Spike Frequency Adaptation and Neocortical Rhythms

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Fuhrmann, Galit, Henry Markram, and Misha Tsodyks. Spike frequency adaptation and neocortical rhythms. J Neurophysiol 88: 761–770, 2002; 10.1152/jn.00848.2001. Spike-frequency adaptation in neocortical pyramidal neurons was examined using the whole cell patch-clamp technique and a phenomenological model of neuronal activity. Noisy current was injected to reproduce the irregular firing typically observed under in vivo conditions. The response was quantified by computing the poststimulus histogram (PSTH). To simulate the spiking activity of a pyramidal neuron, we considered an integrate-and-fire model to which an adaptation current was added. A simplified model for the mean firing rate of an adapting neuron under noisy conditions is also presented. The mean firing rate model provides a good fit to both experimental and simulation PSTHs and may therefore be used to study the response characteristics of adapting neurons to various input currents. The models enable identification of the relevant parameters of adaptation that determine the shape of the PSTH and allow the computation of the response to any change in injected current. The results suggest that spike frequency adaptation determines a preferred frequency of stimulation for which the phase delay of a neuron’s activity relative to an oscillatory input is zero. Simulations show that the preferred frequency of single neurons dictates the frequency of emergent population rhythms in large networks of adapting neurons. Adaptation could therefore be one of the crucial factors in setting the frequency of population rhythms in the neocortex.

INTRODUCTION

Spike-frequency adaptation (SFA) is the decrease in instantaneous discharge rate during a sustained current injection and is a specialized feature of many types of neurons. SFA has been observed in neurons of various systems from several species, including non-mammalian ones such as the crayfish stretch receptor (Michaelis and Chaplain 1975). In mammals, SFA has been observed in rodent motoneurons (Granit et al. 1963; Sawczuk et al. 1995), hippocampal CA1 pyramidal cells (Lancester and Nicoll 1987; Madison and Nicoll 1984), and pyramidal cells of the piriform cortex (Barkai and Hasselmo 1994). In the neocortex of rodents, SFA has been identified in most pyramidal neurons, in particular those that have been traditionally classified as regular spiking cells, but in some bursting neurons as well (Connors and Gutnick 1990; Mason and Larkman 1990; McCormick et al. 1985). SFA has also been identified in neurons of other mammalian systems, including the rabbit CA1 and CA3 pyramidal neurons (Moyer et al. 1996; Thompson et al. 1996), cat motoneurons (Granit et al. 1963; Kernell and Monster 1982) and layer V neurons of the sensorimotor cortex recorded in vitro (Schwindt et al. 1988; Stafstrom et al. 1984), neurons of cat visual cortex in vivo (Ahmed et al. 1998), and even regular spiking cells of the human neocortex (Avoli and Olivier 1989; Foehring et al. 1991; Lorenzon and Foehring 1992).

The biophysical mechanisms underlying SFA are not yet established. SFA has most commonly been linked to the phenomena of afterhyperpolarization (AHP), found to follow current-induced repetitive firing (Madison and Nicoll 1984; Schwindt et al. 1988). AHP is an action-potential-dependent hyperpolarized potential that markedly summates with successive spikes. Because the build-up of AHP with successive spikes is relatively slow, its effects on discharge frequency are greater at later inter-spike intervals (Madison and Nicoll 1984). The ionic mechanisms underlying AHPs and their functions have been studied in neurons from several species, such as the cat (Schwindt et al. 1988; Stafstrom et al. 1984), guinea pig (Connors et al. 1982; McCormick et al. 1985), and rat (Madison and Nicoll 1984), and have been suggested to be largely produced by Ca2+-activated slow K+ currents (Connors et al. 1982; Hotson and Prince 1980; Madison and Nicoll 1984; Schwindt et al. 1988). In slices of human cortical tissue, AHP was observed, and the currents underlying the medium and slow AHPs were shown to influence the interspike interval during repetitive firing and to produce SFA (Avoli et al. 1994; Lorenzon and Foehring 1992). Other ionic currents that have been suggested to contribute to the development of SFA include the M-current (I_M), which is a slow-activating noninactivating voltage-sensitive potassium current (Michaelis and Chaplain 1975; McCormick et al. 1993), and the slow Na inactivation (Michaelis and Chaplain 1975; Schwindt and Crill 1982).

The functional significance of SFA is not clear either. Some possible roles of SFA have been suggested. These include the phenomena of forward masking and selective attention (Liu and Wang 2001; Wang 1998). In forward masking, when two or more inputs are presented sequentially in time, the neuronal response to the first input inhibits responses to subsequent inputs by activating I_AHP with a delay. In selective attention, in the presence of two or more inputs, the adaptation process can selectively suppress the neuronal responses to weaker inputs so that the response to the strongest input “pops-out” in time.
lating the input-output properties of a neocortical neuron embedded in a noisy environment. In particular, the response properties of an adapting neuron to oscillatory inputs suggest a role for SFA in the synchronization of neuronal assemblies. Previous results suggested a role for adaptation in stabilizing synchronous behavior (Crook et al. 1998; van Vreeswijk and Hansel 2001). Here we show that by knowing the characteristics of SFA in individual neurons of the population, it is possible to predict the frequency of oscillations for which synchronization could occur, i.e., the frequency of possible spontaneously emerging population rhythms.

METHODS

Experimental

Slice preparation and recording procedures as in Markram et al. (1997). Briefly, Wistar rats (13-15 days) were rapidly decapitated, and neocortical slices (sagittal; 300 mm thick) were sectioned (DSK, Microslicer, Japan). Neurons in the somatosensory cortex were identified using IR-DIC video-microscopy (Zeiss Axioplan, fitted with [mult]40-W/0.75 NA objective; Zeiss, Oberkochen, Germany), and patch-clamp recordings were obtained. Recorded neurons were selected up to 120 µm below the surface of the slice and separated from each other by up to 150 µm. Experiments were performed at 32-34°C with extracellular solution that contained (in mM) 125 NaCl, 2.5 KCl, 25 glucose, 25 NaHCO3, 1.25 NaH2PO4, 1.5 mM CaCl2, and 1.5 mM MgCl2. Somatic whole cell recordings (10-20 M access resistance) were obtained, and signals were amplified using Axoclamp-2B amplifiers (Axon Instruments), captured on the computer using pulse control (by Dr. R. Bookman and colleagues, Miami University), and analyzed in programs written in Igor (Igor Wavemetrics, Lake Oswego, OR). Pipettes solution contained (in mM) 100 K-glucuronate, 20 KCl, 4 ATP-Mg, 10 phosphocreatine, 0.3 GTP, 10 HEPES, and 0.5% biocytin (pH 7.3, 310 mOsm).

Modeling

Two models are used in this study. The first is an integrate-and-fire model of a spiking adapting neuron, used for detailed simulations. The second is a mean firing-rate model of an adapting neuron.

INTEGRATE-AND-FIRE MODEL OF AN ADAPTING NEURON. To simulate the spiking behavior of a pyramidal neuron exhibiting SFA, we consider a model of an adapting neuron, based on the classical leaky integrate-and-fire model of a neuron (Tuckwell 1988). The model for an adapting neuron takes into account an additional hyperpolarizing potassium current, referred to as the adaptation current (Treves 1993).

Below threshold θ, the membrane potential of the neuron evolves according to the following differential equation

\[ \tau_m \frac{dV}{dt} = -(V - V_{\text{rest}}) + R_m \cdot (I_{\text{ext}} + I_{\text{syn}} - I) \]

(1)

where \( V \) is the membrane potential of the cell, \( V_{\text{rest}} \) is the resting potential, \( R_m \) is the input resistance, and \( \tau_m \) is the membrane’s time constant. \( I_{\text{syn}} \) is the synaptic current, which is non-zero in cases where the neuron is embedded in a network, and \( I_{\text{ext}} \) is an external current representing inputs from other brain areas.

Whenever the membrane potential \( V \) reaches threshold, a spike is emitted and \( V \) is instantaneously set to a constant resetting value (\( V_{\text{reset}} \)).

In most of the analysis we study the neuron’s response to noisy currents. We therefore consider

\[ I_{\text{ext}}(t) = \mu(I) + \sigma \sqrt{\tau_m} \eta(t) \]

(2)

where \( \mu(I) \) and \( \sigma \sqrt{\tau_m} \) are the mean and standard deviation of the current. \( \eta(t) \) is an uncorrelated white noise with unit variance. We use the parameter \( \sigma \), which is in picoampere units, to characterize the amplitude of the noise.

We also consider an alternative, conductance-based model, in which external inputs cause changes in the membrane’s conductance, rather than simple current injections. According to this model

\[ I_{\text{ext}}(t) = \mu(I(t)) \cdot (V - V_t) \]

(3)

where \( \mu(I) \) and \( \sigma \sqrt{\tau_m} \) are the mean and standard deviation of the conductance, and \( V_t = 0 \) is the reversal potential of excitatory synapses.

The adaptation current, \( I_a \), is given by

\[ I_a(t) = \tilde{g}_a \cdot n(t) \cdot (V - V_i) \]

(4)

where \( V_i \) is the reversal potential of \( K^+ \), \( \tilde{g}_a \) is the maximal conductance for the adaptation current, and \( n \) is the fraction of the open conductance, computed according to the following equation

\[ \frac{dn}{dt} = -\frac{n}{\tau_a} + \alpha \cdot (1 - n) \cdot \delta(t - \tau_{\text{off}}) \]

(5)

with \( \tau_{\text{off}} \) being the time of a spike occurrence in the adapting (postsynaptic) neuron, \( \alpha \) is a constant determining the step increase in \( n \) that occurs for each spike, and \( \tau_a \) is the time constant for deactivation of the adaptation current. Thus the adaptation current tends to accumulate when the neuron fires and decays between spikes with the time constant of \( \tau_a \). This current is a phenomenological current and does not aim at describing a specific biophysical mechanism but could be related to the outward calcium-activated potassium current (I_{AK}).

In this study, simulations were performed in the parameter regime where \( n \) is significantly smaller than 1. Therefore to simplify the analysis, the term \((1 - n)\) could be dropped off Eq. 5 without changing the qualitative behavior of the model.

MEAN FIRING RATE MODEL OF AN ADAPTING NEURON. To enable analytical calculations, a simplified model was constructed to simulate the mean instantaneous firing rate of an adapting neuron under noisy conditions, averaged over many repetitions of the same input. The model is based on two differential equations for the mean firing rate of the neuron and for the mean adaptation current, and a third analytical equation that translates mean voltages into mean firing rates.

The dynamics of the mean adaptation current, \( \mu(I) \), is derived from the integrate-and-fire model of an adapting neuron by averaging over Eq. 5 for the case of Poisson firing statistics, with rate \( E \)

\[ \frac{d\mu(I)}{dt} = -\frac{\mu_t}{\tau_t} + \alpha \cdot I_{\text{max}} \cdot E \]

(6)

where we approximate \( I_{\text{max}} \) to be \( \tilde{g}_a \cdot (V_{\text{thres}} - V_i) \), assuming that the voltage for these current injections remains close to threshold.

To approximate the dynamics of the mean firing rate (\( E \)) of the neuron, we use a standard formulation, first presented in Wilson and Cowan (1972). The model was developed for the mean firing rate averaged over a population of neurons. Here we apply it to describe the dynamics of the instantaneous firing rate of a single neuron, averaged over many responses to different realizations of the same average input

\[ \tau_{\text{def}} \frac{dE}{dt} = -E + \beta_4 R_m \cdot (\mu(I) + \mu_e - \mu_s(I)) \]

(7)

where \( \mu_s(I) \) is the mean amplitude of the synaptic current and \( \tau_e \) is the time constant underlying the dynamics of the mean firing rate. In the case of white noise input statistics, the parameter \( \tau_e \) is mainly controlled by the membrane time constant, but its numerical value depends on parameters of the input, such as its mean amplitude. This ...
differential equation approximates the evolution of $E$ toward its stationary value in case of a constant input, which is given by a function $\beta_E(\mathbf{R} \cdot I)$ with $\sigma = \mathbf{R} \cdot \sigma_0 \sqrt{\tau_m}$.

In the case of uncorrelated white noise, this function was computed by Ricciardi (1977)

$$\beta_E(\mu) = \left( \tau_r \sqrt{\frac{\tau_m}{\sigma}} \int_0^t \exp \left( \frac{\tau_m (x - \mu)}{\sigma} \right) \left( \exp \left( \frac{\sqrt{\tau_m} (x - \mu)}{\sigma} \right) + 1 \right) \right)^{-1}$$

with $\theta = \theta - V_{res} \cdot H = V_{reset} - \theta$. For $\mu$ above threshold, the function $\beta_E(\mu)$ is approximately linear and may be written as $\beta_E(\mu) = b_1 \cdot \mu + b_0$, thus simplifying subsequent analytical analysis.

Although Eq. 7 cannot be rigorously derived from the detailed integrate-and-fire model, and although it was shown not to accurately describe the firing rate dynamics (Gerstner 2000), it can still provide useful insights for understanding the neuron’s behavior.

SIMULATIONS OF NETWORKS COMPOSED OF ADAPTING NEURONS.

We consider small networks of only a few neurons, with manually designed architecture of connections as well as large scale randomly connected networks. The activity of the networks, composed of adapting neurons, is simulated using the detailed integrate-and-fire model formulated in Eqs. 1 and 5. All neurons can be driven by an externally injected current ($i_{ext}$) as well as by synaptic current ($i_{syn}$), which is induced by the activity of the presynaptic neurons. For each simulated neuron, once a spike occurs, a synaptic current is activated in all of its postsynaptic targets. Synaptic currents (EPSCs) are simulated by the difference of two exponentials, multiplied by the synaptic strength, $J$

$$\text{EPSC}(t) = J \cdot (e^{-\tau_d - e^{-\tau_r}}) \cdot (V_{syn} - V(t))$$

where $\tau_r$ and $\tau_d$ are the rise and decay time constants of EPSCs and $V_{syn}$ is the synaptic reversal potential in use.

RESULTS

Response properties: comparison between experiments and models

To compare the performance of the model neuron with that of real neurons, similar current injections were applied to both model neurons and also to several layer II-IV pyramidal neurons, whose voltage responses were recorded in slice preparations of rat somatosensory cortex. Under in vivo conditions, however, a neocortical neuron is exposed to the background activity of its presynaptic neurons and thus experiences noisy input currents (Softky and Koch 1993). This study, therefore, focuses on the response of an adapting neuron to various noisy current injections.

RESPONSE TO NOISELESS STEP CURRENTS.

The response of the neurons to noiseless step currents was used primarily to compare the response of the model neuron to that of real neocortical neurons and to extract realistic model parameters for subsequent analysis. In Fig. 1A, we show the typical response of an adapting neuron to a constant current injection. It can be seen that the interval between subsequent spikes in the train is increasing.

Figure 1B depicts the evolution of the first 20 inter-spike intervals (ISIs) within an experimental trace, as recorded from a layer IV pyramidal neuron. In the responses of all the recorded pyramidal neurons, the predominant effect was a progressive increase in ISIs until a steady state was approached, referred to as the early phase of adaptation. In many traces, preceding the early phase, an initial fast increase in the first few ISIs was observed. The initial phase is regarded as emerging from the bursting property of these neurons (McCormick et al. 1986) and therefore was not considered as part of the spike frequency adapting behavior of the studied neurons. In some traces, a slower process followed the early phase and caused an additional increase in ISI. All three components were previously observed by Kernell and Monster (1982) and Sawczuk et al. (1995) and were referred to as the initial, early and late phases of adaptation. The construction of the model aimed at simulating the early phase of adaptation only.

The experimental traces were fit using the model by searching for the most appropriate set of model parameters ($\alpha$, $g_h$, and $\tau_N$) that approximates the experimental results. Using the chosen parameters, it was possible to replicate the evolution of ISIs within the train (Fig. 1B, solid line). The experimental first ISI is significantly shorter than that of the model, supporting the possibility that it may be caused by a different mechanism, perhaps related to the bursting behavior of these neurons (McCormick et al. 1985). In other traces with the same model parameters but a different amplitude of current injected, a good match to the responses of the same neuron was also obtained for all ISIs (not shown), excluding the first few, further supporting the possibility of a different underlying mechanism for the first ISIs.

RESPONSE TO NOISY STEP CURRENTS.

Under in vivo conditions, where spontaneous activity of presynaptic neurons causes strong background fluctuations in the membrane potential, non noisy step currents represent unrealistic inputs to a neocortical neuron. We therefore explored the behavior of the adapting neuron in response to a fluctuating input.

Figure 2A illustrates an example of voltage responses of a model neuron to a step current with added white noise. Apparently, in the case of noisy injections, adaptation cannot be characterized simply as an increase in the length of subsequent

FIG. 1. The response of adapting neurons to noiseless step current injections. A: the voltage response of a model neuron to a non noisy current. Parameters: $\tau_m = 58$ ms, $R_m = 0.2$ G$\Omega$, $g_h = 10$ (G$\Omega)^{-1}$, $\tau_N = 230$ ms, and $\alpha = 0.02$. Amplitude of injected current: 210 pA. B: inter-spike interval (ISI) curves for a layer IV pyramidal cell and for the model neuron, whose parameters were chosen to fit the ISI curve of the real neuron.
it was used to study the mean firing rate response properties of adapting neurons under noisy conditions.

RESPONSE TO NOISY OSCILLATORY CURRENTS. The response of the model neuron to oscillatory currents of the form \( I(t) = I_0 + I_1 \sin(2\pi f t) \), with white noise, was examined. An example of an adapting neuron’s response to such an injected current is illustrated in Fig. 3A (the initial transient is not shown). Note that the oscillatory response has the same frequency as that of the injected current. However, in the presented example, the phase of the response is advanced relative to that of the current by almost \( 40^\circ \).

To calculate the phase of the response, we construct, for each of the spikes emitted by the neuron, a vector of unit length and an angle equal to the phase of the spike relative to the input cycle. The angle of the vector sum of all unit vectors is taken as the phase of the response.

The phase shift of the discharge response, relative to the current injected, was found to be affected by the parameters of the neuron, such as its input resistance and parameters of the adaptation current, as well as by the characteristics of the input current. In particular, it was found to be dependent on the frequency of the injected current, as summarized in Fig. 3B. Low-frequency modulated stimuli produce a negative phase shift of the mean firing rate response, such that the response phase advances that of the injected current. High-frequency oscillatory stimuli produce only positive phase shifts, such that the response phase is always delayed. The frequency that ISIs. In this case, the response is characterized using the poststimulus time histogram (PSTH) of the neuron. In Fig. 2B, the PSTH of a model adapting neuron for 500 different realizations of a noisy step current is shown. In each trial, the noise realization was different. Parameters: \( \tau_M = 6 \text{ ms} \), \( R_m = 0.2 \text{ G}\Omega \), \( \delta_k = 12 \text{ (G}\Omega)^{-1} \), \( \tau_N = 214 \text{ ms} \), and \( \alpha = 0.014 \). Amplitude of the current injected is 130 pA, and the chosen bin size is 4 ms. —, the response of the mean firing rate model of an adapting neuron for the same model parameters, with \( \tau_e = 6 \text{ ms} \). C: PSTH obtained from experimental traces recorded in vitro from a layer IV pyramidal neuron for the same injection protocol. PSTH computed for 107 different realizations of the noisy current. Bin size as in B.

**Fig. 2.** The response of adapting neurons to noisy step current injections. The injected current had a mean of 130 pA and \( \sigma_i = 43.5 \text{ pA} \). A: voltage response of a model adapting neuron. Parameters as in Fig. 1 with \( \tau_M = 4 \text{ ms} \). B: response of a model adapting neuron. Poststimulus time histogram (PSTH) is computed for 500 different realizations of the noisy current injection. In each trial, the noise realization was different. Parameters: \( \tau_M = 6 \text{ ms} \), \( R_m = 0.2 \text{ G}\Omega \), \( \delta_k = 12 \text{ (G}\Omega)^{-1} \), \( \tau_N = 214 \text{ ms} \), and \( \alpha = 0.014 \). Amplitude of the current injected is 130 pA, and the chosen bin size is 4 ms. —, the response of the mean firing rate model of an adapting neuron for the same model parameters, with \( \tau_e = 6 \text{ ms} \). C: PSTH obtained from experimental traces recorded in vitro from a layer IV pyramidal neuron for the same injection protocol. PSTH computed for 107 different realizations of the noisy current. Bin size as in B.

**Fig. 3.** The response of model adapting neurons to oscillatory current injections. A: PSTH of a model adapting neuron computed in response to injected current with an oscillatory mean (top) and added white noise. Frequency of oscillations: 4 Hz. White line indicates the solution of the corresponding mean firing rate model, with \( \tau_e = 10 \text{ ms} \). Model parameters: \( \tau_M = 40 \text{ ms} \), \( R_m = 0.2 \text{ G}\Omega \), \( \delta_k = 25 \text{ (G}\Omega)^{-1} \), \( \tau_N = 80 \text{ ms} \), and \( \alpha = 0.05 \). The oscillatory current had a mean of 1,000 pA, and 50-pA amplitude oscillations, \( \sigma_i = 53 \text{ pA} \). B: the phase shift of the firing rate relative to the phase of the current injected, plotted as a function of the frequency of oscillations. Phase shift was determined according to the phase of the vector sum of the phases of all the spikes emitted over all the trials. Arrow indicates the preferred frequency of the neuron, for which the phase shift of the firing rate, relative to the phase of the input current, is 0.
segregates these frequency regimes (γ Hz) is the frequency at which no phase shift occurs. We define γ to be the preferred frequency of the neuron or the zero phase frequency. Note that the firing rate of the neuron, and thus the number of spikes per cycle, is also affected by the frequency of the input current, and there exists also a special frequency for which the gain of the response, in terms of the average firing rate, is maximal. However, we stress that in the context of this study we define the preferred frequency of the neuron to be the frequency at which the phase shift between the discharge rate of the adapting neuron and its input current is zero.

The existence of this property of an adapting neuron can be explained by the interplay between two opposing mechanisms. On one hand, the time constant of the firing rate dynamics (τe) tends to cause a delay in the response of the neuron to its injected current (Eq. 7). This mechanism dominates at high-input frequencies. On the other hand, the dynamics of the adaptation current Ia (Eq. 6) tends to advance the phase of the mean firing rate. This is prominent at lower input frequencies and is due to the accumulation of adaptation current during the rising phase of the discharge rate, which induces an advanced decline of the firing rate. The preferred frequency, where zero phase shift is obtained, is reached when the two opposing mechanisms balance each other. Note that at very low frequencies, the phase shift approaches zero again because Eqs. 6 and 7 are effectively at their steady-state solutions and the firing rate follows the oscillations of the input.

Simulations of the conductance based model of an adapting neuron (Eq. 3) result in similar phase-frequency curves, with a preferred frequency of zero phase shift. For parameters chosen such that the mean input current is the same as that of the corresponding current-based neuron, the preferred frequency changes only slightly, even when the average input conductance increases up to 200% from its initial value, as reported to occur under in vivo conditions (Borg-Graham et al. 1998). Therefore for simplicity, further analysis was performed for the current-based neuron.

To gain insight on the dependence of the preferred frequency, γ, on the parameters of adaptation, we used the simplified model for the mean firing rate, to analytically compute γ, under a linear approximation for small amplitudes of oscillations

\[ \gamma(\text{Hz}) = \frac{1}{2\pi} \sqrt{\frac{R_{\text{eq}} \delta_k \cdot C}{\tau_e} - \frac{1}{\tau_s}} \]  

(10)

where C is a constant parameter that is determined for every neuron according to the slope of its f-I curve (see APPENDIX for details).

This relation suggests that the preferred frequency of an adapting neuron could be tuned by modulating the adaptation parameters (κ, δk, and τs in the model), which determine the degree and time course of adaptation. Experimental studies have shown that neuromodulators, such as ACh, can reduce the degree of adaptation (Tang et al. 1997) e.g., by reducing δk. The data acquired from simulations of the detailed integrate-and-fire model of an adapting neuron, presented in Fig. 4, demonstrate that reducing δk indeed results in lower preferred frequencies, as expected from Eq. 10.

To test the predictions of the models, three layer IV pyramidal neurons were patched, and their response to noisy oscillatory currents at different frequencies was recorded. The phase shift of the discharge rate response was extracted from the PSTHs of the neurons. The results are shown in Fig. 5. The phase-frequency curves all have the predicted shape. Moreover, two of the neurons have a preferred frequency in the range of the tested frequencies (around 13 Hz for 1 and 16 Hz for the other), whereas the preferred frequency of the third neuron is apparently above the highest tested frequency (over 20 Hz).

Simulations of the detailed integrate-and-fire model of adapting neurons show that γ is not a constant value dictated by the parameters of the neuron alone but is also modulated by the parameters of the input current. In particular, increasing the mean value of the input current (I0) causes an increase in γ (Fig. 6A). In the framework of the firing rate model of an adapting neuron, this dependence is related to the fact that the time constant underlying the dynamics of the mean firing rate (τe) depends on the parameters of the input current (Holt 1998). Increasing I0 pushes the voltage closer to the firing threshold, resulting in faster dynamics of the discharge response, i.e., a shorter τe. Therefore increasing I0 causes τe to decrease, which in turn determines a higher preferred frequency γ (Eq. 10). Increasing the amplitude of current oscillations (I1) induces lower preferred frequencies (Fig. 6B). However, this dependence is much weaker than the dependence on the mean value of the input current (I0).

Emergence of population rhythms in networks of adapting neurons

To study the implications of the preferred frequency on synchronization in neural networks, small networks of model

![FIG. 4. The effect of changing the degree of adaptation on the preferred frequency of a model neuron. A: the phase shift of the firing rate relative to the phase of the current injected, for different degrees of adaptation, simulated by varying δk (all the other parameters as in Fig. 3). Results obtained from simulations of the detailed integrate-and-fire model of an adapting neuron, with δk = 0.15, 5, 10, 15, 20, and 25 μS. B: the dependence of the preferred frequency upon δk. Data points are extracted from the curves in A.](http://jn.physiology.org/ by 10.220.33.6 on June 22, 2017)
We therefore expected the neurons to synchronize at their intrinsic phase-frequency curve relative to their own input current (Fig. 7). Because the neurons are identical, they all have the same intrinsic phase shift to keep them firing at the same mean discharge rate. The input current that each neuron in the population receives is a combination of the externally injected current, as well as the synaptic current. The mean input current ($I_0$) and the amplitude of the oscillations of the injected current ($I_f$) that a representative neuron of the population received on average in the simulation were determined. This was used to construct the corrected phase-frequency curve for a single neuron in the homogenous network, taking into account the phase of the synaptic delay at each of the input conditions.

In Fig. 7, results are presented for a network of four identical neurons, in which one neuron receives an oscillatory external input and the others receive a constant current injection (DC shift) to keep them firing at the same mean discharge rate. The neurons synchronize at a frequency in which they all produce a phase shift that exactly opposes the phase shift caused by the synaptic delay at that frequency. Therefore, we expect that the corrected preferred frequency will determine the rhythms in neocortical networks.

This prediction was tested in a large, randomly connected, homogeneous network of 200 identical adapting neurons, each receiving an uncorrelated noisy current injection with a constant mean, to induce spontaneous firing (Fig. 8). Under conditions in which the average firing rate of the neurons was well above zero at all times, a synchronized oscillatory spiking activity appeared spontaneously in the network, for sufficiently strong synaptic connectivity. Note that no external oscillatory current was injected to any of the neurons in the network, and therefore the population rhythm is an emergent property of the network. In the presented example (Fig. 8, A and B), the frequency of the synchronized oscillations is 6.64 Hz. The frequency of the population rhythm remains constant over time. The input current that each neuron in the population receives is a combination of the externally injected current, as well as the synaptic current. The mean input current ($I_0$) and the amplitude of the oscillations of the injected current ($I_f$) that a representative neuron of the population received on average in the simulation were determined. This was used to construct the corrected phase-frequency curve for a single neuron in the homogenous network, taking into account the phase of the synaptic delay at each of the input conditions.

A synchronization of discharge rate are achieved if all neurons exhibit the same phase shift of discharge, relative to the external input current, for a given modulation frequency. The neurons, driven by an external oscillatory input, were considered. Synchronous oscillations of discharge rate are achieved if all neurons exhibit the same phase shift of discharge, relative to the external input current, for a given modulation frequency.
Jseq is positively related to $\bar{g}_k$, then decreasing $\bar{g}_k$ results in a decreased $J_{seq}$, and therefore if $J$ is kept unchanged, this would indeed result in higher degrees of synchronization.

It could be argued that it is not realistic to assume that a neocortical network consists of identical neurons. Rather, it is more plausible that the parameters of the neurons are randomly distributed across the population. We therefore explored the effect of having a heterogeneous population of adapting neurons whose parameters are all identical, except that $\bar{g}_k$ is normally distributed around a certain value. The results (Fig.

**FIG. 7.** Implication of preferred frequency for synchronized network oscillations: small network. A network of 4 identical neurons, with asymmetric connectivity is simulated. External current is injected to one neuron only. A: the phase-frequency curves for each of the neurons relative to their inputs. Insert: network connectivity. B: the phase-frequency curves for each of the neurons relative to their inputs, considering the phase of synaptic delay (see Results). C: the phase-frequency curves for each of the neurons relative to the phase of the external current injected. Synchronization of discharge rates is achieved at the frequency where the curves meet. Note that this is the same frequency as the corrected preferred frequency of the neurons. Parameters of the neurons are as in Fig. 3. The injected oscillatory current had a mean of 300 pA and amplitude of oscillation ($I_1$) was 75 pA, $\sigma_0$ set to 32 pA. Synaptic parameters were $\tau_1 = 1$ ms, $\tau_2 = 6.5$ ms, and $V_{syn} = 60$ mV. The synaptic strength, $J$, was set to 1 pA. Under these conditions, the magnitude of oscillations in the mean synaptic current, seen by each neuron, is of the same order of magnitude as $I_1$. The mean firing rate of the neurons is 53 Hz.

Exploration of various homogenous populations revealed that the frequency of the population rhythm is indeed lower for networks composed of neurons with smaller $\bar{g}_k$, as predicted by Eq. 10. The degree of synchronization was found to increase when $\bar{g}_k$ decreases down to a certain value (results not shown). This result can be explained by the fact that for any $\bar{g}_k$, there exists a minimal synaptic strength, $J_{seq}$, which is required in order for network oscillations to emerge; below this critical synaptic strength, the network has a steady state solution with no oscillations. The larger $J$ is relative to $J_{seq}$, the larger are the amplitudes of the emergent population rhythm. Because frequencies (Fig. 8C). The corrected preferred frequency of the neuron was determined as 6.7 Hz. From this result, as well as from simulation results of similar networks with different model parameters, we conclude that the frequency of the emerging population rhythm in a large network is indeed predicted by the corrected preferred frequency of the single neurons.

**FIG. 8.** Implication of preferred frequency for synchronized network oscillations: large network. A network of 200 adapting neurons is simulated. Each neuron receives inputs from 50 other randomly chosen neurons. All neurons receive a noisy DC current of 200 pA, with $\sigma_0 = 32$ pA. A: the raster plot of a homogenous network of adapting neurons. The activity of 1 of every 3 neurons is shown. Model parameters: $\tau_m = 40$ ms, $R_m = 0.2$ GΩ, $\bar{g}_k = 20(\text{GΩ})^{-1}$, $\tau_y = 80$ ms, and $\alpha = 0.05$. Synaptic parameters were $\tau_1 = 1$ ms, $\tau_2 = 6.5$ ms, and $V_{syn} = 60$ mV. The synaptic strength, $J$, was set to 0.0615 pA. B: the population histogram of the homogenous network whose activity is shown in A. Bin size of histogram is 5 ms. A population rhythm emerges with a frequency of 6.64 Hz. C: the corrected phase-frequency curve of a single adapting neuron of the population, considering the phase of synaptic delay that the neuron experiences. $I_0 = 253$ pA and $I_1 = 12.5$ pA were determined according to the mean input current to which the neuron was exposed in the simulation of A and B. The corrected preferred frequency of the neuron is 6.7 Hz. Curve was constructed according to simulations of the detailed integrate-and-fire model of an adapting neuron. D: the population histogram of a heterogeneous network. All neurons are identical, except for $\bar{g}_k$ which is normally distributed around 20(Ω)⁻¹, with SD = 2(Ω)⁻¹. Bin size as in B. Population rhythm is still obtained and at the same frequency as in B.
The response of a neuron under such conditions was quantified in terms of the activity of its presynaptic neurons. We simulate this back-propagation of inhibitory activity to the presynaptic neurons in vivo experiences noisy inputs due to the background activity of its presynaptic neurons. It is therefore generally assumed that a neuron responds to the firing activity of its presynaptic neurons with an instantaneous average discharge rate.

If the strength of the connections is increased, the network can switch to a different regime of activity. This regime is characterized by synchronous bursts of firing across the network, with zero activity between the bursts, and was recently studied in noiseless networks of adapting neurons (van Vreeswijk and Hansel 2001).

**Discussion**

Spike-frequency adaptation in neocortical pyramidal neurons was examined using the whole cell patch-clamp technique and phenomenological models of neuronal activity. Noisy current was injected to reproduce the irregular firing typically observed under in vivo conditions (Softky and Koch 1993). Spike-frequency adaptation was shown to play an important role in shaping the response of a neocortical neuron to such noisy stimulations. A detailed model was used to simulate the spiking response of the neocortical pyramidal neuron as well as a simplified model that captures its response in terms of the instantaneous average discharge rate.

In the intact brain a neuron is embedded in large, spontaneously active networks. It is therefore generally assumed that a neuron in vivo experiences noisy inputs due to the background activity of its presynaptic neurons. We simulate this background activity by adding white noise to the injected stimuli. The response of a neuron under such conditions, was quantified by computing the poststimulus time histogram (PSTH) of the neuron and thus reflects mean firing rate characteristics only.

The study of the output of a model adapting neuron exposed to oscillatory inputs revealed a dependence of the firing rate response on the frequency of stimulation. Low-frequency modulated inputs produced a phase advance of the output response relative to the input current, whereas high-frequency modulated stimuli induced a phase delay of the response. A special frequency was observed, referred to as the preferred frequency of stimulation, for which the phase delay of neuron’s activity relative to the input is zero. The prediction of such phase-frequency curves was confirmed by recordings of neocortical pyramidal neurons. Additional experimental support for the existence of the predicted phase-frequency curves is obtained from the firing rate responses of thalamic relay neurons in the cat’s lateral geniculate nucleus (Smith et al. 2000) and of regular spiking neurons in the guinea pig visual cortex (Carandini et al. 1996), both recorded in brain-slice preparations. The latter study also supports the predicted dependence of the phase-frequency curves of neocortical neurons on the DC level of current injection, $I_0$ (see also Kamondi et al. 1998 for low-frequency modulation).

Recently, it was shown that the response of nonadapting integrate-and-fire neurons to noisy oscillatory currents is also sensitive to the statistical properties of the noise (Brunel et al. 2001; Rudolph and Destexhe 2001). In particular, if the noise is low-pass filtered, etc., due to the finite duration of synaptic currents, the dynamics of the firing rate becomes very fast for high-frequency oscillations. Hence, the phase of the delay approaches zero even in the absence of an adapting mechanism. However, for realistic values of parameters, this deviation of behavior from the white noise case occurs at frequencies that are significantly above the range we focus on in this study.

The significance of the preferred frequency of an adapting neuron for the emergence of synchronous population rhythms in the neocortex was investigated. The study of small networks, composed of only four neurons, one of which was stimulated by an externally oscillatory noisy current, suggested that the neurons may synchronize at a corrected preferred frequency, which takes into account the phase of the synaptic delay. This prediction was tested in recurrent networks of 200 adapting neurons with no externally oscillatory current injection. Nevertheless an oscillatory synchronized population activity spontaneously emerged. We found that the frequency of the population rhythm was indeed predicted by the corrected preferred frequency of single neurons. We conclude that the frequency of population rhythms can be predicted by the parameters of single neocortical neurons.

According to the model analysis, the preferred frequency depends on the parameters of adaptation and thus can be adjusted by neuromodulators, such as ACh (Tang et al. 1997), that affect the degree of adaptation of pyramidal neurons. High concentrations of neuromodulators can result in the shut off of adaptation currents and hence in the abolishment of population rhythms. Adaptation could therefore be one of the crucial factors in setting the frequency of population rhythms in the neocortex. Indeed, in Sanchez-Vives and McCormick (2000), it is suggested that the slow oscillations in the neocortex are generated through a recurrent network of excitatory connections and that the periodicity is affected largely by the time course of the outward currents generating the slow AHP of pyramidal and spiny stellate cells. Moreover, it has been shown that the low-frequency oscillations are indeed suppressed by a variety of neurotransmitters, including ACh and noradrenaline (NE), presumably through the reduction of specialized K+ conductances, such as that underlying the AHP currents (Stein et al. 1993). Faster rhythms are possibly determined by other mechanisms, which depend on the activity of inhibitory interneurons, and could therefore be less sensitive to the effect of neuromodulators (Brunel 2000; Tsodyks et al. 1997; Wilson and Cowan 1972).

In addition to the expected significance of adaptation in determining possible frequencies for neocortical population rhythms, theoretical models have also suggested that the phase relation of spike occurrence relative to the population cycle may be capable of carrying sensory information (e.g., Buzsáki and Chrobak 1995; Hopfield 1995; Kamondi et al. 1998; Laurent 1996; Lisman and Idiart 1995; Tsodyks et al. 1996). Experimental support for such “phase coding” has been specifically demonstrated by the phenomenon of spike phase precession observed in CA1 pyramidal “place cells” (O’Keefe and Recce 1993; Skaggs et al. 1996). These place cells undergo progressive phase precession during the time that the rat crosses the place field of the cell. In this sense, the phase shift...
of the spike discharge relative to the theta population cycle encodes the rat’s position in space. It has been suggested (Kamondi et al. 1998) that this phase precession is explained by increasing depolarization due to increased excitation by afferents in the center of the field, causing the cells to fire progressively earlier during the theta cycle. Such a dependence of the phase on the DC level (I_0) for low-frequency modulated inputs is in accordance with our observations. In the context of ‘phase-coding’ of sensory information, adaptation might have a role in enriching the coding language, by adding negative phase shifts to the vocabulary of the code.

**APPENDIX**

**Derivation of the preferred frequency of an adapting neuron**

(Eq. 10)

Equation 10 was derived under the assumption that the input current is in the linear range of \( \beta_n(\mu) \). In this range, \( \beta_n(\mu) \) can be approximated by \( \beta_0 + \mu. \) We analyze the approximated mean firing rate model, formalized in Eqs. 6 and 7. If the externally injected current is oscillatory, it can be represented as

\[
\mu_i = I_0 + I_1 \cos(\omega t) = Re[I_0 + I_1 e^{i \omega t}]
\]

If \( I_1 = 0 \) (DC current injection), one can calculate the values of \( E \) and \( \mu_a \) at the fixed point

\[
E^* = b_1 + b_1 R_n I_1 - \mu \gamma, \quad \mu_a^* = \frac{a \alpha \tau_0 (b_0 + b_1 R_n I_1)}{1 + R_n b_1 a \alpha \tau_0 \tau_n}
\]

We now turn our considerations, with small \( I_1 \) to get a small deviation of \( E \) and \( \mu_a \) from their fixed point values, so that \( E = E^* + E_1 e^{i \omega t}; \quad \mu_a = \mu_a^* + \mu_1 e^{i \omega t} \). The derivatives with respect to \( t \) are therefore

\[
\frac{dE}{dt} = i \omega E_1 e^{i \omega t} \quad \text{and} \quad \frac{d\mu_a}{dt} = i \omega \mu_1 e^{i \omega t}.
\]

By inserting the preceding terms into Eqs. 6 and 7, respectively, one can compute

\[
E_i = \frac{b_1 R_n I_1}{i \omega (\tau_n + \tau_i) + (1 - \tau_n \tau_i \omega^2 + D)}
\]

To find the angle of \( E_i \), we rewrite Eq. A2 in the following form

\[
\phi_i = \tan^{-1}(\tau_n \omega) - \tan^{-1}\left(\frac{\tau_n + \tau_i}{1 - \tau_n \tau_i \omega^2 + R_n a \alpha \tau_0 \tau_n \tau_i b_1}\right)
\]

The preferred frequency of a neuron is calculated as the frequency for which there is no phase shift in the firing rate of the neuron, relative to the current injection. Therefore by equating \( \phi_i = 0 \), we can compute the \( \omega \) that satisfies this condition

\[
\omega = \frac{1}{\tau_n} \cdot \left( b_1 R_n a \alpha \tau_0 \tau_i b_1 - \tau_i \right) \frac{R_n a \alpha \tau_0 \gamma c}{\tau_n} \frac{1}{\tau_x}
\]

with \( C = b_1 (V_{\text{thresh}} - V_k) \).

The preferred frequency of the neuron is \( \gamma = \frac{1}{2 \pi \omega} \).

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