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Gap junctions facilitate propagation of synchronous firing in the cortical neural population: A numerical simulation study

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ABSTRACT

This study investigates the effect of gap junctions on firing propagation in a feedforward neural network by a numerical simulation with biologically plausible parameters. Gap junctions are electrical couplings between two cells connected by a binding protein, connexin. Recent electrophysiological studies have reported that a large number of inhibitory neurons in the mammalian cortex are mutually connected by gap junctions, and synchronization of gap junctions, spread over several hundred microns, suggests that these have a strong effect on the dynamics of the cortical network. However, the effect of gap junctions on firing propagation in cortical circuits has not been examined systematically. In this study, we perform numerical simulations using biologically plausible parameters to clarify this effect on population firing in a feedforward neural network. The results suggest that gap junctions switch the temporally uniform firing in a layer to temporally clustered firing in subsequent layers, resulting in an enhancement in the propagation of population firing in the feedforward network. Because gap junctions are often modulated in physiological conditions, we speculate that gap junctions could be related to a gating function of population firing in the brain.

1. Introduction

Gap junctions form electrical connections between two cells via a specific protein, connexin (Bloomfield & Völgyi, 2004, 2009; Mills & Massey, 1995). Theoretically, the role of gap junctions has mainly been investigated with respect to synchronization between electrically coupled neurons (Moortgat, Bullock, & Sejnowski, 2000; Pfeuty, Mato, Golomb, & Hansel, 2003), and with respect to interactions between gap junctions and synaptic connections (Bem & Rinzel, 2004; Lewis & Rinzel, 2003; Nomura, Fukai, & Aoyagi, 2003; Pfeuty, Mato, Golomb, & Hansel, 2005). Physiologically, gap junctions are quite common between inhibitory neurons in the mammalian cortex (Fukuda, Kosaka, Singer, & Galuske, 2006; Galarreta & Hestrin, 1999; Gibson, Beierlein, & Connors, 1999). Because inhibitory neurons are highly organized in a layered structure (Cruikshank, Urabe, Nurmikko, & Connors, 2010), the activity of inhibitory neurons could be crucial for information processing in the cortex. Amitai et al. specified the detailed spatial characteristics of gap-junctional connections in the barrel cortex (Amitai et al., 2002), representing a densely connected gap-junction network. The fact that the synchronization of gap junctions is spread over several hundred microns (Beierlein, Gibson, & Connors, 2000) suggests that it would have strong effects on the dynamics of cortical networks (Connors & Long, 2004). However, the effects of gap junctions have not been considered enough, although many theoretical studies of feedforward neural network models have assumed models of the cerebral cortex. Gap junctions in the cerebral cortex mainly connect inhibitory cells, suggesting that the effect might occur through an inhibitory effect. Many theoretical studies have reported that gap junctions cause synchronization (Hjorth, Blackwell, & Kotaleski, 2009) and oscillation (Bartos et al., 2002; Stacey, Krieger, & Litt, 2011; Stacey, Lazarewicz, & Litt, 2009; Traub, Contreras, & Whittington, 2005) on inhibitory neurons, and some physiological studies have suggested that inhibitory input is crucial for oscillatory activity in the cortex (Hasenstaub et al., 2005; Sohal, Zhang, Yizhar, & Deisseroth, 2009). However, the detailed mechanism as to how the synchronization of inhibitory neurons affects the dynamics of an excitatory neural population has not yet been clarified. Although shunting inhibition is effective on inhibitory neurons because the resting potential is close to the synaptic reversal potential of inhibitory input (Bacci & Huguenard, 2006; Vida,

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Bartos, & Jonas, 2006), it might not be so effective for excitatory neurons, which have higher resting potential. Our previous study reported a new mechanism whereby weak inhibition effectively synchronized the excitatory neural population which spontaneously fires (Shinozaki, Okada, Reyes, & Câteau, 2010). When neurons are firing spontaneously, there are two sources of degrees of freedom, the membrane potential and the extent of opening of sodium channels. The degrees of freedom enable the neural population to trap environmental noise. Hyperpolarization by a weak inhibitory input stops the spontaneous firing and closes the sodium channels, resulting in a decrease in the number of degrees of freedom, causing a reduction of noise and synchronization of the neural population (Shinozaki et al., 2010). This synchronization has been validated in both theoretical and biological contexts. In this study, we investigated how gap-junctional synchronization among inhibitory neurons affects the excitatory neural population and its feedforward propagation in a large-scale network.

To evaluate the effect of gap junctions in a large-scale network, we adopted the synfire chain network model, which is a model of neural firing propagation in a feedforward network (Abeles, 1991), and is considered to represent neural information flow in a brain (Diesmann, Gewaltig, & Aertsen, 1999; Guo & Li, 2011; Hamaguchi, Okada, & Aihara, 2007; Hamaguchi, Okada, Yamana, & Aihara, 2005; Yazdanbakhsh, Babadi, Rouhani, Arabzadeh, & Abbassian, 2002). The synfire chain has been mainly investigated with regard to the spike propagation mode with fixed parameters, and only a few papers have studied the control of propagation (Kremkow, Aertsen, & Kumar, 2010; Shinozaki, Câteau, Urakubo, & Okada, 2007; Shinozaki et al., 2010). In these studies, balancing the activities of excitatory and inhibitory neurons (Kremkow, Perrinet, Masson, & Aertsen, 2010; Vogels & Abbott, 2005) or preceding activities of inhibitory neurons (Shinozaki et al., 2007, 2010) was shown to be crucial in controlling firing propagation. This reinforces our need to understand the effects of gap junctions.

One of the behavioral representations of neural modulation could be attention. Recent physiological studies have shown that attention more strongly affects inhibitory neurons than excitatory neurons (Gentet, Avermann, Matyas, Staiger, & Petersen, 2010; Mitchell, Sundberg, & Reynolds, 2007, 2009). These results suggested that attentional modulation on inhibitory neurons may modulate the activities of excitatory neurons. In contrast, some non-invasive studies have reported the relationship between oscillatory activity and attention (Hipp, Engel, & Siegel, 2011). Indeed, some model studies have reported that inhibitory neurons play a key role in the oscillatory activity of excitatory neurons in the auditory cortex (Oswald, Doiron, Rinzel, & Reyes, 2009). Therefore, understanding the effects of gap junctions on the neural population is important for understanding the neural dynamics in a network.

In our study, we investigated the effects of gap junctions by performing numerical simulations in a large-scale feedforward network with biologically realistic parameters. First, we evaluated the effect in a single-layer model; then, we examined the propagation in a multilayer feedforward network in the presence of gap junctions. Our results suggest that gap junctions make temporally uniform firing more temporally clustered in style. Moreover, synchrony increases, thereby resulting in aiding the synfire propagation with well-tuned properties.

2. Methods

We chose the Izhikevich neuron model for the numerical simulation (Izhikevich, 2003). Our previous study reported that a weak inhibitory input effectively synchronized the excitatory neural population with spontaneous firing (Shinozaki et al., 2010). The report suggested that non-linear dynamics near the firing threshold are crucial in analyzing neural synchronization. Thus, the model should employ non-linear dynamics and, moreover, appropriate parameters to mimic the physiologically observed dynamics of both excitatory pyramidal neurons and inhibitory fast-spiking neurons. The Izhikevich neuron model satisfies these conditions with good simplicity and clarity. The dynamics of the Izhikevich neuron are given as follows:

$$dv/dt = 0.04v^2 + 5v + 140 - u + I_{\mathrm{syn}} + I_{\mathrm{gap}}, \quad (1)$$

$$du/dt = a(bv - u), \quad (2)$$

where v and u represent respectively the membrane potential and an adaptation variable, and I_{syn} and I_{gap} represent currents through synapses and gap junctions. Variables v and u are reset as $v \rightarrow c, u \rightarrow u + d$ every time v crosses the threshold at 30 mV. The model parameters in our simulations are set to $a = 0.02, b = 0.2, c = -65, d = 8$ for excitatory neurons, and $a = 0.1, b = 0.2, c = -65, d = 2$ for inhibitory neurons; the two sets result in the typical voltage trajectories of pyramidal cells and fast-spiking neurons, respectively (Izhikevich, 2003).

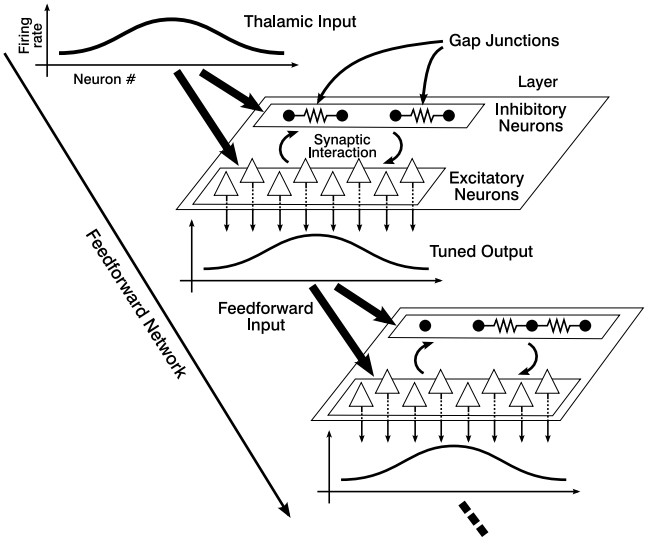

Fig. 1. Feedforward network of excitatory and inhibitory neurons modeled with Eqs. (1) and (2). Each box shows a layer containing excitatory and inhibitory neurons. Excitatory and inhibitory neurons are connected by chemical synapses. Moreover, there are gap junctions among the inhibitory neurons in the same layer. For each layer and trial, both synapses and gap junctions are randomly generated using characteristics from physiological data (Table 1). The first layer has a thalamic afferent input, and the subsequent layers have feedforward inputs from preceding layers. Interlayer connections are stochastically determined based on physiological parameters for connections from the thalamus to the cortex.

Fig. 1 shows a schematic illustration of the feedforward network used for the simulation. Each layer represents a rectangular sheet of neurons of dimension 100 μm $\times$ 1000 μm. The neuronal densities are physiologically based, 100 excitatory neurons/10 000 μm^2 and 16 inhibitory neurons/10 000 μm^2, resulting in 1000 excitatory neurons and 160 inhibitory neurons for each layer.

Synapses among neurons are based on experimentally measured values of connection probability between neurons in rodent cortex (Levy & Reyes, 2011, 2012; Oswald & Reyes, 2011) (Table 1). Gap junctions only connect inhibitory neurons in the same layer (Fukuda et al., 2006; Galarreta & Hestrin, 1999), and these connections are based on distance dependency data from a previous physiological study. As connection probabilities for gap junctions, we use 0.5 for near connections ($d < 100$ μm) and 0.3 for distant connections ($d < 200$ μm) to fit non-linear distance dependency in physiological data. Based on physiological data, there is no gap-junction coupling at distances more than 200 μm (Amitai et al., 2002). To minimize the chance that a particular connection pattern plays a role in neural dynamics, new probabilistic realizations