Impact of synaptic noise and conductance state on spontaneous cortical firing

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Cortical neurons in-vivo operate in a continuum of overall conductance states, depending on the average level of background synaptic input throughout the dendritic tree. We compare how variability, or fluctuations, in this input affects the statistics of the resulting 'spontaneous' or 'background' firing activity, between two extremes of the mean input corresponding to a low-conductance (LC) and a high-conductance (HC) state. In the HC state, we show that both firing rate and regularity increase with increasing variability. In the LC state, firing rate also increases with input variability, but in contrast to the HC state, firing regularity first decreases and then increases with an increase in the variability. At high levels of input variability, firing regularity in both states converge to similar values. *NeuroReport* 18:1371–1374 © 2007 Lippincott Williams & Wilkins.

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Introduction

The analysis of stochastic mechanisms on cortical neurons is crucial for understanding cortical function and the nature of the neural code. Stochasticity is manifested most obviously by the highly variable spiking response of neurons *in vivo* to a repeated sensory input [1,2]. In response to injected currents, evoked spikes *in vitro* are much more regular than those *in vivo* [3,4], and as the in-vitro procedure greatly diminishes the spontaneous synaptic activity observed *in vivo* [5], the increased in-vivo spike variability is probably due to the variability of synaptic inputs [5,6]. In fact, cortical neurons *in vivo* are subject to varying overall levels of stochastic synaptic background activity [7], which is particularly intense during active states of the brain, where the neurons fire at high levels [8]. To understand the interaction between neural message and noise, it is important to explore the relation between this activity and any resulting 'quiescent' or 'spontaneous' spikes. Thus, following the description of Pospischil and colleagues [9], we can consider the nature of spontaneous firing in cortical neurons between two extreme regimes mediated by stochastic synaptic input: low-conductance (LC) and high-conductance (HC) states.

Statistical properties of the integrated synaptic input, including the average and variance, can have significant effects on the neuron's input–output characteristics [5,10,11]. In the HC state, mean synaptic background activity accounts for up to 80% of the input conductance of the cell [10], with a mix of excitation and inhibition that results in typical in vivo 'resting potentials' about 15 mV depolarized from the in-vitro condition. Completely uncorrelated background synaptic inputs lead to small-amplitude fluctuations in the membrane potential, whereas increasing correlations lead to large amplitude fluctuations [12], underlining the direct link between synaptic population statistics and the variability of the integrated input. In HC states this variability typically produces ∼10 mV voltage fluctuations, with a standard deviation of ∼4 mV [5,10,11]. Synaptic correlations can also influence the firing rate and variability of a postsynaptic neuron [13], and cortical neurons are able to detect changes in the correlation among the synaptic inputs on millisecond timescales [14]. In this computational study, we compare how the variability in the synaptic background activity in the two extreme conductance states affects the regularity of spontaneous firing of cortical neurons.

Methods

Various computational models have been proposed to reproduce the stochastic membrane potential fluctuations characterizing the dynamics of neurons *in vivo*. Biophysically detailed models can include the dendritic morphology, allowing the explicit simulation of a large number of excitatory and inhibitory synaptic inputs underlying background activity [10,15]. Recently, Destexhe *et al.* [15] introduced a point-conductance model of background activity, which we use here, that considers a single-compartment neuron with excitatory and inhibitory

conductances that represent the sum of a large number of synaptic inputs. The membrane equation is described as [15]:

$$C\frac{dV}{dt} = -I_{Na} - I_{Kd} - I_M - I_{Leak} - \frac{1}{a}I_{syn}, \qquad (1)$$

where $C = 1\,\mu\text{F/cm}^2$ is the specific membrane capacitance, V is the membrane potential and $a = 34636\,\mu\text{m}^2$ is the total membrane area for a layer VI cortical pyramidal cell [15]. I_{Na} is the voltage-dependent Na$^+$ current, I_{Kd} is the delayed-rectifier K$^+$ current, I_M the noninactivating K$^+$ current, and I_{Leak} the leak current. The parameters of the passive and voltage-dependent currents are taken from Ref. [15].

The total synaptic current in Eq. (1), I_{syn}, is decomposed into a sum of two independent currents [15]:

$$I_{syn} = g_e(t)(V - E_e) + g_i(t)(V - E_i), \qquad (2)$$

where $g_e(t)$ and $g_i(t)$ are time-dependent global excitatory and inhibitory conductances, respectively, with reversal potentials of $E_e = 0\,\text{mV}$ and $E_i = -75\,\text{mV}$. The synaptic conductances are described by Ornstein–Uhlenbeck stochastic processes [15]:

$$\frac{dg_y}{dt} = -\frac{1}{\tau_y}(g_y - g_{y0}) + \sqrt{\frac{2\sigma_y^2}{\tau_y}}\chi(t), \quad y = \{e, i\}, \qquad (3)$$

where g_{e0} and g_{i0}, τ_e and τ_i, and σ_e and σ_i, are the average conductances, the time constants, and the standard deviations, respectively, for the excitatory and inhibitory inputs, respectively. $\chi(t)$ is a Gaussian white noise process of unit standard deviation and zero mean. The parameter values of Eq. (3) were taken as $g_{i0} = g_{e0} = 12.1\,\text{nS}$, $\tau_e = 2.73\,\text{ms}$, $\tau_i = 10.49\,\text{ms}$, and $\sigma_i = 26.4\,\text{nS}$ for the LC state, with the HC state differing only by a higher value of $g_{i0} = 57.3\,\text{nS}$ [7]. In this study, we were interested in the relationship between the input variability and spike variability, thus we stimulated the neuron with different values of σ_e ranging between 1.5 and 72 nS ($\sigma_e = 12\,\text{nS}$ corresponds to a standard deviation of the membrane voltage of $\sim 4\,\text{mV}$ in the HC state). Varying σ_e also mimics the effect of input correlations between individual synapses. In particular, there is a one-to-one correspondence of σ_e and the correlation coefficient of the synaptic input [5,15]; for example, with the present model parameters, values of σ_e of 5 and 11 nS give similar voltage dynamics of a detailed model with synaptic correlations of 0.1 and 0.9, respectively (Fig. 5 in Ref. [5]).

To measure the regularity of the spiking activity, we used the coefficient of variation (CV) of the interspike intervals (ISIs), a commonly used measure of spike train regularity [1,3,15,16–20]:

$$CV = \frac{\sigma_{ISI}}{\langle ISI \rangle} = \frac{\sqrt{\langle ISI^2 \rangle - \langle ISI \rangle^2}}{\langle ISI \rangle}, \qquad (4)$$

where $\langle ISI \rangle$ and $\langle ISI^2 \rangle$ denote the mean and the mean squared ISIs, respectively. The timing of an action potential is determined by the upward crossing of the membrane voltage past a detection threshold of $-10\,\text{mV}$. All simulations were made using the NEURON simulation environment [21].

Results

We performed computations to examine the effect of variability of the synaptic input on the regularity of spiking activity of cortical neurons, at two extreme regimes of

overall background synaptic input: LC and HC states. Specifically, we varied the standard deviation of the excitatory conductance, σ_e, while maintaining a constant average conductance of both the excitatory and inhibitory input. In the LC state the mean excitatory and inhibitory conductances are equal, whereas in the HC state the mean inhibitory conductance is several times larger than the mean excitatory conductance [9].

The mean and standard deviation of the CV of ISIs were collected for 100 simulation trials of 200 s duration each, for 28 values of σ_e, in the range of 1.5–72 ns, for both conductance states (Fig. 1). In HC states, the mean CV values are near 1 for small input variability, decreasing almost linearly as the variability increases. In contrast, the LC state demonstrates a resonance-like relation between input variability and spiking regularity: as the variability in the excitatory input increases, the CV of ISIs first increases and then decreases. It may also be noted that although the CV values in LC states are smaller than those in HC states, they still fall in the physiological range of 0.5–1.0 reported by Softky and Koch [1] over the entire range of values of σ_e in the simulations.

Larger values of the input variability decrease the difference between the CV measures of the two conductance states, eventually converging to a value around 0.7 (Fig. 1), consistent with the measured variability of spontaneous discharge of cortical neurons in awake animals [1,2,15], suggesting that larger values of the input variability shifts the firing characteristics of LC states toward that of HC states.

The error bars in Fig. 1 show a significant variability of the regularity measure, CV, from trial to trial, consistent with experimental data, indicating that the degree of irregularity of neuronal firing is itself noisy [16]. Although increasing the variability in the synaptic input has different effects on the regularity between the LC and HC states, for both states there is a consistent reduction in the standard deviations of CV with increased input variability. However, whereas in
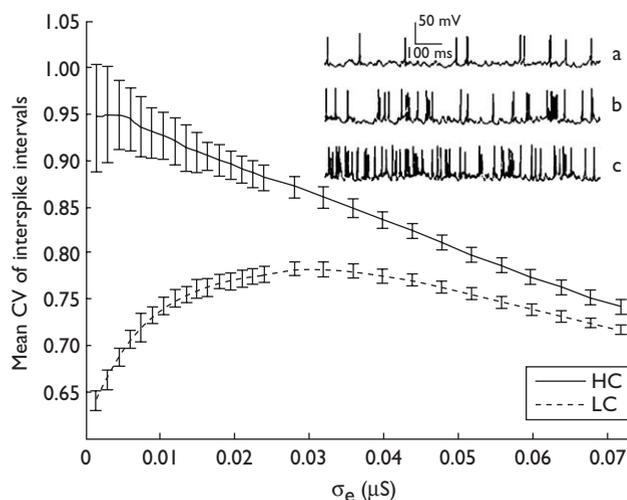
Fig. 1 Mean CV of interspike intervals vs. σ_e in LC and HC states of a point neuron model. Error bars show standard deviations over 100 trials of 200 s each. Inset: sample voltage traces for HC states. (a) CV=0.92, firing rate F=10 Hz and average membrane potential $V_M = -67.1 \pm 4.8\,\text{mV}$ for $\sigma_e = 0.015\,\mu\text{S}$. (b) CV=0.87, F=27 Hz and $V_M = -68.2 \pm 5.5\,\text{mV}$ for $\sigma_e = 0.03\,\mu\text{S}$. (c) CV=0.73, F=54 Hz and $V_M = -69.7 \pm 6.2\,\text{mV}$ for $\sigma_e = 0.07\,\mu\text{S}$. CV, coefficient of variation; HC, high conductance; LC, low conductance.

the LC state, the dispersion of the CV is small over the entire range of the input variability and only weakly sensitive to the variability, in the HC state the variance of the CV is large for small input variability, dropping rapidly as the variability increases, and eventually becoming similar to that of the LC state.

We also examined the spike CV vs. firing frequency curves for both conductance states (Fig. 2), finding CV values in the physiological range of 0.5–1.0 [1] for high firing rates. As would be expected from the fact that the HC and LC states differ by the larger amplitude of inhibition in the former, the mean firing rate at a given value of the input variability is greater for the LC state (Fig. 3). This figure also shows that increasing input variability, which gives larger membrane voltage fluctuations, increases the firing rate in both conductance states [14] (see inset of Fig. 1).
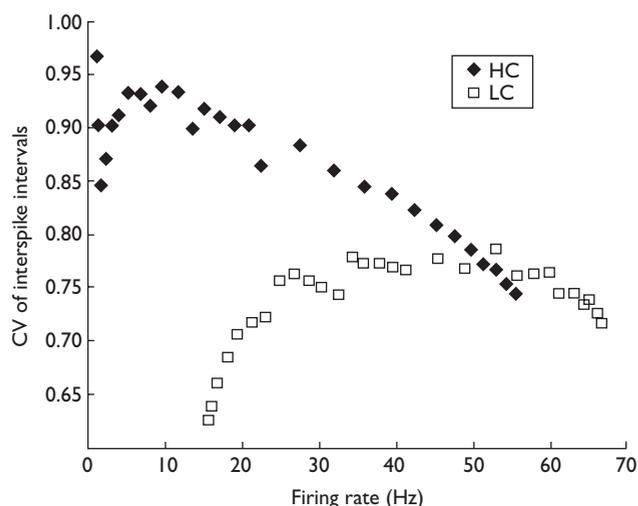
Fig. 2 CV vs. firing rate showing the irregularity at high firing rates in LC and HC states. Each point was computed by a simulation of 200 s of the point-conductance model. CV, coefficient of variation; HC, high conductance; LC, low conductance.
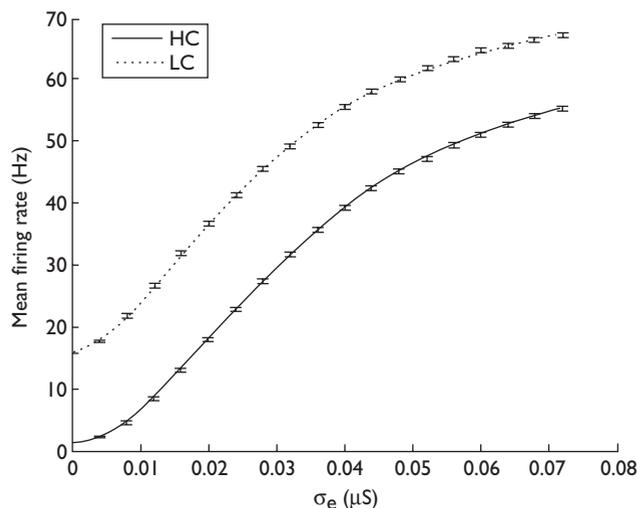
Fig. 3 Mean firing rates vs. σ_e in LC and HC states. Increasing the input fluctuations causes an increase of firing rates in both HC and LC states. Error bars show standard deviations over 100 trials of 200 s each. HC, high conductance; LC, low conductance.

Discussion

In this study, we compared the effect of variability in the synaptic background activity on the regularity of spikes evoked by that activity, of the cortical neuron at the two extreme conductance regimes, corresponding to the LC and HC states. We showed that CV of ISIs fall in the physiological range of 0.5–1.0 reported by Softky and Koch [1] for both conductance states (Fig. 1) for input parameters corresponding to a large range of input fluctuations. Increasing the variability of the input causes an increase of firing rates (Fig. 3) and decreases the noisiness of CV in both conductance states (Fig. 1). In the HC state, the spike CV decreases with increasing input variability, but in the LC state the spike CV increases with an initial increase in the input variability and decreases with a further increase in the variability. The spike CV in the two conductance states approach a similar value for large values of the variability and in particular, the spike CV decreases with higher firing rates (Figs 1 and 2), as observed experimentally [1] and computationally [22].

The spike output CV in the HC state is always greater than that in the LC state (Fig. 1). As the neuron in the HC state has stronger inhibition, this suggests that one role of background inhibitory activity is to increase the firing variability for the same input variability relative to the LC state [16] or alternatively, that the background inhibition allows the neuron output to more closely replicate the variations in the input.

The only source of variability in this study is from the excitatory synaptic input, quantified by the standard deviation of the Ornstein–Uhlenbeck input process [Eq. 3]. With respect to firing variability, one might expect that the output CV of a neuron would tend to increase for a larger input variability, but in this study, we find more complex behavior. This result may be understood by first considering events obtained by applying a threshold to a continuous random process. The upper bound on CV of the event interval, 1, is reached when there is no memory in the system. As this applies for an arbitrary probability distribution feeding the threshold, increasing the standard deviation of that distribution, as in the present case, does not change CV of the intervals. Increasing the standard deviation does increase the probability of the passing threshold, and thus increases the event rate, precisely what we see in both conductance states (Fig. 3).

Any mechanism that adds memory to the process will tend to reduce the CV of the event intervals – here there are three mechanisms that impact the results. Two of these tend to reduce CV as the firing frequency increases. The first is memory in the input, specifically the limited bandwidth of the Ornstein–Uhlenbeck input processes, parameterized by the (nonzero) values of τ_e and τ_i. The second is memory in the output, specifically the refractory period of spike generation, or the minimum time between two spikes imposed by the kinetics of the Na^+ and K^+ currents. As firing frequency increases, the refractory period becomes more significant relative to the diminishing ISI, contributing to a reduction in the output CV [22].

The third mechanism for reducing output CV is the low-pass filter characteristic of the cell membrane, which can be considered as a memory mechanism interposed between the two described above. The effect of the membrane filter is relevant at low-firing rates, specifically low amplitudes of the input variations, because the standard deviation term in Eq. 3

is directly related to the high-frequency content of the Ornstein–Uhlenbeck input process. Thus, the slower the cutoff frequency of the filter, the larger the increase in the output CV for a given increase in the input variability, as the stronger high frequency content of the larger variations are better 'seen' by the spike threshold. As the LC state has a longer average membrane time constant, or stronger 'memory', and therefore stronger low-pass filtering, the frequency-dependent attenuation of the input 'information' will be stronger in the LC state than in the HC state. By the same token, the faster membrane time constant of the HC state, or less 'memory', causes the variability of the membrane potential to be more directly slaved to the variability of the synaptic input, as compared with the LC state.

The net result is competing state-dependent relationships between input fluctuations and output variability. A positive dependency due to membrane filtering dominates for low values of the input variability (thus low firing rates) in the LC state but not in the HC state, because the two states differ precisely by their membrane properties. A negative dependency due to the bandwidth of the input and spike refractoriness dominates for high values of the input variability (thus high firing rates) in both conductance states, because both mechanisms are independent (to a first approximation) of the membrane's average conductance. As mentioned, the variability of the input process in the model, or the size of the fluctuations, may be related to the strength of the correlations between synapses in a full model. As neurons *in vivo* can, in principle, operate between the two extreme conductance states, the physiological implication is a state-dependent operational range for how a neuron's quiescent firing state reflects the inherent correlations of the network bombardment, as opposed to simply the mean of that activity.

Conclusion

We show that the regularity of spike trains and the firing rate of cortical neurons increase in HC states with the increasing variability of the background synaptic input. In LC states, although firing rate increases with the increasing variability, firing regularity decreases with the initial increase in the variability and increases with further increase of the input variability. The qualitative difference between these relationships for the LC and HC states suggests that the functional transmission by cortical neurons of network variability or correlations may depend on different states of the overall network activity.

Acknowledgements

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