Gamma Rhythmic Bursts: Coherence Control in Networks of Cortical Pyramidal Neurons

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Much evidence indicates that synchronized gamma-frequency (20–70 Hz) oscillation plays a significant functional role in the neocortex and hippocampus. Chattering neuron is a possible neocortical pacemaker for the gamma oscillation. Based on our recent model of chattering neurons, here we study how gamma-frequency bursting is synchronized in a network of these neurons. Using a phase oscillator description, we first examine how two coupled chattering neurons are synchronized. The analysis reveals that an incremental change of the bursting mode, such as from singlet to doublet, always accompanies a rapid transition from antisynchronous to synchronous firing. The state transition occurs regardless of what changes the bursting mode. Within each bursting mode, the neuronal activity undergoes a gradual change from synchrony to antisynchrony. Since the sensitivity to Ca$^{2+}$ and the maximum conductance of Ca$^{2+}$-dependent cationic current as well as the intensity of input current systematically control the bursting mode, these quantities may be crucial for the regulation of the coherence of local cortical activity. Numerical simulations demonstrate that the modulations of the calcium sensitivity and the amplitude of the cationic current can induce rapid transitions between synchrony and asynchrony in a large-scale network of chattering neurons. The rapid synchronization of chattering neurons is shown to synchronize the activities of regular spiking pyramidal neurons at the gamma frequencies, as may be necessary for selective attention or binding processing in object recognition.

1 Introduction

In sensory perception, learning and memory, motor control, and attention, cortical neurons are known to exhibit synchronized oscillations in the gamma-frequency range (20–70 Hz) (Gray & McCormick, 1996; Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1997). These rhythmic cortical activities are clearly stimulus and task specific, and therefore are thought to engage in higher cognitive functions (Buzsaki, Leung, & Vanderwolf, 1983; Steriade, McCormick, & Sejnowski, 1993). If we clarify the cellular origin of the gamma oscillation, we can gain better insight into the functional role of the oscillation. In the hippocampus, synchronous gamma oscillation is considered to occur through the GABA-A-mediated mutual inhibition among interneurons (Buhl, Halasy, & Somogyi, 1994; Cobb, Buhl, Halasy, Paulsen, & Somogyi, 1995; Freund & Buzsaki, 1996). Several theoretical studies have also addressed the synchronization among inhibitory neurons (Wang & Buzsaki, 1996; White, Banks, Pearce, & Kopell, 2000). In the neocortex, it is known that a class of pyramidal neurons termed fast rhythmic bursting cells (Steriade, Timofeev, Durmuller, & Grenier, 1998) or chattering cells (Gray & McCormick, 1996) generates fast rhythmic bursts in the gamma-frequency range. This raises the possibility that the chattering cell is the neocortical pacemaker to synchronize local cortical activities at the gamma frequencies. Few theoretical studies, however, have addressed the mechanism of synchronization among chattering cells.

How synchronization is realized in a network of chattering neurons heavily depends on the ionic mechanism underlying the gamma-frequency bursting of the neurons. The mechanism, however, remains controversial. Some experimental results suggested that a persistent sodium current plays a crucial role in the generation of rhythmic bursts (Azouz, Jensen, & Yaari, 1996; Brumberg, Nowak, & McCormick, 2000; Llinas, Grace, & Yarom, 1991; Mantegazza, Franceschetti, & Avanzini, 1998). On the basis of these results, computational models were proposed to show that the rhythmic bursting of 20 to 40 Hz occurs through the so-called Ping-Pong mechanism, that is, the electronic interplay between soma and dendrites (Williams & Stuart, 1999; Wang, 1999). A similar backpropagation mechanism was also employed in modeling the gamma-frequency bursting of the pyramidal cells in the electrosensory lateral line lobe of an electric fish (Doiron, Longtin, Turner, & Maler, 2001). Other experimental studies have suggested that a subtype of the Ca\(^{2+}\)-dependent nonselective cationic current contributes decisively to the generation of the gamma frequency bursts in neocortical neurons (Kang, Okada, & Ohmori, 1998). We have modeled chattering neurons by incorporating the calcium-dependent cationic current, with the reversal potential being approximately \(-45\) mV (Kang et al., 1998) and have successfully described the burst generation in the entire gamma frequency range (20–70 Hz) (Aoyagi, Kang, Terada, Kaneko, & Fukai, 2002; Aoyagi, Terada, Kang, Kaneko, & Fukai, 2001).
In this article, we study how the activities of our model chattering neurons (Aoyagi et al., 2002, 2001) are synchronized or desynchronized when they are coupled through the AMPA glutamate receptor-mediated mutual excitation. To study the synchronization phenomena analytically, we apply the phase-oscillator analysis to a system of two chattering neurons exhibiting two, three, or more spikes per burst (doublet, triplet, . . . ). Then the essential results of the phase-oscillator analysis are confirmed by numerical simulations in a large-scale network of chattering neurons. We also study whether synchronous firing of chattering neurons may set synchronous activity in a network consisting of both chattering and regular-spiking pyramidal neurons. In order to elucidate the basic properties of synchronization among pyramidal neurons, we ignore the effects of inhibitory interneurons in the simulations. Synchronous activity in a more realistic model of the local cortical circuitry will be analyzed elsewhere.

2 The Model

2.1 Single-Neuron Model. Our model of chattering neuron has a single compartment and has only the ionic currents essential for generating fast rhythmic bursts (Aoyagi et al., 2002, 2001) (see Figure 1A). The time evolution of the membrane potential, \( V \), is described as

\[
C_m \frac{dV}{dt} = -I_{Na} - I_K - I_{Ca} - I_{cat} - I_{SK} - I_L + I_{app}, \tag{2.1}
\]

where \( C_m = 1 \mu F/cm^2 \) is the membrane capacitance and \( I_{app} \) is an applied current or stimulus. The leak current is given by \( I_L = g_L(V - V_L) \), with \( g_L = 0.13 \) mS/cm\(^2\) and \( V_L = -68.8 \) mV. Further details are described below.

2.2 Voltage-Dependent Currents. The voltage-dependent currents are described by the Hodgkin-Huxley formalism (Hodgkin & Huxley, 1952): A gating variable \( x \) (\( x = m \) for activation and \( x = h \) for inactivation) satisfies the first-order kinetics \( dx/dt = \Phi_x [\alpha_x(V)(1 - x) - \beta_x(V)x] \), with \( \Phi_x \) being the temperature factor. The fast spike-generating sodium current is given by \( I_{Na} = g_{Na}m^2h(V - E_{Na}) \), with \( \alpha_m = -0.1(V + 25)/(\exp(-0.1(V + 25)) - 1) \), \( \beta_m = 4\exp(-(V + 50)/12) \), \( \alpha_h = 0.07\exp(-(V + 42)/10) \), and \( \beta_h = 1/(\exp(-0.1(V + 12)) + 1) \). The delayed rectifier is given by \( I_K = g_Km^4(V - E_K) \), with \( \alpha_m = -0.01(V + 26)/(\exp(-0.1(V + 26)) - 1) \) and \( \beta_m = 0.125\exp(-(V + 36)/25) \). The high-voltage activated calcium current (Kay & Wong, 1987) is given by \( I_{Ca} = m^2I_{CHK} \), with \( \alpha_m = 1.6/(1 + \exp(-0.072(V - 5))) \) and \( \beta_m = 0.02(V + 8.69)/(\exp((V + 8.69)/5.36) - 1) \). The Goldman-Hodgkin-Katz current \( I_{CHK} \) is given by \( I_{CHK} = P_{max}V(\{Ca^{2+}\}_{in} - [Ca^{2+}]_{out})/(1 - \xi) \), with \( \xi = \exp(-2FV/RT) \). The parameter values used here are \( g_{Na} = 130 \), \( g_K = 35 \) (mS/cm\(^2\)), \( E_{Na} = 55 \), \( E_K = -97 \) (mV), \( F = 96.5 \)
Figure 1: Schematic representation of the chattering neuron model and the typical response to a short current pulse. (A) The ionic channels included in this model are the minimum necessary for replicating the fast rhythmic bursting of chattering neurons based on the present Ca\(^{2+}\)-dependent mechanism. For the calcium dynamics, we incorporate three processes: the influx via voltage-gated Ca\(^{2+}\) channels, extrusion via Ca\(^{2+}\)-pump, and buffering of calcium. (B) As the maximum conductance of the cationic current, \(g_{\text{cat}}\), is decreased, the amplitude of a hump-like depolarizing afterpotential (DAP) is decreased until it finally vanishes at \(g_{\text{cat}} = 0\). (C) A decrease in \(g_{\text{SK}}\) results in a transient burst of spikes. In B and C, the gray traces represent the responses at the typical parameter values employed throughout the present simulations. The same scale bars apply to both figures.

\[ C/\text{mol}, T = 293 \, \text{K}, R = 8.31 \, \text{J/(K\cdot mol)}, \text{and } P_{\text{max}} = 0.01 \, \mu\text{A}/(\mu\text{M} \cdot \text{mV} \cdot \text{cm}^2). \]

For all temperature factors, a single value is used (\(\Phi_x = 10\)).

2.3 Calcium-Dependent Currents. Our neuron model has two calcium-dependent currents: a small conductance potassium current \(I_{\text{SK}}\) (Kohler et al., 1996) and a calcium-dependent nonselective cationic current \(I_{\text{cat}}\). The SK current is a well-known calcium-activated potassium current that contributes to the afterhyperpolarization potentials (AHP). The calcium-dependent cationic current in cortical pyramidal neurons was recently stud-
ied electrophysiologically and pharmacologically (Kang et al., 1998). The current was shown to generate the depolarization afterpotential (DAP), on top of which a burst of spikes were generated. The calcium-dependent cationic currents are described as

\[ I_y = g_y m_y (V - E_y) \]

(where \( y \) represents SK or cat), and the kinetics of the gating variables \( m_y \) are given by

\[ \frac{d m_y}{dt} = \frac{m_y^\infty (\text{[Ca}^{2+}]_{\text{in}}) - m_y}{\tau_y (\text{[Ca}^{2+}]_{\text{in}} + K_d, y)} \]

and \( m_y^\infty = \frac{\text{[Ca}^{2+}]_{\text{in}}}{\text{[Ca}^{2+}]_{\text{in}} + K_d, y} \) and \( \tau_y = \frac{\varphi_y}{(\text{[Ca}^{2+}]_{\text{in}} + K_d, y)} \). There are two functionally important differences between the two currents. One is in the reversal potential: \( E_{\text{cat}} = -42 \text{ mV} \) while \( E_{\text{SK}} = E_K = -97 \text{ mV} \).

The calcium entry via \( I_{Ca} \), slow pump extrusion, and fast buffering, as follows (Robertson, Johnson, & Potter, 1981):

\[
\frac{d [\text{Ca}^{2+}]_{\text{in}}}{dt} = -\eta I_{Ca} + k_- [B] O_c - k_+ [\text{Ca}^{2+}]_{\text{in}} [B] (1 - O_c) \\
- \frac{g_{pump} [\text{Ca}^{2+}]_{\text{in}}}{[\text{Ca}^{2+}]_{\text{in}} + K_{m, \text{pump}}} \\
\frac{d O_c}{dt} = -k_- O_c + k_+ [\text{Ca}^{2+}]_{\text{in}} (1 - O_c). \quad (2.2)
\]

Here, \( O_c \) represents the fraction of the binding sites that are occupied by \( \text{Ca}^{2+} \) and \([B]\) is the total concentration of the binding sites. The parameter values are set as \( k_- = 0.3 \text{ msec}^{-1}, k_+ = 0.1 \text{ msec}^{-1} \mu M^{-1}, K_{m, \text{pump}} = 0.75 \mu M, g_{\text{pump}} = 3.6 \mu M/\text{msec}, [B] = 30 \mu M, \) and \( \eta = 0.027 \). The values are within biologically reasonable ranges.

### 2.4 Calcium Dynamics.

The calcium dynamics of the model chattering neuron is determined by the calcium entry via \( I_{Ca} \), slow pump extrusion, and fast buffering, as follows (Robertson, Johnson, & Potter, 1981):

### 2.5 Coupling Dynamics.

The AMPA receptor-mediated excitatory synaptic current is modeled as

\[ I_{\text{syn}} = g_{\text{syn}} \alpha(t - \tau_{\text{delay}})(V - E_{\text{syn}}), \quad (2.3) \]

where \( E_{\text{syn}} \) is the reversal potential and \( \tau_{\text{delay}} \) is the synaptic transmission delay (Rall, 1967). The function \( \alpha(t) \), which represents the time evolution of the synaptic current evoked by a presynaptic spike arriving at \( t = 0 \), is...
given by a dual exponential function:

\[ \alpha(t) = \frac{1}{t_2 - t_1} \left\{ \exp \left( -\frac{t}{t_2} \right) - \exp \left( -\frac{t}{t_1} \right) \right\} \]  \hspace{1cm} (2.4)

When multiple presynaptic spikes occur in succession, the total change in the conductance is given by a temporal summation of the \( \alpha(t) \)'s evoked by the individual presynaptic spikes. We could have used a different model of synapse, such as the kinetic model (Destexhe, Mainen, & Sejnowski, 1994), that describes the saturation behavior of the synaptic responses to multiple spikes more accurately. Results of preliminary simulations, however, have confirmed that both models of synapses give no qualitative difference in the performance of synchronization. Therefore, we employ the alpha function–based manipulation since it reduces computational load significantly. Typically, we use the following parameter values in simulations: \( t_1 = 0.2 \text{ msec} \), \( t_2 = 5.0 \text{ msec} \), \( g_{\text{syn}} = 0.05 \text{ mS/cm}^2 \), \( E_{\text{syn}} = 0 \text{ mV} \), and \( \tau_{\text{delay}} = 2 \text{ msec} \).

2.6 Externally Applied Current. In elucidating the basic properties of a single chattering neuron, we set \( I_{\text{app}} \) as a constant external current and let the neuron fire periodically. However, in investigating the synchronization behaviors of the neurons, we regard \( I_{\text{app}} \) as a temporal summation of many excitatory synaptic inputs mediated by the AMPA glutamate receptors and adopt the following equation:

\[ I_{\text{app}} = g_{\text{app}}(V - E_{\text{app}}), \]  \hspace{1cm} (2.5)

where the summed effective synaptic conductance, \( g_{\text{app}} \), may be constant (Tiesinga, Jose, & Sejnowski, 2000). The reversal potential is fixed at \( E_{\text{app}} = 0 \text{ mV} \). In some cases where we are interested in more realistic situations, we employ that the synapse (\( g_{\text{app}} \)) is activated by a Poisson spike train of a constant mean rate.

2.7 Numerical Methods. Numerical computations were performed on Pentium PCs and DEC Alpha machines running with the LINUX operating system. The software for the computations was written in C++. The ordinary differential equations were integrated using the formula of Dormand and Prince, with an adaptive step size that ensures an error tolerance of \( 10^{-6} \) (Dormand & Prince, 1980). To examine the validity of the numerical results, some simulations were conducted with smaller error tolerances. In addition, we repeated some simulations using the Fehlberg-Runge-Kutta method and found no significant differences in the results obtained by the two numerical algorithms.
3 Results

3.1 Single Neuron. In our model neuron, gamma rhythmic bursting arises from successive activation and inactivation of the Ca\(^{2+}\)-dependent cationic current and the SK current, if the magnitudes of both currents are appropriately adjusted. The details regarding the single-neuron responses were reported in previous work (Aoyagi et al., 2002). Here, we briefly review the essential properties of the gamma rhythmic bursting in this model. In particular, we show how modulations of the Ca\(^{2+}\)-dependent nonselective cationic current affect the bursting pattern of the model neuron. Many experiments have reported cholinergic modulations of the Ca\(^{2+}\)-dependent nonselective cationic current in hippocampal neurons (Caeser, Brown, Gahwiler, & Knipfel, 1993; Fraser & MacVicar, 1996; Guerineau, Bossu, Gahwiler, & Gerber, 1995) and the resultant induction of hippocampal gamma oscillations (Fisahn et al., 2002). In this study, modulations of the cationic current are crucial for regulating the coherence of the network activity, as shown later.

Figure 1B shows the responses to a short current pulse when the maximal conductance of the Ca\(^{2+}\)-dependent cationic current or the Ca\(^{2+}\)-dependent potassium current is varied. The gray traces represent the neuronal responses for the typical parameter values used in numerical simulations. A depolarizing afterpotential (DAP) follows each action potential and is essential for the gamma-rhythmic bursting. Without the Ca\(^{2+}\)-dependent cationic current, no DAP is observed (the black trace). A decrease in the maximum conductance of the SK current enhances the amplitude of the DAP, eventually generating a burst of spikes (see Figure 1C). In the simulations shown below, the values of the parameters were tuned such that the amplitude of the DAP is consistent with the results of electrophysiological studies (Gray & McCormick, 1996; Kang, 1997; Haj-Dahmane & Andrade, 1997).

The responses of the model neuron to long-lasting depolarizing current pulses are quite similar to the chattering patterns observed in real neurons (Kang & Kayano, 1994; Gray & McCormick, 1996; Steriade et al., 1998; Brumberg et al., 2000). The bursting frequency (the inverse of the inter-burst interval) increases with the intensity of the injected current \(I_{\text{app}}\) (see Figure 2A), until the bursting behavior is finally replaced by tonic firing. Most importantly, the model neuron exhibits stable doublet firing (two spikes per burst) over a wide range of the current intensity. For a given intensity of the injected current, the model neuron displays an increasing number of intra-burst spikes as \(K_{d,\text{cat}}\) is increased (see Figure 2C). Note that the lower the value of \(K_{d,\text{cat}}\), the more sensitive the cationic current is to Ca\(^{2+}\). Although the number of intraburst spikes varies in this way, the bursting frequency remains almost constant against the modulations of the cationic current. The behavior of the neuron model is depicted in Figures 2B and 2D in terms of interburst frequency and intraburst ISI (interspike interval in a
Figure 2: Typical responses of the model neuron to prolonged current pulses. (A) An increase in the current intensity results in a decrease in the interburst interval (equivalently, an increase in the bursting frequency). (B) The number of spikes per burst, the bursting frequency, and the intraburst ISI are plotted as functions of the current intensity. (C) A decrease in $K_{d,cat}$, which implies an increased sensitivity to Ca$^{2+}$ of the cationic current, increases the number of spikes per burst without significantly affecting the bursting frequency. (D) The number of intraburst spikes, the bursting frequency, and the interval between every successive spike pair in a burst are plotted as functions of $K_{d,cat}$.
burst). As the current intensity is increased, the interburst frequency increases almost linearly from 20 Hz to 70 Hz (see Figure 2B, middle), which constitutes the entire gamma-frequency band (Gray & McCormick, 1996). By contrast, the intraburst spike interval remains almost constant, specifically, less than 3 msec, except for weak injected current (see Figure 2B, bottom). Thus, the current intensity has little effect on the intraburst ISI. Figure 2D displays the dependence of the number of intraburst spikes and the bursting frequency on $K_{d, \text{cat}}$. Within each bursting mode (defined by each fixed number of intra-burst spikes), the interburst frequency is a weakly increasing function of $K_{d, \text{cat}}$ (see Figure 2D, middle). At the points where the number of spikes per burst increases, the interburst frequency falls discontinuously to a lower frequency. Consequently, the bursting frequency changes little over a wide range of $K_{d, \text{cat}}$.

To summarize, we have two parameters to control the burst firing in the chattering neuron model. The interburst frequency and the number of intraburst spikes are almost independently regulated by the current intensity and the calcium sensitivity of the cationic current, respectively. By simulations, we have found that a decrease in the maximal conductance of the cationic current and an increase in $K_{d, \text{cat}}$ produce a similar change in bursting behavior. Therefore, we modulate the value of $K_{d, \text{cat}}$ but not that of $g_{\text{cat}}$ in most of the following simulations.

3.2 A System of Two Coupled Neurons

3.2.1 Phase Reduction Technique. Our primary interests are in the synchronization phenomena appearing in large-scale networks of chattering neurons. As a first step, we consider a network of two identical neurons coupled symmetrically with excitatory synapses. The so-called phase reduction technique provides a useful framework for analyzing the synchronization of the coupled neurons. In the following, we briefly describe this technique. (Readers who are not interested in the mathematical details of this technique may skip this section.)

Any system of two coupled neurons can be reduced to a system of simple coupled phase oscillators if the synaptic coupling is weak, that is, if the periodic orbit of an isolated neuron is kept unchanged by the coupling. In the reduced model, the state of each neuron can be characterized by a single phase variable $\phi_i$, which is defined along the orbit and describes the timing of periodic spikes of neuron $i$ ($i = 1, 2$). The reduced phase equations then take the general form (Kuramoto, 1984; Ermentrout & Kopell, 1984)

$$\frac{d\phi_1}{dt} = \omega + \Gamma(\phi_2 - \phi_1),$$

$$\frac{d\phi_2}{dt} = \omega + \Gamma(\phi_1 - \phi_2).$$

(3.1)
where $\omega$ is the intrinsic firing frequency of an uncoupled neuron. The interaction function $\Gamma(\phi)$ is determined by the specific form of synaptic coupling and the dynamical nature of the periodic orbit of an isolated neuron. For the synaptic coupling given in equation 2.3, the interaction function is given by

$$\Gamma(\phi) = \frac{1}{T} \int_0^T Z_V(t)(-g_{syn}\alpha(t + \phi - \tau_{delay}))(V(t) - E_{syn})\, dt,$$

(3.2)

where $T$ is the period of repetitive firing. The function $Z_V(t)$ is the voltage component of the phase response function and describes how an external perturbation advances or delays the phase in the reduced system (Ermentrout, 1996; Hansel, Mato, & Meunier, 1995).

Since the interaction function in equation 3.1 depends on only the phase difference between the two neurons, the phase dynamics in equation 3.1 can be rewritten in terms of $\Delta\phi = \phi_2 - \phi_1$ as

$$\frac{d}{dt} \Delta\phi = \Gamma_{odd}(\Delta\phi),$$

(3.3)

where $\Gamma_{odd}(\phi) = \Gamma(-\phi) - \Gamma(\phi)$. Any mode of phase locking in this system corresponds to a solution to the equation $\Gamma_{odd}(\Delta\phi) = 0$. There are always two obvious solutions, $\Delta\phi = 0$ and $\Delta\phi = \pi$, which define a synchronous firing state and an antisynchronous firing state, respectively. A solution $\Delta\phi$ can be reached in a steady state if it satisfies the stability condition,

$$\Gamma_{odd}'(\Delta\phi) < 0,$$

(3.4)

where the prime denotes differentiation with respect to $\Delta\phi$.

3.2.2 Typical Simulation Results: A Transition Between Synchrony and Antisynchrony. Figure 3 depicts the typical behavior of the two-neuron network when the bursting mode is changed. Here, the bursting mode is controlled by altering the value of $K_{d,cat}$ in each neuron. The magnitude of $g_{app}$ in equation 2.5 is set as $g_{app} = 0.068 \text{ mS/cm}^2$ such that the individual neurons, when they are decoupled, may discharge periodically. As shown in Figure 3A, neurons fire antisynchronously when they exhibit singlet firing. If the calcium sensitivity of the cationic current is slightly increased, the bursting mode changes to doublet firing, and at the same time, a synchronous state becomes stable (see Figure 3B). If the calcium sensitivity is increased further, the synchronous state becomes unstable and the coupled system again evolves into the antisynchronous state (see Figure 3C). Interestingly, when the bursting pattern is changed from doublet firing to triplet firing with a slight increase in the calcium sensitivity, a similar transition from almost antisynchrony to synchrony occurs (see Figure 3D). It can be more clearly shown by the phase reduction technique that the network simultaneously undergoes the changes in the firing mode and the transitions between synchrony and antisynchrony.
3.2.3 The Reduced Phase Model of Coupled Chattering Neurons. Applying the phase oscillator analysis explained above, we examined the stable value of the phase difference between spikes of two coupled chattering neurons. In Figure 3E, the results of the analysis are given for the cases considered in Figures 3A and B. The top panel in Figure 3E displays the voltage component of the phase response functions over one period, and the bottom panel displays the odd part of the interaction function derived from the obtained phase response function and the synaptic coupling form. In Figure 3E, we can see a rapid switch of the stable state from antisynchrony to synchrony when singlet spiking is replaced by doublet bursting. A similar transition takes place when the doublet bursting mode is replaced by the triplet bursting mode (see Figure 3F). Both transitions from antisynchrony to synchrony accompany a sudden emergence of a narrow peak at $\phi \approx 0$ in $Z_V(\phi)$. These results are consistent with the general observations that a synchronous state is usually stable if $Z_V(\phi)$ has a significant peak near zero phase and an antisynchronous state tends to be stable if the peak vanishes.

To study the relationship between the bursting mode and the stable network states, we calculated the interaction function $\Gamma(\phi)$ while varying the value of $K_{d,\text{cat}}$ to change the number of spikes per burst. With this manipulation, the bursting pattern of the individual chattering neurons changes from singlet firing to quartet firing, until it finally reaches a high-frequency tonic firing at $K_{d,\text{cat}} < 8\mu M$. The obtained values of the equilibrium phase difference are plotted in Figure 3G as a function of $K_{d,\text{cat}}$. The results clearly show a close relationship between the sudden exchanges of the stability and the changes in the bursting mode. Figure 3G also shows that the prediction of the reduced phase model is in fair agreement with the result obtained by the direct numerical simulations in the full original model. Although the theory of phase reduction is explicit only in the weak coupling limit, we have found numerically that the theory captures the qualitative behavior of the coupled neuron system for larger coupling as well.

3.2.4 Effects of Other Model Parameters. The bursting mode can be changed not only by altering the calcium sensitivity of the cationic current, but also by altering other model parameters, such as the maximal conductance of the cationic current ($g_{\text{cat}}$) and the intensity of an applied current ($g_{\text{app}}$; see equation 2.5). In this section, we prove that a change in the bursting mode, regardless of the cause of the change, results in a transition between synchrony and antisynchrony. For this purpose, we calculated the values of the stable phase difference between the spikes of a neuron pair as functions of several model parameters. Figure 4A depicts the stable phase difference as a function of the stimulus current intensity, $g_{\text{app}}$. As $g_{\text{app}}$ is increased, the bursting mode changes from singlet firing to doublet firing, eventually reaching tonic firing. At the boundary between singlet and doublet firing, the stable state switches from the antisynchronous state to the synchronous state.
Such a sudden exchange of the stability also occurs when the bursting mode is changed by altering either $g_{\text{cat}}$ (see Figure 4B) or $g_{\text{SK}}$ (see Figure 4C). These results strongly indicate that the exchange of the stability between synchrony and antisynchrony is always induced by some change in the bursting mode regardless of what causes the change.
So far, spike transmission delays between the neuron pair were assumed to be a constant value $t_{\text{delay}} = 2 \text{ msec}$. Next, we investigated the effect of the synaptic delay on the stable phase difference. Figure 4D plots the stable phase differences as the functions of the synaptic delay, $t_{\text{delay}}$, for the two values of $K_{d,\text{cat}}$, one yielding singlet firing and one yielding doublet bursting. Interestingly, in a physiologically reasonable range of synaptic delay ($0.5 \sim 4.5 \text{ msec}$), a perfectly synchronous firing is established by doublet bursting, whereas a perfectly antisynchronous firing is obtained for singlet firing. Thus, the synaptic delay enhances the separation between the synchronous doublet firing and the antisynchronous singlet firing in the coupled chattering neurons.

3.2.5 Robustness of Switching Phenomena Against Noisy Stimuli. In reality, cortical neurons are innervated by a large number of synaptic inputs. Therefore, we use an equation similar to equation 2.3 instead of equation 2.5 to describe the external stimuli generated by random synaptic inputs. The activation times of the synapses are determined according to an independent Poisson process with mean rate $\lambda$. We denote the maximum conductance of these synapses as $g_{\text{inj}}$ and that of the recurrent excitatory synapses as $g_{\text{syn}}$ to...
Figure 4: Roles of various parameters in determining the stable phase difference. (A–C) If we increase the maximal conductance of any of the following currents—the effective external current ($g_{\text{app}}$), the cationic current ($g_{\text{cat}}$), and the SK current ($g_{\text{SK}}$)—an upward transition is induced in the bursting mode. As in the previous case, a rapid transition from synchronous firing to asynchronous firing occurs at every point where the number of spikes per burst increases. (D) The stable phase differences are plotted against the synaptic delay $\tau_{\text{delay}}$ for singlet firing (gray circles) and doublet firing (black circles). In B–D, the vertical arrows indicate the typical parameter values used throughout the simulations.

avoid confusion. In the following simulations, the mean firing rate and the maximal conductance were set as $\lambda = 68$ spikes per msec and $g_{\text{inj}} = 0.001 \text{ mS/cm}^2$.

The left panels in Figure 5 display the time evolutions of the membrane potentials of two neurons at various levels of the calcium sensitivity of the cationic current. In the right panels, the respective spike cross-correlograms are displayed. In Figures 5A and 5B, neuronal responses are shown on either side of the boundary between the singlet firing state and the doublet firing state in the parameter space. The central peak in the cross-correlogram in Figure 5B appears at almost zero phase lag, which indicates coincident firing of the two neurons with spike doublets. In the case of singlet firing in Figure 5A, in contrast, the peaks are displaced by finite phase lags of about
Figure 5: Transitions between antisynchrony and synchrony in a pair of the chattering neurons responding to random synaptic input currents. The voltage traces of the two neurons (left) and the cross-correlograms between the neuron pair (right) are shown for the values of $K_{d,\text{cat}}$ specified in the figure. The cross-correlograms (bin size = 1 msec) in A and C show finite phase lags (~10 msec) between the two neurons, while those in B and D show no phase lag. These changes indicate the stability exchange between antisynchrony and synchrony, as in the case of a constant applied stimulus.

10 msec, which indicates that the two neurons fire in almost antiphase. Figures 5C and 5D display the voltage traces and the cross-correlograms on either side of the boundary between the doublet bursting state and the triplet bursting state. In this case, doublet bursting shows antiphase synchrony, and triplet bursting shows synchrony. Thus, as was the case for the constant applied current, the stability exchange occurs between in-phase synchrony and antiphase synchrony at the boundary where the bursting mode of the individual neurons is also changed. The phenomenon is robust as long as the randomness of synaptic inputs is not too strong.
3.3 Large-Scale Excitatory Networks. In this section, we investigate the dynamics of a large-scale network of chattering model neurons. It is well known that in the week coupling limit, a globally coupled network of identical neurons cannot achieve full synchrony if a synchronous state is unstable in two coupled neurons of the same type (Okuda, 1993). Given this fact and on the basis of the previous results for two coupled neurons, we may expect that the coherence of the activity in a large network can be enhanced or suppressed by changing the intensity of an external input or the intrinsic properties of the cationic current, such as the calcium sensitivity and the maximum conductance. To see how the coherence of activity is regulated in a large-scale network by, for instance, the modulations of the calcium sensitivity, we simulated fully connected excitatory networks of 100 to 300 neurons. As for the external stimuli to the individual neurons, independent Poisson spike trains of mean rate $\lambda = 132$ spikes/msec were given to the summed effective synapses having a maximal conductance of $g_{\text{inj}} = 0.0005 \text{ mS/cm}^2$. Wherever necessary, the conductance of the recurrent synaptic connections is specified in figure captions.

3.3.1 Rapid Synchrony-Asynchrony Transitions in a Large-Scale Network of Chattering Neurons. Figures 6A and 6B display a simulated rastergram and a spike histogram of 100 chattering neurons (bin width is 1 msec). From 500 msec to 1000 msec, the sensitivity of the cationic current to Ca$^{2+}$ was raised to a high level ($K_{d,\text{cat}} = 16.4 \mu\text{M}$). Otherwise, $K_{d,\text{cat}} = 18 \mu\text{M}$. At this low level of calcium sensitivity, the neurons show singlet firing, and the timing of the spikes is asynchronous. The asynchronously firing state can be regarded as a counterpart of the antisynchronously firing state in two coupled neurons. In the period of high calcium sensitivity, the neurons exhibit highly coherent doublet firing, as expected from the synchronous doublet firing of a neuron.
pair. The coherence of the network activity increases very quickly within a few gamma cycles of the onset of the high-calcium-sensitivity period. To quantify the degree of the synchronization, we define the normalized cross-correlations of the membrane voltages over the duration $\Delta$ at time $T$, $C_{ij}(T)$, as

$$C_{ij}(T) = \frac{\int_{T-\Delta}^{T} (V_i(t) - \bar{V}_i)(V_j(t) - \bar{V}_j) \, dt}{\sqrt{\int_{T-\Delta}^{T} (V_i(t) - \bar{V}_i)^2 \, dt \int_{T-\Delta}^{T} (V_j(t) - \bar{V}_j)^2 \, dt}},$$

(3.5)
where \( \nabla_i = \int_{T-\Delta}^{T} V_i(t) \, dt \). We average \( C_{ij}(T) \) over all neuron pairs to measure the coherence over the entire network: \( C(T) = \langle \langle C_{ij}(T) \rangle \rangle_{ij} \). We set \( \Delta \) to 100 msec, which makes \( C(T) \) sensitive to the rapid changes in the coherence. The time evolution of \( C(T) \) is displayed in Figure 6C, which manifests the rapid changes at the moments that the calcium sensitivity is altered. These rapid changes in \( C(T) \) indicate rapid transitions between synchrony and asynchrony at these moments.

### 3.3.2 Selective Induction of Synchronization in a Subgroup of Chattering Neurons

Gamma oscillation is considered to induce a coherent activity in a relatively localized area of the cortex (Kopell, Ermentrout, Whittington, & Traub, 2000; von Stein & Sarnthein, 2000). Therefore, it is intriguing to examine whether a selective enhancement of the calcium sensitivity of the cationic current within a local subgroup of chattering neurons can induce a highly coherent activity in the subgroup. In Figure 6D, only those neurons with indices 100 to 200 (labeled \( B \) in the figure) were set in the state of high calcium sensitivity from 500 msec to 1000 msec. Other neurons remained in the state of low calcium sensitivity during the entire period of simulations. Note that all the neurons were mutually connected, as in the previous case.

During the period of the high sensitivity to \( \text{Ca}^{2+} \), only the neurons belonging to the selected subgroup showed doublet firing, while others continued to show singlet firing. The spike histogram (bin width = 1 msec) of the selected subgroup showed increased spike counts during the period, indicating an increased degree of synchronization. Similar histograms of other subgroups (the 100-neuron ensemble, labeled \( A \)) showed almost no increase of the spike count during the same period (see Figure 6E). Correspondingly, we can see that the coherence of the neuronal activity is enhanced in subgroup \( B \), but not in subgroup \( A \), during this period (see Figure 6F). Since both intergroup recurrent synapses and intragroup ones have the same magnitudes and the same connectivity, the differences in the coherence of activity between the two subgroups originate from the differences in the sensitivity to \( \text{Ca}^{2+} \) of the constituent neurons. Similar synchrony-asynchrony transitions could be induced in a subgroup of neurons by selectively changing the intensity of the external current to the subgroup (results not shown).

### 3.3.3 Correlated Changes in the Bursting Mode and the Activity Coherence

The results shown in Figure 6 indicate that in the large-scale network, the abrupt state transitions between synchrony and asynchrony are strongly correlated with the change in the bursting mode, as it was correlated with similar transitions between synchrony and antisynchrony in pairs of chattering neurons (see Figure 3G). To prove this, we have calculated the equilibrium values of \( C(T) \), that is, the overall coherence of the network activity, as a function of \( K_{d,\text{cat}} \) defined over the same range as in Figure 3G. The results are shown in Figure 6G with the averaged number of spikes per burst over all neurons in the network (bottom trace).
It can be clearly seen that the value of $C(T)$ abruptly increases from almost zero to peak levels whenever the value of $K_{d, cat}$ is lower than the critical values at which the averaged number of intraburst spikes is increased. This implies that abrupt transitions from asynchrony to synchrony occur when the number of intraburst spikes is increased in large-scale networks of the chattering neurons.

3.3.4 Regular Spiking Neurons Synchronized by a Small Ensemble of Chattering Neurons. It is likely that the ratio of chattering neurons in the entire population of neocortical pyramidal neurons is not very large. Chattering neurons belong to a minority of the neocortical neuronal subtypes. Therefore, it is important to study whether the rapid synchronization of chattering neurons can synchronize the activity of other regular-spiking pyramidal neurons. Here, we show some preliminary results of simulations on a network consisting of both chattering and regular-spiking pyramidal neurons.

The mixture network consisted of 25 chattering neurons and 75 regular spiking pyramidal neurons. Both types of neurons were uniformly connected by excitatory synaptic connections with $g_{syn} = 0.002 \text{ mS/cm}^2$. The regular spiking neuron was modeled similarly to the chattering neuron, except that the cationic current was absent in the former. The mean firing rates of external inputs were 108 spikes/msec for the chattering neurons and 132 spikes/msec for the regular-spiking neurons. The synaptic conductance of the external inputs was set as $g_{inj} = 0.0005 \text{ mS/cm}^2$.

The typical result is shown in Figure 7. The figure demonstrates that the chattering neurons, which are the minority in the network, can synchronize the activities of the regular-spiking pyramidal neurons and, consequently, the activity of the whole network. It should be noted that the regular-spiking neurons could fire only asynchronously in the absence of chattering neurons (results not shown). In Figure 7, however, the transition from asynchrony to synchrony is rather slow in comparison with the result shown in Figure 6. In fact, in the present case, $C(t)$ reached a peak level after almost 500 msec from the onset of doublet spiking in the chattering neurons (bottom traces).

How is the performance of the network influenced by the ratio of chattering neurons in the whole neural population? To see this, we calculated $C(T)$'s separately for the individual subnetworks of chattering neurons and regular-spiking neurons while varying the population ratio of the chattering neurons ($P_{ch}$). We also measured how long it took for the individual subnetworks to develop synchronously firing states and to desynchronize these states. As shown in Figure 8A, it has been revealed that the subnetworks show phase transition-like behaviors. There is a critical value of $P_{ch}$ below which an increase of $P_{ch}$ results in an improved coherence of the activity in both subnetworks. In this region of the parameter values, the larger the value of $P_{ch}$, the faster are both synchronization (see Figure 8B) and desynchronization (see Figure 8C), although these changes occur only slowly, in 500 msec to 1 sec.
Figure 7: Entrainment of regular-spiking (RS) pyramidal neurons by synchronous firing of chattering (CH) neurons. (A) In the rastergram, the first 25 neurons are chattering neurons, and other 75 neurons are regular-spiking neurons. In the chattering neurons, the value of $K_{d,cat}$, which was otherwise set as $K_{d,cat} = 18 \mu M$, was raised to $K_{d,cat} = 16.5 \mu M$ during the period indicated by the arrow labeled S. This modulation induces the typical transition from singlet firing to doublet firing in the discharging pattern of the chattering neurons. (B) Spike histograms (bin width =1 msec) of regular spiking and chattering neurons display slow increases in the spike count in the period S. In addition, the desynchronization following this period occurs rapidly among chattering neurons but rather slowly among regular-spiking neurons. (C) The overall coherence $C(T)$ shows that the synchronization of regular-spiking neurons follows slightly behind that of chattering neurons and that the desynchronization of regular-spiking neurons lasts long after that of chattering neurons.
Unexpectedly, if $P_{ch}$ is greater than the critical value, the overall performance in synchronization was significantly degraded. The subnetwork of chattering neurons could rapidly fall into a synchronously firing state, but the subnetwork of regular-spiking neurons never achieved synchrony (in Figure 8A, $P_{ch} > 60\%$). This implies that the chattering neurons failed to entrain the regular-spiking neurons at the gamma frequencies. We have found by numerical simulation that this critical value of $P_{ch}$ can be made as small as about 60% with relatively strong recurrent excitatory connections. Making the recurrent connections stronger, however, achieved only such a state that appears in the region $P_{ch} > 60\%$ in Figure 8A. Only chattering neurons, but not regular-spiking neurons, can be synchronized with such stronger recurrent connections. Further studies are required to clarify how this somewhat unexpected behavior appears in the mixture network of chattering and regular-spiking neurons. We do not discuss this issue in detail, as $P_{ch}$ is very likely to be much less than 60% in the neocortical local circuitry. We speculate that synchronization of chattering neurons that occurs too rapidly, which is achievable only for relatively large values of $P_{ch}$, leaves regular-spiking neurons far behind and in an asynchronously firing state.

4 Discussion

Our analysis has revealed that the degree of synchrony in a pair of weakly coupled chattering neurons can be modulated by intensity of the external input and the properties of the calcium-dependent cationic current, such as the maximum conductance and the sensitivity to Ca$^{2+}$. Changing the intensity of the external current changes the interburst interval (bursting frequency) and the number of spikes per burst (the bursting mode), whereas changing the maximum conductance or the calcium sensitivity of the cationic current changes the bursting mode without significantly affecting the interburst interval. We have revealed that a change in the bursting mode systematically modulates the coherence of neuronal firing regardless of which parameter underlies the change. In a two-neuron network (see Figure 4), antisynchronous firing is abruptly replaced by synchronous firing whenever the neuron pair makes a transition to a higher bursting mode, from doublet firing to triplet firing, and so on. Similarly, asynchronous firing is replaced by synchronous firing in a uniformly connected large-scale network of chattering neurons when they enter into a higher bursting mode. Moreover, if only a subgroup of chattering neurons exhibits the transition to a higher bursting mode, the asynchrony-to-synchrony transition also occurs only in that subgroup. The selected neural ensemble is rapidly desynchronized when the modulation is turned off (see Figure 6A).

In in vitro experiments, a repetitive depolarization of a cortical pyramidal neuron changes the response from a regular spiking pattern to a gamma-frequency rhythmic bursting (Kang et al., 1998; Brumberg et al., 2000). In our neuron model, a similar change in the firing pattern was in-
duced by a slight increase of the maximum conductance or the sensitivity to Ca\(^{2+}\) of the Ca\(^{2+}\)-dependent nonselective cationic current (Aoyagi et al., 2001). Although the physiological mechanism of the changes in the in vitro firing pattern is not known yet, modulations by certain neuroactive substances, in particular the cholinergic modulation, may play an active role. In fact, many studies demonstrate the enhancement of Ca\(^{2+}\)-dependent cationic current by activation of muscarinic receptors (Caeser et al., 1993; Constanti & Libri, 1992; Fraser & MacVicar, 1996; Guerineau et al., 1995). Recently, it has been shown that activation of muscarinic M1 recep-
tors modulates a Ca\(^{2+}\)-dependent nonselective cationic current as well as a hyperpolarization-activated cationic current (\(I_h\)) in hippocampal CA3 pyramidal neurons (Fisahn et al., 2002). The activation of the M1 receptors was required for induction of hippocampal gamma oscillations. Several modeling studies have attempted to show how neuroactive substances including acetylcholine may affect the activity of hippocampal neurons and networks (Pinsky & Rinzel, 1994; Menschik & Finkel, 1999; Tiesinga, Fellous, Jose, & Sejnowski, 2001). Similar to the hippocampus, cholinergic enhancement of the Ca\(^{2+}\)-dependent nonselective cationic current in chattering neurons may be crucial for induction of neocortical gamma oscillations.

This study, however, has suggested that a network of chattering neurons may not suffice for entraining a majority of pyramidal neurons at the gamma frequencies. Modeling studies showed that the AMPA-type excitatory glutamatergic synapses tend to desynchronize rather than synchronize regular spiking pyramidal neurons (Hansel et al., 1995; Vreeswijk & Abbott, 1994). In addition, it was theoretically argued that neurons with a nonnegative phase response function (type I) cannot achieve in-phase synchrony (Ermentrout, 1996). Therefore, whether the synchronous firing of chattering neurons, which belong to a minority group in the cortical network, can synchronize the activity of other pyramidal neurons is not a trivial issue. The results of our simulations remain inconclusive. If the population ratio of chattering neurons to regular-spiking neurons is appropriate, bursting of chattering neurons synchronizes slowly in a transient time of several hundred milliseconds to entrain the activities of regular spiking pyramidal neurons. If the synchronization of chattering neurons occurs much more

Figure 8: Facing page. Entrainment of regular-spiking neurons at various population ratios of chattering neurons \(P_{ch}\) in a large-scale network. \(g_{syn} = 0.002\) mS/cm\(^2\). In the figures, bold curves are plotted for chattering neurons, and dashed curves are for regular-spiking neurons. (A) The averaged overall coherence \(C(T)\) in the equilibrium state was calculated as functions of \(P_{ch}\) for the populations of chattering neurons and of regular-spiking neurons. \(C(T)\) was obtained by averaging \(C(T)\) over the interval of 1000 msec following an initial transient period. The error bars display the standard deviations in 10 trials. There are two distinct regions. At \(P_{ch} > 60\%\), chattering neurons may rapidly evolve into a synchronously firing state, but they fail to entrain regular-spiking neurons; at \(P_{ch} < 60\%\), chattering neurons can entrain regular-spiking neurons, but the synchronization occurs rather slowly. (B) The time spent by each neuron group in evolving into the coherent state clearly indicates the phase transition-like behavior. At \(P_{ch} > 60\%\), the convergence time for regular spiking neurons is not shown since they could not be synchronized. (C) The time spent by the neuron groups in desynchronizing the once established coherent states are plotted. In the figures, the vertical arrows indicate the population ratio employed in Figure 7.
rapidly, which seems to be realistic, the entrainment does not occur (see Figure 8).

How can we remedy the difficulties in synchronizing the entire network activity? It is likely that some interneurons should be incorporated into our network of pyramidal neurons. In fact, results of recent experiments have suggested that networks of interneurons, which are often connected simultaneously by electric and GABAergic synapses, may enhance the synchrony in cortical activity (Galarreta & Hestrin, 1999, 2001). In order to describe the synchronization phenomena in the local cortical circuitry more accurately, we must clarify how the dual synaptic wiring facilitates synchrony among interneurons and how interneurons cooperate with chattering neurons in synchronizing and desynchronizing cortical activity. These topics are under investigation.

The results have indicated that a diversity in the intrinsic bursting patterns of neurons is essential and important in a speedy regulation of the coherence among pyramidal cell activities. It seems intriguing to study whether the correlated occurrence of the change in the bursting mode and the asynchrony-synchrony transition is merely a specific feature of the model or the generic feature widely seen in synchronization of bursting neurons. For instance, is this correlation between the two phenomena also found with the burst firing generated by the so-called Ping-Pong mechanism (Wang, 1999)? What mathematical type of the bursting mechanism (Izhikevich, 2000) leads to the correlation? These questions remain for further study.

In conclusion, we have shown that modulations of the Ca$^{2+}$-dependent cationic current in chattering neurons allow these neurons to synchronize their spikes within a few cycles of the gamma oscillation. The rapid establishment of synchrony at the gamma frequencies in sensory and motor cortices may represent stimulus-driven attentional influences of higher cognitive centers (Engel, Fries, & Singer, 2001). Although we must await further studies to make a conclusive statement on the role of the gamma oscillation, chattering neuron is a promising candidate for the cortical pacemaker of the oscillation.

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**References**


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