



Intrinsic sodium currents and excitatory synaptic transmission influence spontaneous firing in up and down activities

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ABSTRACT

Periodic up and down transitions of membrane potentials are considered to be a significant spontaneous activity. These kinds of oscillations always accompany with some spontaneous firing in up state. Our previous theoretical studies mainly looked at the subthreshold up and down transitions and characteristics of up and down dynamics. In this paper, we focus on suprathreshold spontaneous firing of up and down transitions based on improved network model and its stimulations. The simulated results indicate that fast sodium current is critical to the generation of spontaneous neural firing. While persistent sodium current plays a part in spontaneous fluctuation. Both intrinsic fast and persistent sodium dynamics influence spontaneous firing rate and synchronous activity in up and down behavior. Meanwhile, blocking excitatory synaptic transmission decreases neural firing and reveals spontaneous firing. These simulated results are basically in accordance with experimental results. Through the observation and analysis of the findings, we prove the validity of the model so we can further adopt this model to study other properties and characteristics of the network, laying the foundation for further work on cortex activity.

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1. Introduction

Periodic up and down transitions of membrane potentials are considered to be a significant spontaneous activity. Neural electrophysiology experiments have shown that membrane potentials make spontaneous transitions between two different levels called up and down states (Parga & Abbott, 2007) in the primary visual cortex of anesthetized animals (Anderson, Lampl, Reichova, Carandini, & Ferster, 2000; Lampl, Reichova, & Ferster, 1999; Steriade, Nuñez, & Amzica, 1993) and also in the somatosensory cortex of unanesthetized animals (Petersen, Hahn, Mehta, Grinvald, & Sakmann, 2003).

These two states characterize the bistability of the membrane potentials, which is an important feature of neural system, accompanying with complex nonlinear dynamics (Jun & Tang, 2015; Ma & Tang, 2017; Ma & Xu, 2015). Further, recordings in vivo show up and down transitions occur synchronously (Lampl et al., 1999; Stern, Jaeger, & Wilson, 1998). In neurodynamical system, synchronized transition often indicates formation of spatial pattern (Gu & Pan, 2015; Tao, Gu, & Ding, 2017; Xiao, Gu, & Liu, 2016; Zhao & Gu, 2015).

Another characteristic of up and down transitions is that these kinds of oscillations always accompany with some spontaneous firing in up state. Intracellular recordings in vivo showed that the

slow oscillation is mediated by two phases: a period in which nearly all cell types within the cerebral cortex are depolarized and generate action potentials at a low rate (the so-called up state) interdigitated with a period of hyperpolarization and relative inactivity (the down state) (A, MV, DA, & X-J, 2003). So in this paper, our study adds to the literature describing the spontaneous firing of up and down activities.

We previously worked on spontaneous up and down transitions and tried to explain the dynamic mechanism involved in these transitions at the ionic channel level. At the single neuron level, we introduced three significant characteristics – bistability, directivity and spontaneity – of a single neuron up and down transitions (Xu & Wang, 2014)[p] and at the network level with constant connections, the cortical average membrane potential adopted as the local field potential (LFP) also showed up and down transitions over time (Xu & Wang, 2013). LFP is often used to describe the state of the whole cortex (Liu, Wang, Zhang, & Jiao, 2010; Wang & Zhang, 2007; Wang, Zhang, & Chen, 2009). Further, we put forward a neural network model of spontaneous up and down transitions, which reflects the in vivo mechanism better (Xu, Ni, & Wang, 2016). Using this model, we explored the factors that influence spontaneous periodic up and down transitions and synchronous transitions of up and down activities based on stimulations (Xu et al., 2016; Xu, Ni, & Wang, 2017).

In this paper, we focused on the spontaneous firing during up and down transitions and improved our previous work by adding fast sodium current to model neurons, to simulate the small

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amount of action potentials during up state. We found that the fast sodium dynamics was critical to the generation of spontaneous neural firing during up and down activities. While persistent sodium current played a role in spontaneous fluctuation. Both intrinsic fast and persistent sodium dynamics influence spontaneous firing rate and synchronous activity in up and down behavior. Meanwhile, blocking excitatory synaptic transmission decreased neural firing and revealed spontaneous firing. These simulated results are basically in accordance with experimental results.

2. Methods

2.1. Model neurons

In this paper, we considered a neural network connected by both excitatory and inhibitory neurons.

For the excitatory neurons, the main dynamical equation is described by

$$C \frac{dV_i}{dt} = -I_{\text{NaF}}(V_i) - I_{\text{NaP}}(V_i) - I_h(V_i, h_i) - I_K(V_i, b_i) - I_l(V_i) - I_{\text{AMPA}}(V_i, s_{\text{AMPA}i}) - I_{\text{NMDA}}(V_i, s_{\text{NMDA}i}) - I_{\text{GABA}_A}(V_i, s_{\text{GABA}_Ai}). \quad (1)$$

For the inhibitory neurons, the main equation is given by

$$C \frac{dV_i}{dt} = -I_{\text{NaF}}(V_i) - I_{\text{NaP}}(V_i) - I_h(V_i, h_i) - I_K(V_i, b_i) - I_l(V_i) - I_{\text{AMPA}}(V_i, s_{\text{AMPA}i}) - I_{\text{NMDA}}(V_i, s_{\text{NMDA}i}). \quad (2)$$

Where, the intrinsic currents, I_{NaF} , I_{NaP} , I_h , I_K , I_l , and synaptic currents, I_{AMPA} , I_{NMDA} , I_{GABA_A} were integrated together with the membrane capacitance $C = 1 \mu\text{F}/\text{cm}^2$.

2.2. Ionic channel kinetics and conductances

The intrinsic currents consist of the following five ionic currents: two kinds of inward sodium currents, a slow h-like current, and two outward currents—a slow potassium current and a leak current.

Roughly speaking, there are two kinds of sodium currents: the fast sodium current and the persistent sodium current. The fast sodium current is also known as transient sodium current, and the persistent one is also called as slow sodium current. These two kinds of currents both follow the Hodgkin–Huxley-type formalism. The fast sodium current has a rapid activation variable and an inactivation one. While the persistent sodium current activates instantaneously and it does not inactivate. The word slow in its name refers to inactivation.

The fast sodium current is given by $I_{\text{NaF}} = g_{\text{NaF}} m_{\text{F}\infty}^3 h_{\text{F}}(V - V_{\text{Na}})$ (Golomb & Amitai, 1997), where, $m_{\text{F}\infty} = (1 + \exp^{-\frac{V - T_{\text{Fm}}}{\sigma_{\text{Fm}}}})^{-1}$, $\frac{dh_{\text{F}}}{dt} = \frac{h_{\text{F}\infty} - h_{\text{F}}}{\tau_{\text{Fh}}}$, $h_{\text{F}\infty} = (1 + \exp^{-\frac{V - T_{\text{Fh}}}{\sigma_{\text{Fh}}}})^{-1}$, $\tau_{\text{Fh}} = 0.37 + 2.78(1 + \exp^{-\frac{V - T_{\text{Fh2}}}{\sigma_{\text{Fh2}}}})^{-1}$, with parameters $g_{\text{NaF}} = 20 \text{ ms}/\text{cm}^2$ (unless otherwise specified), $V_{\text{Na}} = 55 \text{ mV}$, $T_{\text{Fm}} = -30 \text{ mV}$, $\sigma_{\text{Fm}} = 9.5 \text{ mV}$, $T_{\text{Fh}} = -53 \text{ mV}$, $\sigma_{\text{Fh}} = -7 \text{ mV}$, $T_{\text{Fh2}} = -40.5 \text{ mV}$, $\sigma_{\text{Fh2}} = -6 \text{ mV}$.

The persistent sodium current is given by $I_{\text{NaP}} = g_{\text{NaP}} m_{\text{P}\infty}(V - V_{\text{Na}})$ (Loewenstein, Mahon, Chadderton, Kitamura, Sompolinsky, Yarom, & Häusser, 2005), where, $m_{\text{P}\infty} = (1 + \exp^{-\frac{V - T_{\text{Pm}}}{\sigma_{\text{Pm}}}})^{-1}$, with parameters $g_{\text{NaP}} = 0.06 \text{ ms}/\text{cm}^2$ (unless otherwise specified), $V_{\text{Na}} = 55 \text{ mV}$, $T_{\text{Pm}} = -53.8 \text{ mV}$, $\sigma_{\text{Pm}} = 3 \text{ mV}$.

The slow h-like current is described by $I_h = g_h h(V - V_h)$ (Loewenstein et al., 2005), where $\frac{dh}{dt} = \frac{h_{\infty} - h}{\tau_h}$, $h_{\infty} = (1 + \exp^{-\frac{V - T_h}{\sigma_h}})^{-1}$, $\tau_h = \frac{1}{\alpha + \beta}$, $\alpha = (a_{\alpha} V + b_{\alpha}) / (1 - \exp^{-\frac{V + b_{\alpha}}{k_{\alpha}}})$, $\beta =$

Table 1

Values of the intrinsic ionic channel kinetic parameters.

Parameters	Value	Unit	Parameters	Value	Unit
C	1	$\mu\text{F}/\text{cm}^2$			
g_{NaF}	20	ms/cm^2	V_{Na}	55	mV
T_{Fm}	-30	mV	σ_{Fm}	9.5	mV
T_{Fh}	-53	mV	σ_{Fh}	-7	mV
T_{Fh2}	-40.5	mV	σ_{Fh2}	-6	mV
g_{NaP}	0.06	ms/cm^2	V_{Na}	55	mV
T_{Pm}	-53.8	mV	σ_{Pm}	3	mV
g_h	0.2	ms/cm^2	V_h	-30	mV
T_h	-76.4	mV	σ_h	20	mV
a_{α}	-2.89	$/(\text{mV s})$	b_{α}	-445	/s
k_{α}	24.02	mV	k_{β}	-17.4	mV
a_{β}	27.1	$/(\text{mV s})$	b_{β}	-1024	/s
g_K	0.165	ms/cm^2	V_K	-85	mV
T_b	-54	mV	σ_b	5	mV
τ_b^0	3000	ms			
g_l	0.1	ms/cm^2	V_l	-70	mV

$(a_{\beta} V + b_{\beta}) / (1 - \exp^{-\frac{V + b_{\beta}}{k_{\beta}}})$, with parameters $g_h = 0.2 \text{ ms}/\text{cm}^2$, $V_h = -30 \text{ mV}$, $T_h = -76.4 \text{ mV}$, $\sigma_h = 20 \text{ mV}$, $a_{\alpha} = -2.89 /(\text{mV s})$, $b_{\alpha} = -445 /s$, $k_{\alpha} = 24.02 \text{ mV}$, $a_{\beta} = 27.1 /(\text{mV s})$, $b_{\beta} = -1024 /s$, $k_{\beta} = -17.4 \text{ mV}$.

The slow potassium current is given by $I_K = g_K b(V - V_K)$ (Loewenstein et al., 2005), where $\frac{db}{dt} = \frac{b_{\infty} - b}{\tau_b}$, $b_{\infty} = (1 + \exp^{-\frac{V - T_b}{\sigma_b}})^{-1}$, $\tau_b = \tau_b^0 \cdot \text{sech}(\frac{V - T_b}{4\sigma_b})$, with parameters $g_K = 0.165 \text{ ms}/\text{cm}^2$, $V_K = -85 \text{ mV}$, $T_b = -54 \text{ mV}$, $\sigma_b = 5 \text{ mV}$, $\tau_b^0 = 3000 \text{ ms}$.

The leak current is described by $I_l = g_l(V - V_l)$, with parameters $g_l = 0.1 \text{ ms}/\text{cm}^2$, $V_l = -70 \text{ mV}$.

The values of all the parameters of intrinsic ionic channel kinetics are shown in Table 1 (Destexhe, Mainen, & Sejnowski, 1994; Golomb & Amitai, 1997; Koch & Segev, 1998; Loewenstein et al., 2005) for readers' convenience.

2.3. Synaptic kinetics

Here, we considered a neural network connected by both excitatory and inhibitory connections, adjusted by excitatory or inhibitory neurotransmitter, respectively. Glutamate is an important excitatory neurotransmitter which modulates two types of receptors. AMPA receptors are responsible for most of the fast excitatory synaptic transmission, and NMDA receptors are responsible for slow excitatory synaptic transmission. On the other hand, inhibitory neurotransmitter GABA mediates the GABA_A receptors which is a kind of fast spiking GABAergic receptor. The three types of synaptic currents are represented by the following equations.

$$I_{\text{AMPA}i} = g_{\text{AMPA}}(V_i - V_{\text{AMPA}}) \sum_j w(j, i) s_{\text{AMPA}j}, \quad (3)$$

$$\frac{ds_{\text{AMPA}j}}{dt} = \alpha_{\text{AMPA}}[T](V_j)(1 - s_{\text{AMPA}j}) - \beta_{\text{AMPA}} s_{\text{AMPA}j}. \quad (4)$$

$$I_{\text{NMDA}i} = g_{\text{NMDA}} f_{\text{NMDA}}(V_i)[T](V_j)(V_i - V_{\text{NMDA}}) \sum_j w(j, i) s_{\text{NMDA}j}, \quad (5)$$

$$\frac{ds_{\text{NMDA}j}}{dt} = \alpha_{\text{NMDA}}[T](V_j)(1 - s_{\text{NMDA}j}) - \beta_{\text{NMDA}} s_{\text{NMDA}j}. \quad (6)$$

$$I_{\text{GABA}_Ai} = g_{\text{GABA}_A}(V_i - V_{\text{GABA}_A}) \sum_j w(j, i) s_{\text{GABA}_Aj}, \quad (7)$$

$$\frac{ds_{\text{GABA}_Aj}}{dt} = \alpha_{\text{GABA}_A}[T](V_j)(1 - s_{\text{GABA}_Aj}) - \beta_{\text{GABA}_A} s_{\text{GABA}_Aj}. \quad (8)$$

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