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● **RESEARCH ARTICLE**

Modulation of neuronal dynamic range using two different adaptation mechanisms

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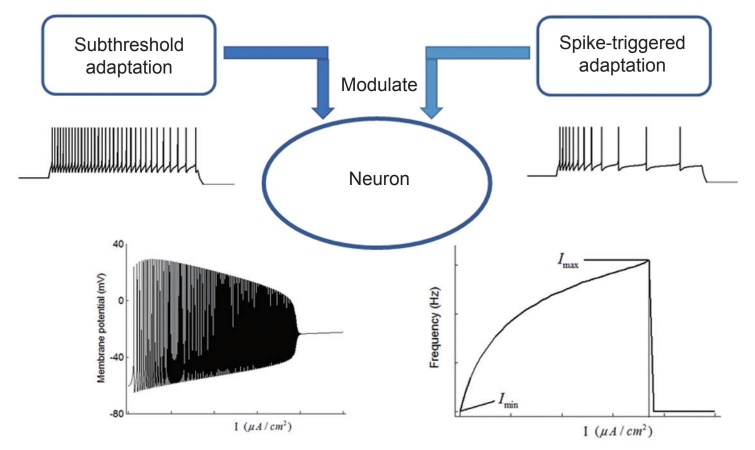
Graphical Abstract

Two different intrinsic adaptation currents modulate neuronal dynamic range



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Abstract

The capability of neurons to discriminate between intensity of external stimulus is measured by its dynamic range. A larger dynamic range indicates a greater probability of neuronal survival. In this study, the potential roles of adaptation mechanisms (ion currents) in modulating neuronal dynamic range were numerically investigated. Based on the adaptive exponential integrate-and-fire model, which includes two different adaptation mechanisms, *i.e.* subthreshold and suprathreshold (spike-triggered) adaptation, our results reveal that the two adaptation mechanisms exhibit rather different roles in regulating neuronal dynamic range. Specifically, subthreshold adaptation acts as a negative factor that observably decreases the neuronal dynamic range, while suprathreshold adaptation has little influence on the neuronal dynamic range. Moreover, when stochastic noise was introduced into the adaptation mechanisms, the dynamic range was apparently enhanced, regardless of what state the neuron was in, *e.g.* adaptive or non-adaptive. Our model results suggested that the neuronal dynamic range can be differentially modulated by different adaptation mechanisms. Additionally, noise was a non-ignorable factor, which could effectively modulate the neuronal dynamic range.

Key Words: *nerve regeneration; dynamic range; subthreshold adaptation; suprathreshold adaptation; noise; neuron; adaptive exponential integrate-and-fire model; ion currents; computer simulation; neural regeneration*

Introduction

In natural systems, the dynamic range serves as a good measure to characterize the capability of systems to discriminate between intensity of external stimulus. For example, in neuronal systems, this ability is important for biological cells to avoid danger. Thus, a larger dynamic range indicates a greater probability for neuronal survival (Gollo et al., 2012).

In past decades, several factors have been identified to modulate the dynamic range of neurons. Theoretical investigations suggest that a major effect of active dendritic conductance is to enhance the neuronal dynamic range, further revealing that neurons with larger dendritic trees may exhibit higher levels of dynamic range (Gollo et al., 2009). Through the construction of computational network models of mammalian retina, researchers have shown that electrical synapses between rod-rod, along with appropriate values of rod I_h (hyperpolarization-activated cation current) conductance, could enhance the dynamic range of retinal ganglion cells (Publio et al., 2009). Additionally, our recent model study demonstrated that intrinsic channel fluctuations exhibit a potent effect in modulating the neuronal dynamic range (Wang et al., 2013).

A prominent feature in biological neurons is their ability to adapt to processing afferent signals, called spike-frequency adaptation (SFA) (Chen et al., 2014; Wang et al., 2014c; Keller and Takahashi, 2015; King et al., 2015; Buonocore et al., 2016; Cui et al., 2016; Roach et al., 2016). Past studies focused on the ability of neurons to adapt to changes in incoming stimuli. In collision-detecting neurons, SFA has been shown to significantly contribute to neuronal tuning behaviors by selectively lowering the responses to non-preferred stimuli (Peron and Gabbiani, 2009). Experimental results on electroreceptor afferents showed that SFA helps separate transient signals from slower oscillatory signals in the background (Benda et al., 2005). Moreover, some studies suggested that SFA plays pivotal roles in defining neuronal population rhythms (Fuhrmann et al., 2002), spike timing precisions (Teka et al., 2014; Keller and Takahashi, 2015; Liu and Gollisch, 2015), and synchronous behaviors (Crook et al., 1998; van Vreeswijk and Hansel, 2001; Li et al., 2012; Pakdaman et al., 2014; Wang et al., 2014b; Norman et al., 2016).

Based on different generation mechanisms, adaptation can be classified into two types: subthreshold adaptation and suprathreshold (spike-triggered) adaptation. Previous reports demonstrated that these two adaptation mechanisms play differential functions in modulating neuronal spiking variability (Ladenbauer et al., 2014; Colliaux et al., 2015), regulating the correlation between sequential interspike intervals (Chacron et al., 2003; Shiau et al., 2015), and population synchronizations (Hansen and Dragoi, 2011; Ladenbauer et al., 2012).

In this study, we investigated how different SFA mechanisms (subthreshold and spike-triggered) influence the dynamic range of neurons. We also analyzed the effect of adaptation currents with stochastic fluctuations.

Materials and Methods

Neuronal model with adaptation currents

The model we employed to investigate was the adaptive exponential integrate-and-fire (aEIF) model, which has been widely used in previous model studies (Schwalger et al., 2010; Ladenbauer et al., 2012) to analyze SFA features in neurons (Hertäg et al., 2014; Buchin et al., 2016; Kobayashi and Kitano, 2016). The model includes the following equations and a reset condition (Schwalger et al., 2010; Ladenbauer et al., 2012):

$$C\frac{dV}{dt} = -g_L(V - V_L) + g_L\Delta_T e^{\frac{V-V_T}{\Delta_T}} - (w+\eta) + I \qquad (1)$$

$$\tau_w \frac{dw}{dt} = a(V - V_L) - w \qquad (2)$$

$$\tau_w \frac{d\eta}{dt} = -\eta + \sqrt{\frac{2\tau_w \sigma^2}{N_a}}\xi(t) \qquad (3)$$

with ancillary after-spike resetting according to the following equation (4):

$$\text{If } V \geq V_{cut}\text{, then } V \leftarrow V_r \text{ and } w \leftarrow w + b \qquad (4)$$

where C is the membrane capacitance, V is the membrane potential of neuron, w is the adaptation variable, η is an additional noise embedded in the adaptation dynamics, and I is the synaptic input. σ characterizes the noise intensity of the adaptation current, and $\xi(t)$ denotes the Gaussian white noise. a quantifies the conductance that mediates subthreshold adaptation, and b quantifies suprashreshold adaptation through the increment in Eq. (4). V_{cut} represents the "cutoff" or maximum value of V, and V_{r} represents the resting potential of V. Detailed explanations and values for the model parameters have been previously described (Schwalger et al., 2010; Ladenbauer et al., 2012). Specifically, g_L is the leak conductance, V_L is the leak reversal potential, Δ_T is the threshold slop factor, V_T is the threshold potential, τ_w is the adaptation time constant, and N_a is the number of stochastic adaptation channels.

To characterize the dynamic range of a neuron, we introduced a widely used measure adopted from (Publio et al., 2009):

$$\Delta = 10\log\left(\frac{I_{90}}{I_{10}}\right) \qquad (5)$$

where, I_{90} and I_{10} represent the stimulus intensity for which the firing frequency of neuron is 10 percent below the maximum and 10 percent above the minimum, respectively.

Simulation method

Simulations were performed using Matlab software (R2010a) (The MathWorks, Natick, MA, USA), and the first-order Euler algorithm was employed to calculate the membrane potential with a time integration of 0.25 ms.

Results

Firing behaviors of an aEIF neuron

Figure 1 demonstrates firing behaviors of an aEIF neuron under different adaptation states. When $a = 0$ and $b = 0$, the neuron fired continuously with nearly identical interspike intervals, and no adaptation phenomenon was observed (**Figure 1A**). However, if $b = 0$ and $a > 0$, or $a = 0$ and $b > 0$, the neuron fires spikes with apparent adaptation phenomena, suggesting that the firing frequency decreased and the interspike intervals were larger (**Figure 1B**, **C**).

Figure 2 presents diagrams showing the variation of firing frequencies under different values of a and b. Results showed that the increase of a maintained the slope (gain) of the F–I (frequency-stimulus) curve, but the rheobase changed from low to high (**Figure 2A**). Although the increase in b maintained the rheobase, the slope of the F–I

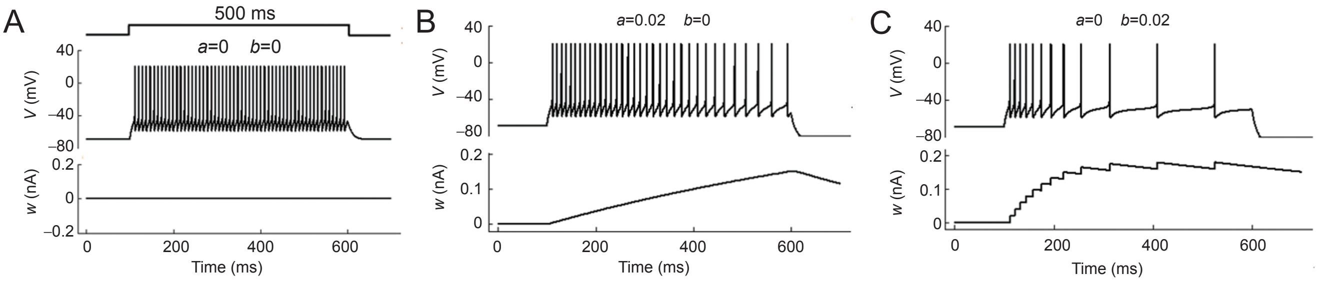

Figure 1 Membrane potential and adaptation current of a typical adaptive exponential integrate-and-fire neuron.
(A) Without adaptation ($a = b = 0$); (B) with subthreshold adaptation ($a = 0.02$, $b = 0$); (C) with suprathreshold adaptation ($a = 0$, $b = 0.02$).

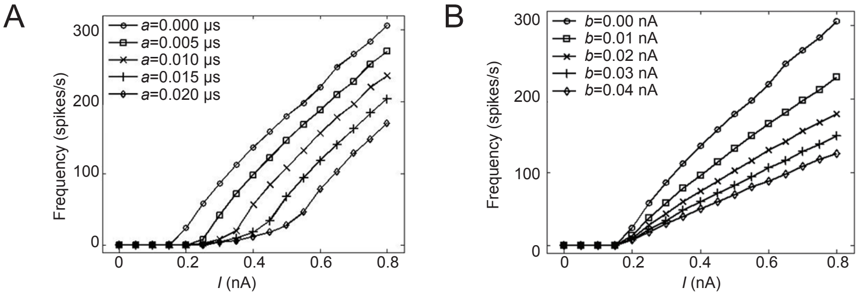

Figure 2 Frequency-stimulus (F–I) curves of adaptive exponential integrate-and-fire neuron under different adaptation mechanisms.
(A) Subthreshold adaptation ($b = 0$). (B) Suprathreshold adaptation ($a = 0$).

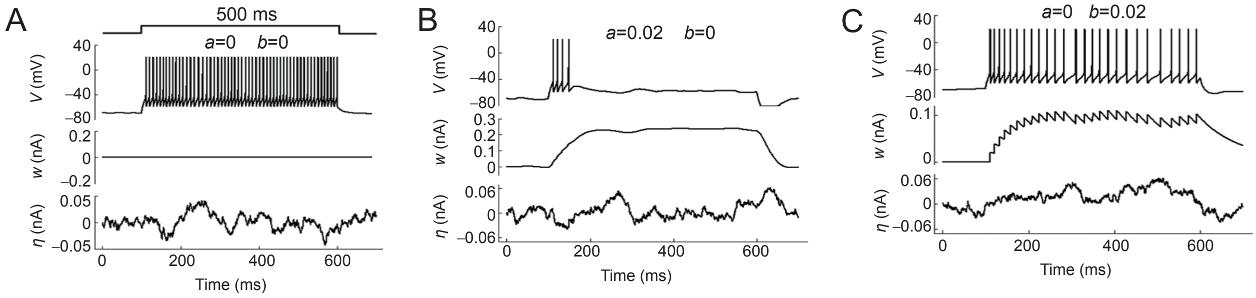

Figure 4 Membrane potential, adaptation current, and noisy current of an adaptive exponential integrate-and-fire neuron.
(A) Without adaptation ($a = b = 0$); (B) with subthreshold adaptation ($a = 0.02$, $b = 0$); (C) with suprathreshold adaptation ($a = 0$, $b = 0.02$).

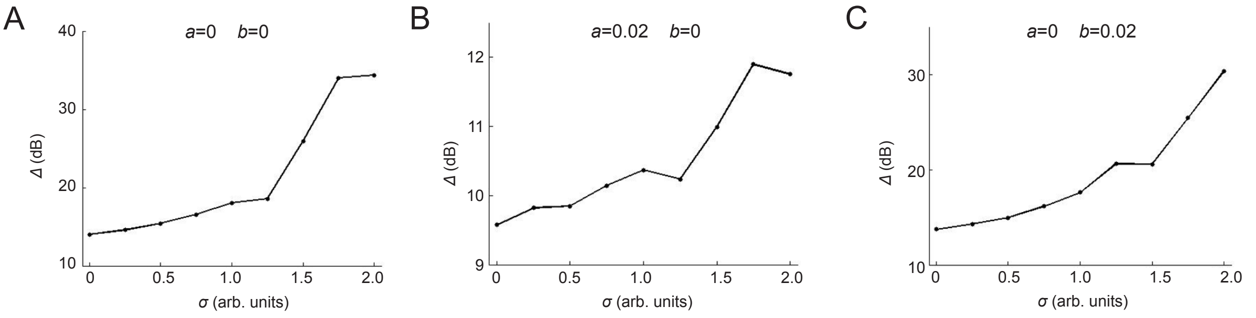

Figure 5 Variation of neuronal dynamic range with respect to noise intensity under different adapting states (repeating 50 times).
(A) Without adaptation ($a = b = 0$); (B) with subthreshold adaptation ($a = 0.02$, $b = 0$); (C) with suprathreshold adaptation ($a = 0$, $b = 0.02$). σ represents noise intensity of the adaptation current; Δ represents the neuronal dynamic range.

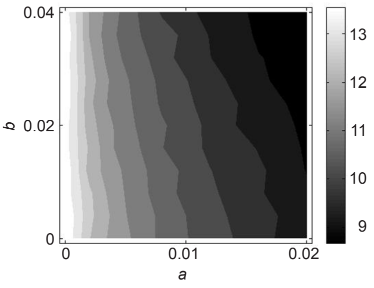

Figure 3 Two-parameter dependence of neuronal dynamic range on the two adaptation mechanisms.
The deeper color denotes the larger dynamic range.

curve changed from high to low (**Figure 2B**). The variations of the F–I curves, which were due to the adaptation variables a and b, were consistent previous reports (Ladenbauer et al., 2012).

Dynamic range of neurons under different adaptation mechanisms

The variations of neuronal dynamic range with respect to a and b are demonstrated in **Figure 3**. Results show that sub-

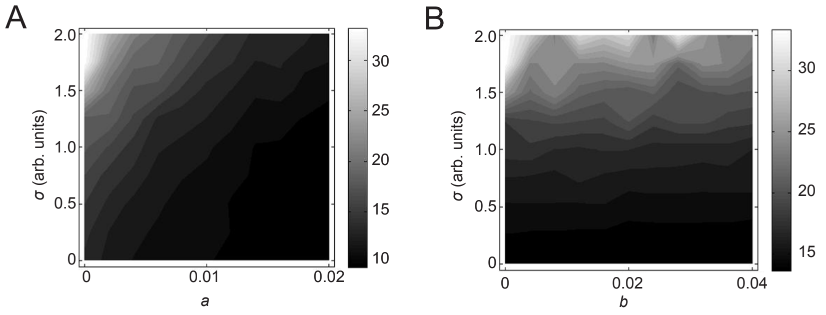

Figure 6 Two-parameter dependence of neuronal dynamic range on noise intensity and adaptation mechanisms (repeating 50 times).
(A) Noise intensity and subthreshold adaptation; (B) noise intensity and suprathreshold adaptation. The deeper color denotes the larger dynamic range.

threshold adaptation a always decreased the dynamic range of neurons, irrespective of the value of b; while suprathreshold adaptation b had little influence on the dynamic range when the value of a was small. However, when a was larger, the increase in b also reduced the neuronal dynamic range.

Influence of noise on neuronal dynamic range

Noise is ubiquitous in natural systems, especially in neuronal systems (Andreeva, 2015; Béhuret et al., 2015; Mokri et al., 2015; Antal and Herrmann, 2016; Lee et al., 2016; Zylberberg et al., 2016). A previous study suggests that noise embedded in adaptation currents affects the shaping interspike interval histograms of spike trains and neuronal correlations (Schwalger et al., 2010). Therefore, we analyzed whether adaptation noise influenced the neuronal dynamic range.

Figure 4 shows several examples of firing behavior of an aEIF neuron under different adaptation states. Compared with results from **Figure 1**, the effect of noise on neuronal spikes was significant. **Figure 5** shows that the variations in neuronal dynamic range varied with increased noise intensity. The presence of noise always enhanced the neuronal dynamic range, regardless of the neuronal state (adaptive or non-adaptive).

The two-parameter dependence of neuronal dynamic range on noise intensity and variables a and b is demonstrated in **Figure 6**. The reduction trend of neuronal dynamic range induced by an increased a was always observed, regardless of the value of noise intensity. However, for fixed values of a, the increased noise intensity reliably enhanced the dynamic range of neurons. Results from **Figure 6B** showed that the variation trend of neuronal dynamic range induced by an increased b always persisted when the noise intensity varied. However, for fixed values of b, the increased noise intensity also undoubtedly enhanced the neuronal dynamic range.

Discussion

SFA has been described as a prominent property in many neurons in the brain (Chen et al., 2014; Wang et al., 2014c; Keller and Takahashi, 2015; King et al., 2015; Buonocore et al., 2016; Cui et al., 2016; Roach et al., 2016). Previous studies revealed that SFA plays significant roles in neural information processing, *e.g.* modulating looming stimulus selectivity (Peron and Gabbiani, 2009), separating transient signals from background oscillations (Benda et al., 2005), mediating synchronous behaviors (Crook et al., 1998; van Vreeswijk and Hansel, 2001; Li et al., 2012; Pakdaman et al., 2014; Wang et al., 2014b; Norman et al., 2016), and reducing the variability of neuronal population activity (Schwalger et al., 2010). Results from the present study suggested that SFA exhibited crucial roles in regulating neuronal dynamic range. Moreover, the detailed regulations behave differently under the two adaptation mechanisms.

In the present paper, we performed a computational study to investigate whether adaptation mechanisms exerted influence on the dynamic range of biological neurons. Based on the aEIF model neuron, which includes two different adaptation mechanisms (subthreshold and suprathreshold), our results indicated that the two adaptation mechanisms had different roles in modulating the neuronal dynamic range: subthreshold adaptation decreased the dynamic range of neurons, while suprathreshold adaptation had little impact on the neuronal dynamic range. These results also suggested that noise embedded in the adaptation current efficiently adjusted the dynamic range of neurons, regardless of the neuronal state. Accordingly, these results could provide a better understanding about the factors that modulate the dynamic range of biological neurons.

Noise is a non-ignorable factor in natural systems, especially in neural systems (Andreeva, 2015; Béhuret et al., 2015; Mokri et al., 2015; Antal and Herrmann, 2016; Lee et al., 2016; Zylberberg et al., 2016). Previous studies have suggested a role for noise in processing neural information (Wang et al., 2014a; Nobukawa and Nishimura, 2015; Lücken et al., 2016). One recent study showed that noise embedded in adaptation currents performs critically in shaping the interspike interval histograms of spike trains and neuronal correlations (Schwalger et al., 2010). Results from the present study showed that adaptation currents with stochastic noise always enlarged the dynamic range of neurons.

It should be noted that we only discuss the effect of adaptation currents on modulating neuronal dynamic range in a single model neuron, but did not consider synaptic connections with many other neurons. In the nervous system, neurons are organized in networks or populations. Therefore, future studies should analyze the variations in dynamic range in neuronal networks.

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