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Research paper

Synaptic dynamics regulation in response to high frequency stimulation in neuronal networks

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ABSTRACT

High frequency stimulation (HFS) has confirmed its ability in modulating the pathological neural activities. However its detailed mechanism is unclear. This study aims to explore the effects of HFS on neuronal networks dynamics. First, the two-neuron FitzHugh–Nagumo (FHN) networks with static coupling strength and the small-world FHN networks with spike-time-dependent plasticity (STDP) modulated synaptic coupling strength are constructed. Then, the multi-scale method is used to transform the network models into equivalent averaged models, where the HFS intensity is modeled as the ratio between stimulation amplitude and frequency. Results show that in static two-neuron networks, there is still synaptic current projected to the postsynaptic neuron even if the presynaptic neuron is blocked by the HFS. In the small-world networks, the effects of the STDP adjusting rate parameter on the inactivation ratio and synchrony degree increase with the increase of HFS intensity. However, only when the HFS intensity becomes very large can the STDP time window parameter affect the inactivation ratio and synchrony index. Both simulation and numerical analysis demonstrate that the effects of HFS on neuronal network dynamics are realized through the adjustment of synaptic variable and conductance.

1. Introduction

The local delivery of high frequency stimulation (HFS) over certain intensity has been proved to be a fast and reversible method to block nerve conduction [1-4], thus it is currently used to provide an alternative treatment for diseases characterized by pathological or undesired neuronal activity, such as obesity control [5,6], pain relief [7-9], and bladder voiding [10,11]. Although HFS has been used in clinical trials [12,13], its mechanisms remain unknown. Therefore, exploring the conduction block mechanisms becomes a research focus of both modeling and experiment studies [14-25]. The team members of Changfeng Tai systematically investigated the nerve conduction block under HFS with different stimulus frequencies based on the lumped circuit model of the myelinated (unmyelinated) axon [14-20]. They concluded that the constant activation of potassium channels or inactivation of sodium channels might be the underlying mechanisms of blocking.

Besides, the value of HFS frequency and amplitude parameter are also believed to be important [26-28]. Kestutis Pyragas et al. derived the averaged FitzHugh–Nagumo (FHN) model using the multi-scale method to analytical study the mechanism of HFS. They demonstrated that the effects of HFS on the pulse propagation along the axon depend on the ratio between the stimulation amplitude and frequency [29,30]. Besides, same conclusions also obtained on single Hodgkin–Huxley (HH)

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and subthalamic nucleus (STN) neuron model and they further proved that the suppression of self-sustained firing by HFS was related to the stabilization of neuron's resting state [22]. The essence of the multi-scale method is the separation of fast and slow time scale dynamics, where the impact of HFS is equivalent to a parameter of the averaged model, thus makes numerical analysis easier [31].

These simulation studies are believed to preferably help verify experiment phenomenon and guide future animal experiments. In real electrophysiology process, the response of postsynaptic neurons to external stimulation modulated presynaptic neurons is also significant for interpreting how stimulation works [32-36]. Seth H. Weinberg applied the multi-scale method to explore the HH neuronal network dynamics under HFS, where the excitatory and inhibitory properties of synaptic currents were the main focus [37]. He proved that the critical stimulation intensity to cease the network electrical activity was dependent on the architecture of the network as well as the relative proportion of excitatory and inhibitory synaptic connections. However, a systematic study about the effect of HFS on neuronal network dynamics is still lacking.

Therefore, our keystone is the network effects of HFS. Inspired by the ability of multi-scale method in analyzing the effects of HFS [22,29,30,37,38], we also use this method in our study. Since small networks are building blocks of brain networks and easy to conduct detailed analysis [39-41], we first use the smallest two-FHN neuron networks with static coupling strength to study the variation of postsynaptic responses when the presynaptic neuron is modulated by different intensities of HFS. Both simulation and numerical results demonstrate the important role of synaptic variable and synaptic coupling strength in shaping the effects of HFS.

In general, synaptic coupling strength varies in terms of certain plasticity rules [42,43]. A well-studied type of plasticity, the spike-timing-dependent plasticity (STDP), can adaptively modify the weight of synaptic couplings based on the spike times of pre- and postsynaptic neurons, which is believed to exist in many neocortical layers and brain regions [44-48]. Therefore, the effects of HFS on Newman–Watts small-world networks [49] with the modulation of STDP are also explored. Simulation results demonstrate that HFS can affect the way of STDP modulated synaptic conductance variation.

The rest of this paper is structured as follows. In Section 2, we specify the neuron model, the synapse model, and the network setup. Besides, we also illustrate and validate the multi-scale method to derive the averaged model. In Section 3, effects of HFS on both static two-neuron networks and STDP modulated small-world networks are studied systematically. Finally, conclusions are given in Section 4.

2. Model and method

2.1. Single neuron model

The two-dimensional FHN model is usually used to study the information processing of the brain due to its simplicity [29,30,50,51]. The time evolution of single neuron states with the modulation of HFS can be defined as follows:

$$\begin{aligned}\dot{v}_i &= v_i - \frac{v_i^3}{3} - w_i + I_i^{DC} + I_i^{syn} + A\rho\omega\cos(\omega t)\\ \dot{w}_i &= \varepsilon(v_i + a - bw_i)\end{aligned} \tag{1}$$

where $i = 1, 2, \cdots, N$ is the label of each neuron. v_i is the membrane potential, and w_i is the slow recovery variable. Parameters of the model are set to be $\varepsilon = 0.008, a = 0.8, b = 0.5$ to ensure the excitability of the neuron. I_i^{DC} represents the constant external direct current, which is used to produce an intrinsic neuron activity without the action of HFS. $\rho\omega\cos(\omega t)$ denotes the high frequency sinusoidal stimulation current, ω is the stimulation frequency and ρ is the ratio between the stimulation amplitude and frequency. The stimulation frequency is chosen in advance, so ρ is defined as the stimulation intensity. $A = 1$ or $A = 0$ denotes the open or close of HFS on neuron i.

2.2. Synapse model

For the chemical coupling, the synaptic current I_i^{syn} takes the form of,

$$I_i^{syn} = -\sum_{j=1(j\neq i)}^{N} g_{ij}C_{ij}s_j(v_i - v_{syn}) \tag{2}$$

where C_{ij} is the connection matrix, if neuron j projects to neuron i then $C_{ij} = 1$ otherwise $C_{ij} = 0$. v_{syn} is the synaptic reversal potential which is chosen as $v_{syn} = 0$ to makes sure all synapses are excitatory. The dynamics of the synaptic variable s_j is governed by v_j, which is defined by,

$$\dot{s}_j = \alpha\left(v_j\right)\left(1 - s_j\right)/\varepsilon - s_j/\tau_{syn} \tag{3}$$

$$\alpha\left(v_j\right) = \frac{\alpha_0}{1 + \exp\left(-v_j/v_{shp}\right)} \tag{4}$$

Here the synaptic recovery function $\alpha(v_j)$ takes the form of Heaviside function. Therefore, when neuron j is in the silent state ($v_j < 0$), s_j is reduced to $\dot{s}_j = -s_j/\tau_{syn}$; otherwise s_j jumps fast to 1 and the presynaptic neuron j acts on the postsynaptic neuron i through the synaptic current. Parameters of the synaptic model are chosen as $\tau_{syn} = 1/1.2, v_{shp} = 0.05$.