Effect of Dendritic Backpropagating Action Potential on Neural Interaction

Toru Aonishi [a,*] Hiroyoshi Miyakawa [b] Masashi Inoue [b]
Masato Okada [a,c]

[a] *Brain Science Institute, RIKEN, 2-1 Hirosawa, Wako-shi 351-0198, Japan*

[b] *Department of Life Science, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachiouji 192-0392, Japan*

[c] *PRESTO, Japan Science and Technology Agency, Wako-shi 351-0198, Japan*

Abstract

We elucidate the effect of dendritic backpropagating action potentials on neural interactions. First, we reduce a solvable oscillator model with passive dendrites to phase description. We show that backpropagating action potentials change the stability structure of the system from monostable to bistable. Next, we obtain phase response curves of a model hippocampal pyramidal neuron with realistic morphology and electroresponsiveness by running a compartmental simulator NEURON. We demonstrate that this realistic model also has such bistability; furthermore, A-type K channels in the dendrite facilitate the bistability.

Key words: dendrite, backpropagating Action Potential, A-channel, oscillator

It has been generally recognized that electrical signals within a nerve cell flow in a *feed-forward* direction: from the input sites (usually the dendrite) to the output sites (usually the soma). This hypothesis is referred to as the principle of dynamic polarization [1]. Almost all formal neuron models in theoretical studies are based upon this hypothesis. In such formal neuron models, the dendrite plays a role of just a cable transmitting synaptic input signals to the soma. However, the properties of the dendrite are more complicated than those of the formal neuron model. It has been reported that many kinds of voltage-activated ion channels are highly distributed over the dendrite, and that action potentials can be generated in the dendrites [2]. Under some conditions, action potentials are initiated at the dendrite by strong EPSP, and

* Corresponding author.
Email address: aonishi@brain.riken.jp (Toru Aonishi).

propagate to the soma (forward propagation). Under some conditions, action potentials are initialized at the soma even by strong EPSP, and propagate to the dendritic input sites (backpropagation). Clearly, the dynamics of the dendrite are complex. In this paper, we focus on the role of the backpropagation in the information processing of a single nerve cell. Backpropagation implies that output signals are fed back to the input sites. There is a possibility that in this case, a single nerve cell might be able to acquire a capacity of *active* information processing through the modification of synaptic responses by backpropagating action potentials. There are many reports on the relationship between backpropagating action potential and postsynaptic potential [3–6]. All these reports have focused on the amplification of backpropagating action potential and shunting inhibition of postsynaptic potential that are caused by interference between these two potentials. If the temporal coding hypothesis (that the information is coded in spike timing) is accepted, any discussion on neural information processing should focus on the timing modification of action potential initiation by the backpropagation rather than the amplification/inhibition of those potentials.

We analyze the impact of the spike-timing modification by backpropagation on neural interaction and neural cooperative behavior. We measure in regular oscillatory states the phase modification of action potential initiation as a function of relative timing between action potential initiation and postsynaptic potential generation. First, we reduce a solvable oscillator model with passive dendrites to a phase description. Our model is simpler than previous models[7]. We can cleanly show that backpropagating action potentials change the stability structure of the system. Next, we derive phase response curves of a compartment model with active dendrites in simulations with the program NEURON. We demonstrate that this realistic model has a stability structure that is the same as that of the solvable model. In the simulations of our physiological experiments, we focused on the A-type K channels (A-channels), which are widely distributed over the dendrite of CA1 pyramidal neurons. It has been reported that the time constant of A-channel activation is short, and A-channels regulate the amplitude of the dendritic action potentials [8]. By comparing results from the compartment model to those of the solvable model, we describe A-channel functions that have not previously been reported.

We consider symmetrically-connected pair of simple neurons. The dynamics of the membrane potentials of the soma in the jth neuron ($j = 1,\ 2$) is expressed by the Stuart-Landau (SL) oscillator[9]:

$$\frac{dv_j^{\rm s}}{dt} = i\Omega v_j^{\rm s} + v_j^{\rm s}\left(1 - \frac{|v_j^{\rm s}|^2}{R^2}\right) + I_j^{\rm sd}, \tag{1}$$

where $v_j^{\rm s}$ is the state variable (a complex number), and $I_j^{\rm sd}$ represents an input

from the dendrite (a complex number). Ω is the natural frequency of two symmetric oscillators. When $I_j^{\rm sd} = 0$, the system has an unstable fixed point at $v_j^{\rm s} = 0$ and a stable limit-cycle orbit of R radius in the complex plane: $v_j^{\rm s}(t) = R\exp i\left(\Omega t + \phi_j\right),\ {}^\forall\phi_j \in \mathbf{R}/2\pi$. Here, the quantity ϕ_j, which depends only on the initial condition, is the phase of the jth oscillator.

Here, we treat two kinds of dendritic models, one with backpropagation and the other without. By comparing the backpropagation and non-backpropagation models, we elucidate the role of the dendritic backpropagation. In the backpropagation case, the dendrite, the synapse, and $I_j^{\rm sd}$ are expressed as

$$C_{\rm d}\frac{dv_j^{\rm d}}{dt} = -g_{\rm dl}v_j^{\rm d} - I_j^{\rm sd} + \epsilon s_k(E_{\rm s} - {\rm Re}\{v_j^{\rm d}\}), I_j^{\rm sd} = g_{\rm d}\left(v_j^{\rm d} - v_j^{\rm s}\right), \qquad (2)$$

$$\tau_{\rm s}\frac{ds_k}{dt} = -s_k + G\Theta(v_k^{\rm s}),\ G = \frac{g_{\rm s}}{\theta_2 - \theta_1},\ \Theta(x) = \begin{cases} 1 & \theta_1 < \arg x < \theta_2 \\ 0 & \text{otherwise} \end{cases}. \qquad (3)$$

Equation (2) represents the dynamics of the dendritic membrane potential approximated to a simple CR circuit (i.e., a first-order lag system). As Eq. (2) reveals, the dendrite has a strong input from the soma. Here, $v_j^{\rm d}$ is the membrane potential, $C_{\rm d}$ is the membrane capacitance, $g_{\rm d}$ is the conductance of the dendritic medium, $g_{\rm dl}$ is the leakage conductance of the dendritic membrane. The term containing coefficient ϵ is the synaptic current. s_k is the synaptic conductance, and E_s is the synaptic reversal potential. This term represents a perturbation, and the quantity ϵ controls the amplitude of the perturbation. Therefore, in this model, the dendrite is strongly driven by the soma and is weakly driven by the synapse. Equation (3) is the synaptic dynamics approximated to the first-order lag system and the threshold element with hysteresis. This hysteresis can mimic the phase shift caused by the asymmetric form of action potentials.

In the non-backpropagation case, the dendrite, the synapse, and $I_j^{\rm sd}$ are expressed as

$$C_{\rm d}\frac{dv_j^{\rm d}}{dt} = -(g_{\rm d} + g_{\rm dl})v_j^{\rm d} + \epsilon s_k E_{\rm s},\ I_j^{\rm sd} = g_{\rm d}v_j^{\rm d},\ \ \tau_{\rm s}\frac{ds_k}{dt} = -s_k + G\Theta(v_k^{\rm s}), \quad (4)$$

where all parameters are equal to their counterparts in the backpropagation model. As Eq. (4) reveals, the dendrite does not receive an input from the soma, thus the dendrite is only driven by the synapse. This model has *feed-forward* information flow, the same as in formal neuron models.

In our model, there is an *adjoint* which can be explicitly obtained as $\Phi_j^*(t) = [iA\exp i(\tilde{\Omega}t + \phi_j - \psi),\ i\exp i(\tilde{\Omega}t + \phi_j)]^T$. Taking the inner product between $\Phi_j^*(t)$ and the perturbation, we obtain a pair of phase equations[9]. Then, using a new variable defined as $\phi = \phi_1 - \phi_2$, we can unite a pair of phase equations

into one equation:

$$(1 + C_{\rm d}A^2 \cos 2\psi)\frac{d\phi}{d\tau} = \Gamma(\phi), \tag{5}$$

$$\Gamma(\phi) = A^2 A^{(2)} \cos(\psi^{(2)}) \cos(\phi) \sin(\phi) - \frac{E_s}{\tilde{R}} A A^{(1)} \cos(\psi + \psi^{(1)}) \sin(\phi). \tag{6}$$

This equation describes the motion of a phase difference between two neurons. Here, $\Gamma(\phi)$ is referred to as a *phase coupling function*. In this case, the equilibrium states consist of in-phase locking, anti-phase locking, and two non-trivial solutions. The non-trivial solutions are caused by backpropagating action potentials.

Next, we show the result of the phase reduction from the non-backpropagation model. The phase difference equation is expressed as

$$\frac{d\phi}{d\tau} = \Gamma(\phi), \Gamma(\phi) = -\frac{E_s}{R} A A^{(1)} \cos(\psi + \psi^{(1)}) \sin(\phi). \tag{7}$$

In this case, the equilibrium states consist of in-phase locking and anti-phase locking.

Here, A, ψ, $\tilde{R}$, and $\tilde{\Omega}$ are satisfied with respect to the equations: $A \exp i\psi = g_{\rm d}/(i\tilde{\Omega}C_{\rm d} + g_{\rm d} + g_{\rm dl})$, $\tilde{\Omega} = \Omega + \beta g_{\rm d} A \sin\psi$, and $\tilde{R} = R\sqrt{1 - \beta g_{\rm d} + \beta g_{\rm d} A \cos\psi}$. A and ψ are self-consistently defined. This equation denotes the transfer function describing the frequency response of the dendrite. Such self-consistency means that the orbit of the SL oscillator driving the dendrite is modified by a reaction from the dendrite. $A^{(m)}$ and $\psi^{(m)}$ $(j = 1,\ 2)$, which correspond to coefficients of the Fourier expansion for the synaptic conductance S_k, are defined by $A^{(m)} = |J^{(m)}|$, $\psi^{(m)} = \arg J^{(m)}$, where $J^{(m)} = \frac{e^{i\xi^{(m)}}\sqrt{2(1-\cos m(\theta_2-\theta_1))}}{m\pi(\theta_2-\theta_1)} \frac{g_{\rm s}}{1+im\tau_{\rm s}\tilde{\Omega}}$, $\xi^{(m)} = \arg\{i\exp(-im\theta_2) - i\exp(-im\theta_1)\}$. $\xi^{(m)}$ denotes the phase shift caused by the hysteresis. At a fundamental frequency component, $J^{(1)}$ stands for the *describing function* in control engineering.

Finally, we compare Eqs. (6) and (7). The fundamental frequency component of Eq. (6) is equivalent to $\Gamma(\phi)$ in Eq. (7). This term represents a part of the neural interaction induced by the orthograde signal. On the other hand, the higher harmonics of Eq. (6) are unique to the backpropagation model. This term, which induces the bistability, is due to the modification of synaptic responses by backpropagating action potentials. We succeeded in separating the two parts of the neural interaction induced by the forward signal and the backward signal, respectively.

In the following simulations, we set the parameters as $\tau_{\rm s} = 6$, $g_{\rm s} = 0.1$, $E_s = -30$, $\theta_1 = 0.6 - \pi/5$, $\theta_2 = 0.6 + \pi/5$, $g_{\rm d} = 0.2$, $g_{\rm dl} = 0$, and $R = 80$. In this case, the inhibitory synapse was used to verify the theoretical results. To estimate the influence of dendritic performance on the bistability, we used three kinds of dendrite with different capacitances: $C_{\rm d} = 1$, $C_{\rm d} = 2$, and $C_{\rm d} = 3$. In

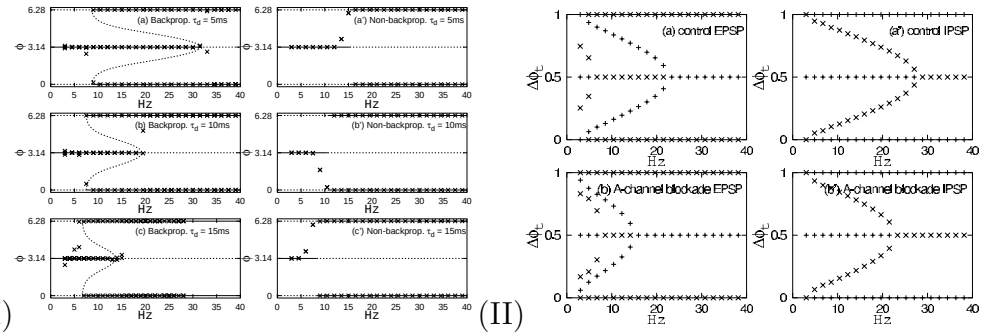

Fig. 1. Equilibrium states as a function of firing frequencies. (I) Solvable model. Solid curves denote stable equilibrium states, and dashed curves represent unstable equilibrium states. The mark $\times$ denotes results obtained from simulations. (II) Compartment model. The mark + denotes stable equilibrium states, and the mark $\times$ represents unstable equilibrium states.

this case, the time constants of these dendrites became $\tau_{\rm d} = 5$, $\tau_{\rm d} = 10$, and $\tau_{\rm d} = 15$, respectively. As Fig. 1 reveals, the dendritic backpropagation induces bistable states that consist of in-phase locking and anti-phase locking. Comparing Figs. 1(I) (a), (b), and (c), we found that as the dendritic time constant τ_d decreased, the region of bistability widened.

In the following simulations with the program NEURON, we used a compartment model of CA1 pyramidal neurons (as constructed by Migliore et al. (1999)[4]), which can reproduce the backpropagation. This model contains only Na, A-type K, and DR-type K channels. In the dendrites, the density of the A-type K channel increases linearly with the distance from the soma [3]. We investigated the phase response properties of a neuron in oscillatory states by using technically realizable methods of physiological experiments [10]. Figure 1(II) shows equilibrium states of phase locking between two neurons as a function of firing frequencies. Figures 1(II)(a) and (b) show the responses to EPSP in the control and A-channel blockade cases, respectively. Figures 1(II)(a') and (b') show the responses to IPSP. At high frequencies the compartment model with EPSP desynchronizes, but the one with IPSP synchronizes; however, at low frequencies both models have bistable states. The stability condition of IPSP models is opposite to that of EPSP models. Such behavior of the compartment models is consistent with that of the solvable model. As these figures reveal, if A-channels are blocked, the bistable regions narrow. This implies that A-channels facilitate the bistability in oscillatory states. Note that these results obtained from experiments for a single neuron qualitatively agree with the simulation results for two reciprocally connected neurons. It has been reported that the interneuronal network in the CA1 area of the hippocampus displays synchronization at frequencies greater than or close to 20 Hz, but not at frequencies significantly below this value [11]. This physiological result is consistent with the behavior of our models with IPSP.

It is well known that such bistability causes multiple phase clustering of the

neural population [12]. This phase clustering is a cogent hypothesis that explains the information representation binding distributed codes in the brain [14]. Moreover, the bistability can selectively control the synaptic plasticity. The in-phase locking facilitates the synaptic plasticity within the same cluster because the spike timing between pre-synapse and post-synapse is within a time window of the temporally asymmetric Hebb learning (TAH)[15]. On the other hand, the anti-phase locking blocks the synaptic plasticity, because the spike timing between pre-synapse and post-synapse is outside the TAH time window.

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