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Consequences of correlated synaptic bombardment on the responsiveness of neocortical pyramidal neurons

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Abstract

Model neocortical pyramidal neurons were investigated to evaluate the impact of correlated synaptic bombardment on cellular responsiveness. The responses to simulated glutamatergic (AMPA-mediated) excitatory inputs were analyzed by comparing correlated and uncorrelated background activity. Pyramidal cells behaved stochastically, consistent with the high variability of responses typically observed in vivo. Interestingly, the responsiveness was enhanced in the presence of correlated background activity, allowing the neuron to respond to inputs that would normally be subthreshold. We suggest that during active states, neocortical neurons should be described by stochastic equations which may better reflect their behavior, compared to a deterministic description. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Cerebral cortex; Synaptic background activity; Stochastic Computational models; Firing probability

1. Introduction

The companion paper [7] has established that the highly fluctuating background activity present in vivo necessary implies the presence of correlations in the release of excitatory and inhibitory synapses. We have analyzed here consequences of this type of activity on the response of pyramidal neurons.

The first consequence of correlated synaptic activity was that the neuron did not respond reliably, thus leading to a probabilistic description of its response. This

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finding is consistent with in vivo observations. Computing the probability of firing in different conditions showed another consequence: correlated synaptic bombardment enhances the response of the cell, contrary to results previously reported [1,2,8,9].

We begin by showing the probabilistic response of the cell, then we show how to compute such a probability and finally, we illustrate the enhancement of responsiveness induced by correlated synaptic activity.

2. Methods

The model used in this paper was described in the companion paper and in Ref. [6]. An AMPA-mediated synaptic input of uniform density of conductance in all the dendrites was simulated in addition to the background activity. This second population of synapses is used to stimulate the neuron without disrupting the background activity.

3. Results

In layer VI pyramidal neuron used in the simulations, synaptic background activity is simulated by Poisson-distributed random release events at glutamatergic and GABAergic synapses [6,7]. The frequency of release is 1 Hz at glutamatergic synapses and 5.5 Hz at GABAergic synapses.

When the release events are uncorrelated, the model does not demonstrate the typical characteristics of in vivo recordings. The membrane potential undergoes only small fluctuations and no action potentials are produced. However, when small correlations are introduced in the background synaptic activity, the model shows the typical features of neurons recorded during the active states: a depolarized membrane potential, low input resistance, high amplitude of membrane potential fluctuations and sustained firing in the 5–20 Hz range [6,7].

The first consequence of correlated synaptic bombardment on the response of the neuron is that it does not respond reliably in this condition. When stimulated by the second population of synapses with a uniform density of conductance in the whole dendritic tree, the output of the cell is very variable. A stochastic description of the neuron's output would thus be more well suited than a deterministic one (see Section 4).

The following protocol is designed to compute the probability of firing (Fig. 1). A simulation is first run without any stimulation. Then, the same simulation is run (same pseudo-random numbers), but with stimulations at every 100 ms. The spikes close in time are removed, leaving only the spikes specifically evoked by the stimulations.

Computing the probability of firing for different stimulus amplitudes gives us the input–output relation of the neuron (probability of firing versus density of conductance of the stimulus). This relation is profoundly affected by the presence of synaptic bombardment. In quiescent conditions (no bombardment), the input–output relation

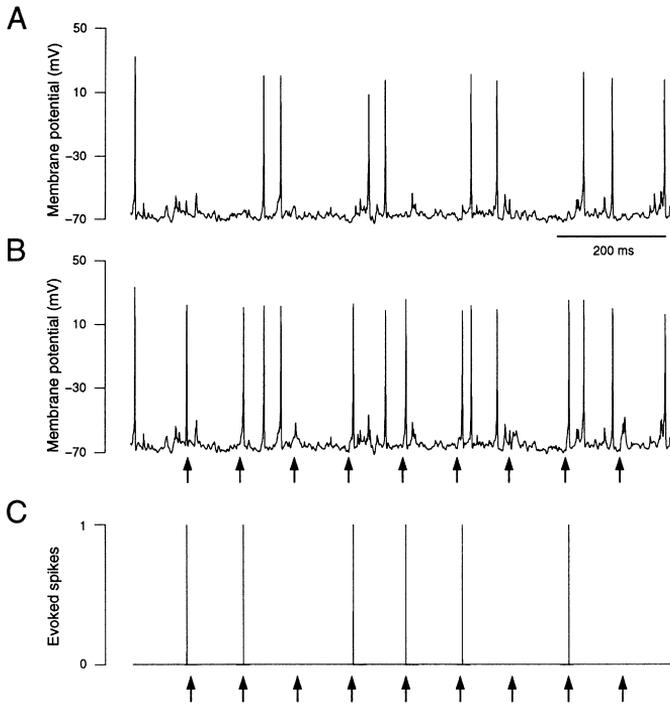


Fig. 1. Computation of the probability of firing. (A) A simulation is run without stimulation. (B) The same simulation is run with stimulations from the second population of synapses for every 100 ms. (C) Spikes close in time are subtracted and only the spikes specifically generated by the stimulations are left.

is all-or-none, reflecting the classic Hodgkin–Huxley threshold for action potentials (Fig. 2A). When uncorrelated synaptic bombardment is added, the curve is shifted towards higher input strength (Fig. 2B), consistent with previous modeling studies [1,2,8]. The curve is also sigmoidal, due to the stochastic nature of the synaptic activity. A more interesting effect is seen when the release events of the synaptic background activity include correlations. The curve now spans over a much larger range of stimulus amplitudes. Furthermore, it is now possible to generate an action potential with a small, but non-zero probability, below the threshold in quiescent conditions (Fig. 2C, arrow). Also, the cell can now distinguish stimulus that were indistinguishable in quiescent conditions (Fig. 2C, *). The cell is therefore more responsive to afferent inputs and can discriminate them more accurately in presence of correlated background activity.

4. Discussion

Neocortical pyramidal neurons receive 5000–60 000 synapses [4,5], 70% of them being from other neocortical neurons. It is therefore possible that such an intense connectivity leads to correlations in the afferent inputs. It has indeed been shown that

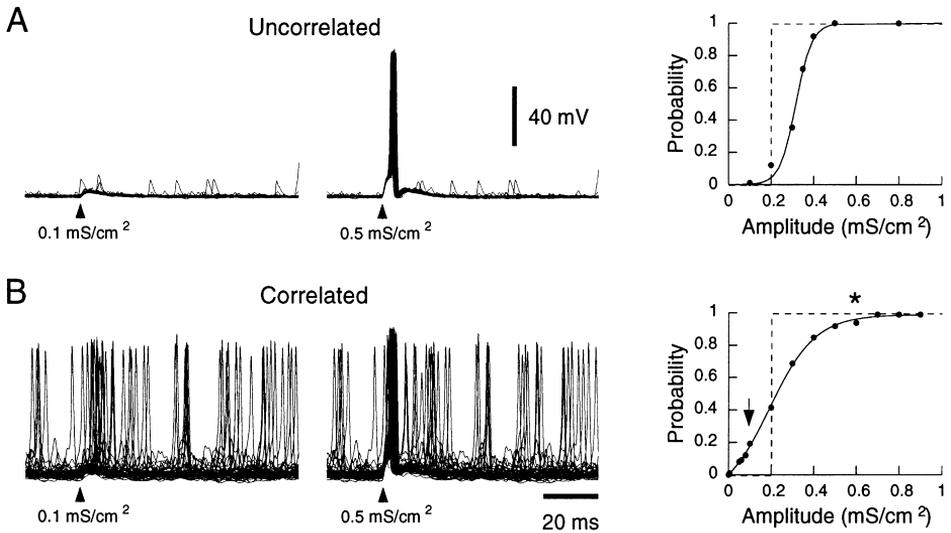


Fig. 2. Response curve in different background conditions. Left: 45 successive trials of synaptic stimulation for two different stimulus amplitudes. Right: Response curves expressed as the probability of evoking a spike (calculated over 100 trials) as a function of stimulus amplitude. (A) Dashed line: In quiescent conditions, the input–output relation is all-or-none, reflecting the threshold for action potential. Continuous line: In presence of uncorrelated synaptic background activity, the curve is shifted towards higher input strength and is sigmoid, due to the inherent randomness of the background activity. (B) Dashed line: Same curve as in A. Continuous line: In the presence of correlated synaptic bombardment, the curve spans over a much larger range of input strength. Inputs that were subthreshold now have a small, but non-zero, probability of evoking an action potential (arrow). Also, inputs that were indistinguishable can now evoke different responses (*).

there is an average correlation of 0.12 measured between pairs of neurons in the cerebral cortex of behaving monkeys [10]. There is, however, no proof that the correlations are induced specifically by the structure of the neocortex. This could be the focus of future research, both experimental and theoretical.

Our analysis suggests that, due to correlated background activity, cortical neurons *in vivo* are intrinsically stochastic. The fluctuations induced by background activity are responsible for a spontaneous firing in the 5–20 Hz range, as typically found in neurons recorded in awake animals. Cortical neurons in active states have therefore a “resting” firing probability which is non zero. Thus, the probability of firing of a given neuron, P_i , can be represented by an equation of the form

$$\frac{dP_i}{dt} = -\frac{1}{\tau}(P_i - P_R),$$

where P_R is the “resting” firing probability and τ is the time constant of the membrane.

In these conditions, when the neuron receives a supplementary excitation, the probability increases transiently, while it shows a transient decrease in the presence of a supplementary inhibition (not shown). In addition, preliminary results (see Figs. 10 and 11, in Ref. [6]) indicate that proximal and distal excitatory inputs have a similar

effect at the soma, suggesting that their effect may be independent of their exact location in the dendritic tree. Together, these results suggest that the probabilistic behavior of neurons in active states is compatible with a phenomenological equation of the form

$$\frac{dP_i}{dt} = -\frac{1}{\tau}(P_i - P_R) - F\left(\sum_{exc} P_j\right)(P_i - P_E) - F\left(\sum_{inh} P_j\right)(P_i - P_I),$$

where $P_E > P_R$ is the steady-state value towards which the probability would converge if all excitatory synapses would be activated, and similarly, $P_I < P_R$ is the steady-state value for maximal inhibitory activation. The location-independent efficacy of synapses is represented by an unweighted sum over all afferent contributions P_j (*exc* and *inh* represent the subset of excitatory and inhibitory neurons, respectively). The function F represents the nonlinear transformation and thresholding in dendrites, and is usually taken as a sigmoid function starting at 0 and saturating to a maximal value.

It should be possible to deduce the exact form of this equation and of the function F by fitting this phenomenological model to the behavior of the detailed biophysical model, and/or to experimental data whenever possible.

The model also suggests that in conditions similar to *in vivo* recordings, the responsiveness of the neuron is enhanced. Correlations in the background activity facilitate the detection of weak inputs and increase the ability to discriminate large inputs. Parameters such as dendritic geometry and the relative conductances present in the dendrites have no major effect on these conclusions (not shown).

This conclusion may seem of limited scope for a single neuron. The implications are much better seen at the network level. The probability of firing of the single neuron is translated in a number of neurons firing in the network. Inputs converging towards the population of “active” neurons can evoke a wide variety of responses, ranging from no neuron firing to all the neurons firing, when a “quiescent” population of neurons can only evoke a very limited range of response. This wide variety of responses could improve the information processing abilities of the network. Correlations could thus play an important role in attentional mechanisms and aroused states.

This predicted increase of responsiveness could be measured experimentally using intracellular recordings *in vivo* in animals anesthetized by urethane or ketamine-xylazine, for which neocortical neurons oscillate synchronously between an active phase and a hyperpolarised phase [3]. The active phase shows an intense synaptic activity and the hyperpolarised phase is characterized by a virtual absence of such an activity. According to the model, stimulations that are subthreshold or indistinguishable should evoke action potential or become distinguishable in the active phase.

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