitatory neuron. The latter shows spontaneous 'up' and 'down' transitions. (c) The average firing frequencies of pyramidal neuron and interneuron ensembles. The two neuronal ensembles show synchronous rate changes.

firing behavior remains to be stable once it is induced in the network. It can be clearly seen that the two neuron types show coincident state transitions from low-frequency firing states to high-frequency firing states ('up' state in the excitatory cells). It is also noticed that the interneurons fire at much higher frequencies than the excitatory neurons. We have found that in the absence of interneurons, the excitatory neurons would always stay in the 'up' state and would fire at very high frequencies.

### 3.3. Mechanism of the 'up' and 'down' transitions

We demonstrate that the 'up' and 'down' transitions occur in the present model through an interplay between the recurrent excitation and an intrinsic property of excitatory neurons. If the excitatory-to-excitatory recurrent synapses are eliminated, the 'up' and 'down' transitions disappear and neurons display only the spontaneous firing caused by noisy background input (Fig. 3a). Therefore, the recurrent

excitation is crucial for the bi-stable state transitions as well as persistent firing of neurons.

In Fig. 3b, the conductance of the H-current is decreased until it finally vanishes. As the conductance is decreased, the distinction between the active epochs and silent epochs becomes less clear. This is because the time which the individual neurons spend in the 'up' state becomes shorter and shorter. The results seem to indicate that activation of the H-current during the up state is crucial for the maintenance of the 'up' state and the high-frequency firing during it.

### 3.4. Asynchronous spikes during the synchronous 'up' states

Many experimental studies have revealed that 'up' and 'down' transitions occur synchronously (Anderson, Lampl, Reichova, Carandini, & Ferster, 2000; Cossart et al., 2003; Lampl et al., 1999; Shu et al., 2003; Stern et al., 1998). It has been, however, suggested that the neuronal firing during the 'up' state is asynchronous (Shu et al., 2003). As mentioned

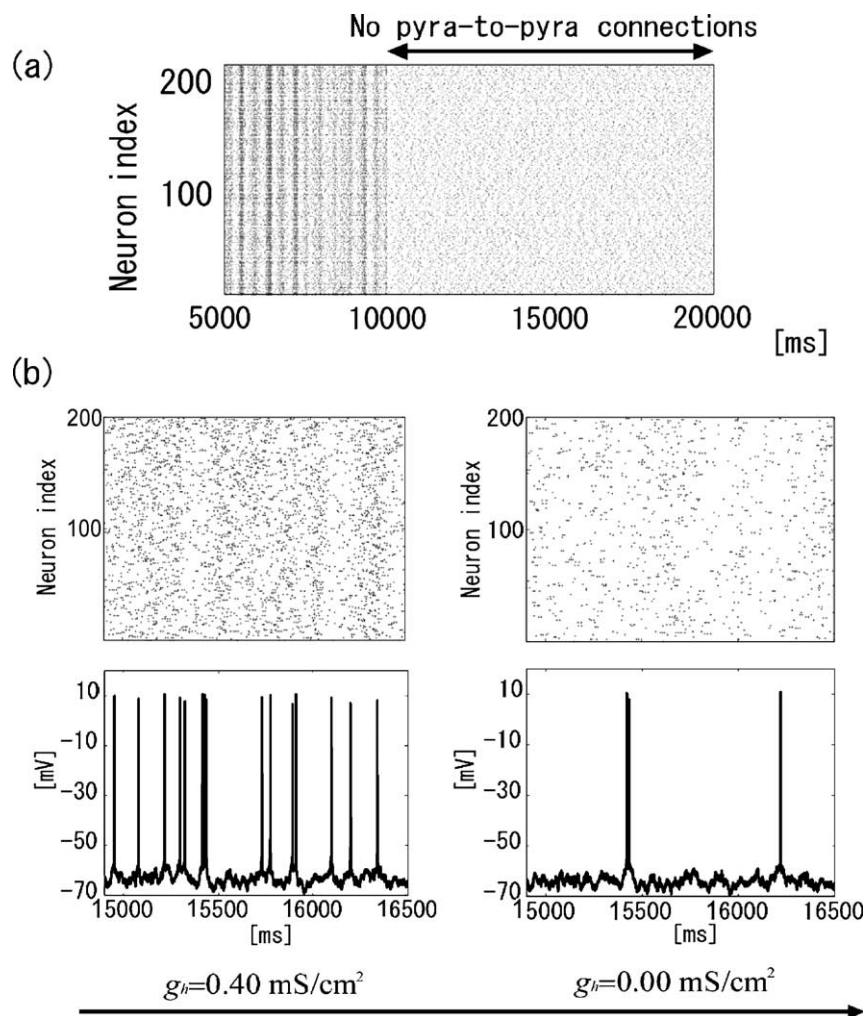


Fig. 3. The mechanisms of the spontaneous state transitions. (a) Pyramidal-to-pyramidal connections are eliminated at 10,000 ms. The spontaneous transitions disappear. (b) The blockade of the H-current makes the mean life time of the 'up' state shorter. As a result, less number of spikes can be generated during each 'up' state.

previously, results of our simulations show a similar tendency of asynchronous spike firing in the neuronal population during the ‘up’ state. Although the synchronicity property often depends crucially on an intrinsic property of neurons, the present results indicate that asynchronous firing can occur during the ‘up’ state in recurrent networks of cortical neurons.

## 4. Discussions

### 4.1. Functional role of STDP

The synapses modifiable by STDP show a bimodal weight distribution that represents competition between the synapses. This synaptic competition is crucial for the regulation of activity of a postsynaptic neuron (Song et al., 2000). Synaptic competitions have been confirmed in the asynchronous persistent firing self-organized by STDP, although the competition seems to be weakened in recurrent networks (Kitano et al., 2002a). Despite of our employment of the same learning rule as in these studies, synaptic competition was not apparent in the present simulations (Fig. 1b). In general, whether synaptic competition occurs in the present STDP learning is determined by the degree of correlations between presynaptic and postsynaptic spikes (van Rossum, Bi, & Turrigiano, 2000; Rubin, Lee, & Sompolinsky, 2001). In addition, the degree of such correlations depends crucially on an intrinsic property of postsynaptic neuron (Câteau & Fukai, 2003). Whether the correlations are weakened by the intrinsic neuronal property characterized by complex dynamics of ionic currents or certain dynamical effects of recurrent input must be clarified by further studies.

### 4.2. Possible improvements in neuronal and network models

In the present study, we employed a single-compartment model including sodium current, delayed-rectifier, transient and slowly activating potassium currents, and hyperpolarization-activated cation current for pyramidal neurons. In real cortical neurons, however, many other types of ionic current are also expressed. In fact, in vivo cortical pyramidal neurons show various activity patterns depending on the cell’s intrinsic property (Dégenétais, Therry, Glowinski, & Gioanni, 2003).

For example, slowly inactivating potassium channel (KS) and persistent sodium channel are well known in cortical neurons. In particular, the latter was crucial for spontaneous activity of in vitro cortical neurons expressing the H-current (Mao et al., 2001). It has also been reported that neuromodulator-like dopamine enhances the persistent sodium current and suppressed the KS current (Yang & Seamans, 1996), and that these effects may be crucial for stabilizing persistent activity of cortical networks (Durstewitz, Seamans, & Sejnowski, 2000). It is also known that

the H-current is strongly expressed only at the distal dendrites in pyramidal cells, which cannot be described by the present single-compartment model. Thus, it seems necessary to investigate the self-organizing process in networks of more realistic neuron models. In our preliminary simulations of a similar network of more realistic neuron models, the qualitative results of the present paper are almost unchanged (data not shown). Results of such an extended study will be reported elsewhere.

In conclusion, the present computational study has revealed that STDP may lead to self-organization of the spontaneous ‘up’ and ‘down’ transitions such as observed in cortical neurons. In the self-organized network, activity of neurons shows synchronous transitions to the ‘up’ state and the H-current expressed in the model pyramidal cells play an active role in the retention of the ‘up’ state. Thus, the spontaneous ‘up’ and ‘down’ transitions are generated by the cooperation of a reverberating excitation and the intrinsic property of single neurons.

## Appendix A

Excitatory pyramidal neurons are modeled as follows. The channel kinetics of  $I_h$ ,  $I_A$  and  $I_M$  follow as those given in Huguenard and McCormick (1992), Wang (1994) and Yamada et al. (1989), respectively. The maximum conductances of those current are set as  $g_h = 0.8$  mS/cm<sup>2</sup>,  $g_A = 6.9$  mS/cm<sup>2</sup>,  $g_M = 0.62$  mS/cm<sup>2</sup>, respectively.

The gating variable  $n$  of the delayed-rectifier K<sup>+</sup> obeys  $dn/dt = \phi_n(n_\infty - n)/\tau_n$ , where  $\phi_n = 12$  in excitatory pyramidal neurons. Membrane capacitances of pyramidal and interneurons are  $C_{\text{pyr}} = 3.0$   $\mu\text{F}/\text{cm}^2$  and  $C_{\text{inter}} = 1.2$   $\mu\text{F}/\text{cm}^2$ . Except for these modifications, we use the same kinetic equations and parameter values as given in Traub et al. (1993) for the spike-generating  $I_{\text{Na}}$  and  $I_{\text{DR}}$  currents.

The synaptic current and the synaptic conductance obey the flowing first-order kinetics defined as

$$I_{\text{syn}} = g_{\text{LEAK}}g(t)r(t)(V - E_{\text{syn}}),$$

$$\frac{dr}{dt} = -\frac{r}{\tau_{\text{decay}}} + \delta(t - t_{\text{pre}}),$$

where  $\tau_{\text{decay}} = 5$  ms and  $t_{\text{pre}}$  represents the time of presynaptic spikes. Both AMPA and GABA<sub>A</sub> receptor-mediated synapses obey the same kinetic equations. As mentioned in Section 2, the component  $g(t)$  is modified according to the STDP rule.

All neurons received a common applied current  $I_{\text{app}} = g_{\text{LEAK}}V_{\text{app}}$ , where  $V_{\text{app}} = 5$  mV. The background noise current is described as  $I_{\text{noise}} = \sqrt{2D}\eta(t)/\tau_{\text{pyr,inter}}$ , where  $\eta(t)$  represents a Gaussian white noise defined by  $\langle \eta(t)\eta(t') \rangle = \delta(t - t')$ . The time constants are given as  $\tau_{\text{pyr,inter}} = C_{\text{pyr,inter}}/g_{\text{LEAK}}$  and the diffusion constant is set

as  $D = 100 \text{ mV}^2 \text{ ms}$ . The time step is 0.05 ms in our simulations.

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