Cortical learning through the spike-timing-dependent plasticity modulated by intrinsic membrane potential fluctuation

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Abstract. Cortical neurons exhibit membrane fluctuations and spontaneous transitions between distinct different two states characterized by subthreshold level of membrane potential. It has been known by modeling study that the mechanism of the spontaneous fluctuation originates from not only reverberation in a cortical circuit but intrinsic factor at a single neuron level. The two-state transitions are widely found in many brain regions and these transitions typically occurred spontaneously and synchronously. However, its computational advantage is still unclear. In this study, we investigated synaptic learning for external inputs in a model neuron whose dynamics of membrane potential fluctuation was modulated through the modification of ionic channel dynamics. It was observed that the membrane fluctuation could modulate the learning property to sequential inputs through the spike-timing-dependent plasticity.

Keywords: Computational neuroscience, Neural network simulation, Learning and memory, Spike-timing-dependent plasticity, UP and DOWN states, Dynamical system

1. Introduction

Many electrophysiological studies found that neurons showed a membrane potential fluctuation in their subthreshold levels. The fluctuation is not inevitable perturbation leading to disadvantage but the active player in brain computation. Stern and colleagues revealed that striatum spiny neurons showed spontaneous and synchronous transitions between a depolarizing UP-state, which is just below spike threshold, and a resting DOWN state [1]. It was expected that synchronous UP-state transition contributes to formation of the cell-assembly character-
ized by neural population to process brain functioning achieved by their suprathreshold activity, that is, spike firing. The two-state transitions were widely observed in many cortical regions [2, 3, 4, 5, 6, 7, 8] and multi-regional interaction was also examined [9]. These subthreshold dynamics were considered as universal and fundamental process of neuronal computation.

Other experiments demonstrated the repeated activation of precisely-timed sequences of UP-transition with millisecond accuracy [10, 11]. Since such kind of sequences often ranged second order, the reactivation of neuronal population has been considered to play the role in bridge of time-scales between fast neuronal dynamics and slow cognitive process.

On the other hand, it was well known that many brain regions showed oscillation which typically originates from synchronous activity of neuronal population and such the oscillation is critical for brain function. For example, memory consolidation is mediated by hippocampal and neocortical interaction during non-REM (rapid eye movement) sleep. The sleep stage is also known as slow wave sleep because it is typically characterized by delta wave around or less than 1 Hz. Interestingly, recent cognitive neuroscience research on human reported that subjects who received transcranial magnetic stimulation (TMS) with delta frequency during non-REM sleep showed significant enhancement of their performance for episodic memory task [12]. More importantly, in vivo intracellular recording in unanesthetized animal revealed that neural origin of the delta wave during non-REM sleep was synchronous two-state transitions of neocortical neurons. Frequency of the two-state transitions corresponds with frequency of delta wave and these subthreshold transitions disappear and they are replaced with continuous UP state during an awake period [13]. Furthermore, it was found that UP-transitions in neocortex and sharp wave ripple in hippocampus interacts during non-REM sleep [14]. These results indicate that two-state transition is critical in memory consolidation during non-REM sleep. However, its functional role in local circuit dynamics such as synaptic learning is still unclear. Here, we computationally examined a functional role of the UP-DOWN transitions for synaptic learning mediated by the spike-timing-dependent plasticity (STDP) for multiple synapses as external sensory inputs. As a result, it is demonstrated that dynamical change of two-state transitions could significantly modulate the STDP learning for spatio-temporal patterns.

2. Methods

The network model consisted of a single pyramidal neuron and input sources to the model neuron (Fig. 1A). Pyramidal neuron is described as a multi-compartment model with various biologically realistic ionic channels because a focus in present research is not morphological but dynamical property of cortical neuron. Input sources are modeled as ten synapses terminating and continuously delivering multiple spikes toward the neuron. Weight of the synapses is modified through the spike-timing-dependent plasticity (STDP). We investigate the weight
Our model neuron is a two-compartment (soma and dendrite) model of a pyramidal neuron [15]. In particular, we employed a model involving various ionic channels and some of them contribute to showing UP-DOWN transitions [16, 17]. Details of dynamics of gate variables and parameters obeyed as the formulation of previous study [17] except for a hyperpolarization-activated cation current $I_h$. We deprived $I_h$ in the present study since a small amount of $I_h$ leads to autonomous UP-transition even without external inputs [17]. The dynamics of the somatic potential $V_s$ and the dendritic potential $V_d$ are as follows:

$$C_mA_s \frac{dV_s}{dt} = -A_s(I_L + I_{Na} + I_K + I_A + I_{KS}) - g_{sd}(V_s - V_d) + I_{noise}, \quad (1)$$

$$C_mA_d \frac{dV_d}{dt} = -A_d(I_{Ca} + I_{KCa} + I_{Nap} + I_{AR}) - g_{sd}(V_d - V_s) + I_{noise} - I_{syn}, \quad (2)$$
where $C_m$, $A_x$, and $V_x$ are a membrane capacitance, surface area, and membrane potential, respectively. The soma involves the spiking currents $I_{Na}$ and $I_K$ with a leak current $I_L$, a transient potassium current $I_A$, a slowly inactivating potassium current $I_{KS}$, and a $Na^+$-dependent $K^+$ current $I_{KNa}$. A dendrite contains the channels for a high-threshold calcium current $ICa$, a calcium dependent potassium current $I_{KCa}$, a non-inactivating persistent sodium current $I_{NaP}$, and a non-inactivating inward rectifier potassium current $I_{AR}$. Both compartments receive the noise current: $I_{noise} = \sqrt{D} \xi$, where a variance of diffusion is $0.1 \text{mV}^2/\text{ms}$, and $\xi$ indicates Gaussian white noise in which $\mu = 0$ and $\sigma = 1$.

The model neuron receives synaptic input currents through $I_{syn}$. The synaptic current is described as follow: $I_{syn} = g_{AMPA} m_{AMPA} (V_d - V_{AMPA})$ where $g_{AMPA} = 8 \text{nS}$ and $V_{AMPA} = 0 \text{mV}$ are a maximum conductance and a reversal potential. $m_{AMPA}$ is a gate variable whose dynamics obey $dm_{AMPA}/dt = -m_{AMPA}/\tau_{AMPA} + \delta(t - t_k)$ where $\tau_{AMPA}$ is a time constant, and $\delta$ is the Dirac’s delta function meaning occurrence of a $k$-th spike.

The recent computational study has revealed that the maximum conductance of $I_{AR}$ ($g_{AR}$) controls duration of UP state [17] such that the membrane potential shows distinct two states, that is, UP-DOWN states in subthreshold level when $g_{AR}$ is large (Fig. 1B, upper), otherwise, UP-DOWN states are suppressed and model neuron shows a continuous UP state when $g_{AR}$ is low (Fig. 1B, lower). In our simulations, $g_{AR}$ was an order parameter which modulates duration of the UP state through the intrinsic mechanism. Behaviors of the model neuron and synapses are investigated for various $g_{AR}$ linearly ranging from 0 to 54 $\mu\text{S/cm}^2$.

2.2. Network organization

Multiple synaptic inputs sources are introduced as a driving force simply mimicking external sensory stimuli to a model neuron. Synaptic currents caused by a pre-synaptic spike are described as first order kinetics which is traditional description of AMPA. In present simulation, ten synapses project and transmitted a spike train onto a pyramidal neuron. An input packet of spike train consists of sequential ten spikes from entire synapses with 10 ms fixed time delays. Input packets were repeatedly applied onto the dendrite of a model neuron during 1,000 s. Note that the inter-packet intervals were 400 ms which corresponded to the intervals of first spikes in individual packet. A synapse coupled an input source and the dendrite of a neuron together. All the synapses were plastic, in other words, the efficacy of synaptic transmission was modified through a learning rule. We periodically applied the input packets including repetitive sequential spikes onto a neuron. Spikes from smaller ID were always transmitted earlier than that from larger ID. Driven by the repetitive application of spatio-temporal spike sequence, plastic synapses dynamically modify their weights through the STDP.
2.3. Synaptic learning rule

All the synapses had plasticity and changed their weights obeying synaptic a learning rule. In this study, we employed one of the well-known learning methods, namely the spike-timing-dependent plasticity (STDP) [18, 19]. The STDP dynamically modifies a synaptic weight as a time-dependent manner. The STDP has been observed in many cortical regions with a variety of its time-dependency. Theoretical studies have suggested that the STDP has critical roles for a neural computation.

The STDP modifies connection strength, that is, synaptic weight based on the time difference between pre- and post-synaptic spikes. In particular, we used an additive-STDP rule in which an amount of modification does not depend on current weight value. Significance of the additive-STDP was proposed and investigated from computational aspect [19]. In a simple feedforward network, the additive-STDP typically reaches synaptic competition in its equilibrium state. The competition mechanism always pushes entire synapses toward extremely high (upper bound of weight) or low (zero weight) values. In other words, all synapses have to be a winner or a loser in their final state.

In the present study, the STDP formulation obeyed that by Gilson et al. [20]. Synaptic modification is described as follow: \( w_i \leftarrow w_i + \Delta w_i \), where \( w_i \) is a current synaptic weight of a synapse between a pre-synaptic input source \( i \) and a post-synaptic neuron, and \( \Delta w_i \) is an amount of weight modification. The amount at one modifying is derived from the equations:

\[
\Delta w_i = \eta(1 + \xi)w(\Delta t),
\]

\[
w(\Delta t) = \begin{cases} c_+ \exp \left(-\frac{\Delta t}{\tau^+}\right) & (\Delta t \geq 0) \\ c_- \exp \left(-\frac{\Delta t}{\tau^-}\right) & (\Delta t < 0) \end{cases},
\]

where \( \eta = 0.05 \) stands for learning rate. The zero-meaned Gaussian random variable \( \xi \) provides physiological variability to a modification. The window function \( w(\Delta t) \) decides whether the additive-STDP strengthens or weakens a synapse depending on the time difference \( (\Delta t = t_{\text{post}} - t_i) \) between a pre-synaptic spike from \( i \)-th synapse \( (t_i) \) and a post-synaptic spike \( (t_{\text{post}}) \)
2.4. Simulation environment

We performed numerical simulations with the neuron simulator library Brian2 in Python language. The simulator solved the differential equations with the white noise, that is, the stochastic differential equations by using the Euler-Maruyama method. We set a simulation time as 1,000 s to make the dynamics of synaptic weights converged in all parameters. A time step of integration was set to 0.01 ms.

3. Results

3.1. Dynamics of synaptic weights

The two neurons which a $g_{AR}$ value is extremely different exhibited different dynamics of synaptic weights. In the case that $g_{AR} = 0 \mu S/cm^2$ (hereinafter referred to as smallest-$g_{AR}$), the synaptic competition rapidly acted and all the synapses took their stationary value until the several tens of seconds (Fig. 2, lower left). As a result, a synaptic weight converged to the maximum or minimum value: a winner or loser. This is because the smallest-$g_{AR}$ neuron is potentially easy to fire due to its depolarized potential. Therefore, the synaptic weights are frequently modified by the spike-timing-dependent learning, and the synaptic weights became winner or loser in early stage of a simulation. On the other hand, synaptic weights on the neuron which $g_{AR} = 54\mu S/cm^2$ (hereinafter referred to as largest-$g_{AR}$) grew up more slowly.

Figure 2: Dynamics of synaptic weights. The left panels display time course of a weight value dynamically modified by the plastic rule. The x- and y-axis indicate time and normalized synaptic weight. Each color corresponds to an individual synaptic weight identified by an input ID. The right panels show stationary values of synaptic weights at the final state.
In the early stage, the STDP gradually strengthened all the synapses. As a result, almost all the synapses once became a winner. After the half of the entire simulation, some synapses eventually fell into a loser. Final states of synaptic modification revealed a learning property of two-state transitions for the sequential inputs. The largest-$g_{AR}$ neuron made the synapse conveying earlier spikes, #1 to 8, a winner (Fig. 2, upper right). This result reflected the causality of the STDP learning between event timing of an input source and the post-synaptic neuron. In other words, cooperation of spikes from input #1 to 8 leads to a post-synaptic firing. Therefore, the STDP selectively potentiated the synapses of earlier input sources. The smallest-$g_{AR}$ neuron also strengthened its synapses. However, the number of synapses was relatively fewer than those of the largest-$g_{AR}$ (Fig. 2, lower right). It means that the smallest-$g_{AR}$ neuron only needed fewer synapses to fire the post-synaptic neuron.

We investigated not only the largest- and smallest-$g_{AR}$ but also intermediate $g_{AR}$ conditions. As a result, we found that a range of winner synapse was broaden as $g_{AR}$ was large. Figure 3 summarizes a final state of synaptic weights in various $g_{AR}$ values. The number of winner synapse increased as $g_{AR}$ increased. The data suggested that a neuron showing the UP-DOWN transitions could capture a large part of a spike sequence, being sensitive for a broader spatial range. The range of sensitivity was modified by the intrinsic mechanism. In other words, the model neuron could alternate how many synapses should be potentiated through the modulation of ionic property generating two-state transitions (Fig. 3).
3.2. Fluctuating synapse

It was well known that the additive-STDP leads to bimodal distribution in synaptic weight through synaptic competition mechanism [19]. In the present study, almost all the synapses fell into upper (winner) or lower (loser) bound. The ratio of the winner and loser was modulated by the mode of a post-neuron. Importantly, boundary synapses locating between winner and loser showed continuous fluctuation during entire simulation as if the synapse succeeded to escape from strong synaptic competition by STDP (Fig. 4). We quantified the fluctuating synapse by Shannon entropy [21]. The entropy was calculated from the probability of staying weight value for the last 300 s. The fluctuating synapses (FS) showed high entropy in their weight value. The ID of FS with high entropy varied corresponding to $g_{AR}$ value and behaved like threshold of winner and loser groups (Fig. 5).

4. Conclusion

In this study, we employed the neuron model which reproduces well the two-state transitions,
and allows us to modify duration of the UP state through the internal variable, $g_{AR}$. Significant UP-DOWN transitions appeared in subthreshold membrane potential of the model neuron when $g_{AR}$ is large. On the other hand, the model neuron showed continuous UP-state in small $g_{AR}$ condition. The model neuron selectively potentiated a target synapse through the modulation of its intrinsic mechanism, gradual change between the two-state transitions and continuous UP-state, even external inputs were identical. In order to elicit a spike, the model neuron with the two-state transitions requires more synaptic input currents compared with the one showing continuous UP-state. In other words, the former requires more temporal integration to reach the threshold due to its longer resting states. However, we could not reproduce our result presented here in a simple model such as a leaky integrate-and-fire neuron (data not shown). Therefore, it was suggested that nonlinear dynamics of various ionic channels and their interaction is more critical than integration time of synaptic input currents for the mode-dependent selective learning.

The STDP rule employed in the present study immediately reflects temporal order to weigh modification. As a result, selectivity of synaptic learning is not sufficient in our simulation because many synapses fell into winner or loser even some fluctuating synapses appeared. It might be caused by too much simplification of input spike sequences. In our preliminary simulation, the selectivity in mode-dependent synaptic learning increases under more biologically plausible inputs such that the model neuron could potentiate an arbitral

Figure 5: Quantification of fluctuating synapse by the entropy of weight variability. A row and column label mean a $g_{AR}$ value and an input ID. Color temperature stands for entropy calculated from a weight histogram. Note that high entropy means the synapse which experienced rich variety of weight value during learning.
In the present study, we examined a simple feedforward network of a post-neuron exhibiting the two-state transitions. In a future study, the mode-dependent synaptic learning in a recurrent network should be examined with rich variety in spatio-temporal patterns of external inputs.

The present results might suggest that the two-state transitions contribute to selective learning for temporal sequences which relate with memory consolidation during non-REM sleep.

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References

[1] E. A. Stern, D. Jaeger, C. J. Wilson: Membrane potential synchrony of simultaneously recorded striatal spiny neurons in vivo, *Nature*, 394:6692 (1998), 475.

[2] I. Lampl, I. Reichova, D. Ferster: Synchronous membrane potential fluctuations in neurons of the cat visual cortex, *Neuron*, 22:2 (1999), 361–374.

[3] J. Anderson, I. Lampl, I. Reichova, M. Carandini, D. Ferster: Stimulus dependence of two-state fluctuations of membrane potential in cat visual cortex, *Nature Neuroscience*, 3:6 (2000), 617.

[4] R. Cossart, D. Aronov, R. Yuste: Attractor dynamics of network UP states in the neocortex, *Nature*, 423:6937 (2003), 283.

[5] C. C. H. Petersen, T. T. G. Hahn, M. Mehta, A. Grinvald, B. Sakmann: Interaction of sensory responses with spontaneous depolarization in layer 2/3 barrel cortex, *Proceedings of the National Academy of Sciences*, 100:23 (2003), 13638–13643.

[6] R. N. S. Sachdev, F. F. Ebner, C. J. Wilson: Effect of subthreshold up and down states on the whisker-evoked response in somatosensory cortex, *Journal of Neurophysiology*, 92:6 (2004), 3511–3521.

[7] Y. Shu, A. Hasenstaub, D. A. McCormick: Turning on and off recurrent balanced cortical activity, *Nature*, 423:6937 (2003), 288.

[8] S. Fujisawa, N. Matsuki, Y. Ikegaya: Single neurons can induce phase transitions of cortical recurrent networks with multiple internal States, *Cerebral Cortex*, 16: (2006), 639–654.

[9] Y. Isomura, A. Sirota, S. Ozen, S. Montgomery, K. Mizuseki, D. A. Henze, G. Buzsáki: Integration and segregation of activity in entorhinal-hippocampal subregions by neocortical slow oscillations, *Neuron*, 52:5 (2006), 871–882.

[10] B. Q. Mao, F. Hamzei-Sichani, D. Aronov, R. C. Froemke, R. Yuste: Dynamics of
spontaneous activity in neocortical slices, *Neuron*, 32:5 (2001), 883–898.

[11] Y. Ikegaya, G. Aaron, R. Cossart, D. Aronov, I. Lampl, D. Ferster, R. Yuste: Synfire chains and cortical songs: temporal modules of cortical activity, *Science*, 304:5670 (2004), 559–564.

[12] L. Marshall, H. Helgadóttir, M. Mölle, J. Born: Boosting slow oscillations during sleep potentiates memory, *Nature*, 444:7119 (2006), 610.

[13] M. Steriade, I. Timofeev, F. Grenier: Natural waking and sleep states: a view from inside neocortical neurons, *Journal of Neurophysiology*, 85:5 (2001), 1969–1985.

[14] A. Sirota, J. Csicsvari, D. Buhl, G. Buzsáki: Communication between neocortex and hippocampus during sleep in rodents, *Proceedings of the National Academy of Sciences*, 100:4 (2003), 2065–2069.

[15] P. F. Pinsky, J. Rinzel: Intrinsic and Network Rhythmogenesis in a Reduced Traub Model for CA3 Neurons, *Journal of Computational Neuroscience*, 1:1-2 (1994), 39–60.

[16] A. Compte, M. V. Sanchez-Vives, D. A. McCormick, X. J. Wang: Cellular and network mechanisms of slow oscillatory activity (< 1 Hz) and wave propagations in a cortical network model, *Journal of Neurophysiology*, 89:5 (2003), 2707–2725.

[17] S. Kang, K. Kitano, T. Fukai: Structure of spontaneous UP and DOWN transitions self-organizing in a cortical network model, *PLOS Computational Biology*, 4:3 (2008), e1000022.

[18] G. Q. Bi, M. M. Poo: Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type, *The Journal of Neuroscience*, 18:24 (1998), 10464–72.

[19] S. Song, K. D. Miller, L. F. Abbott: Competitive Hebbian learning through Spike-timing-dependent synaptic plasticity, *Nature Neuroscience*, 3:9 (2000), 919.

[20] M. Gilson, T. Fukai: Stability versus neuronal specialization for STDP: long-tail weight distributions solve the dilemma, *PLOS ONE*, 6:10 (2011), e25339.

[21] C. E. Shannon: A mathematical theory of communication, *Bell system technical journal*, 27:3 (1948), 379-423.