Location independence and fast conduction of synaptic inputs in neocortical neurons *in vivo*

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Abstract

Neocortical neurons *in vivo* operate in a high-conductance state characterized by an intense intracellular fluctuating activity. Here we investigate how these conditions impact on the dendritic integration of synaptic inputs by using biophysical models of morphologically-reconstructed neocortical pyramidal neurons. We find that the combined effect of high conductance and fluctuating activity due to the synaptic background activity may set pyramidal neurons into an integrative mode which is determined by the intensity of network activity, which is fast-conducting and in which the impact of inputs is roughly location-independent.

Key words: cerebral cortex, dendritic integration, synaptic background activity, dendritic spikes, computational models

1 Introduction

Active cortical states *in vivo* are characterized by a marked tonic increase of conductance compared to quiescent states, as well as sustained and irregular voltage fluctuations due to the presence of synaptic background activity [4,7,9]. However, how these conditions shape the integration of synaptic inputs remains unknown, mainly due to the technical difficulties of performing controlled experiments during activated states of the network in the intact brain.

Here we address this problem by using computational models of morphologically-reconstructed neocortical pyramidal neurons in which *in vivo* conditions were simulated by random excitatory and inhibitory synaptic inputs in soma and dendrites. We show that the presence of background activity defines a

dynamic state in which mechanisms of dendritic integration are qualitatively different compared to quiescent states.

2 Methods

Simulations were performed based on several morphologically-reconstructed pyramidal cells of cat cortex (layer II-III, V and VI) [1]. Different combinations of passive parameters were used, including different values of the axial resistivity (80 to 250 Ωcm), and different distributions of leak conductances in soma and dendrites [10].

Voltage-dependent currents included fast Na^+ and delayed-rectifier K^+ currents with different kinetics, a voltage-dependent K^+ currents, a Ca^{2+}-dependent K^+ current, a high-threshold Ca^{2+}-current, a persistent Na^+ current, as well as A-type K^+ currents. All currents were simulated by Hodgkin-Huxley type models. Various combinations and densities (e.g. 3 to 12 mS/cm^2 for fast Na^+, and 5 to 10 mS/cm^2 for delayed-rectifier K^+ currents) were tested. For details we refer to [6,8].

Synaptic currents corresponding to AMPA and $GABA_A$ receptors were simulated according to two-state kinetic models [2] with quantal conductances of 1.2 nS for AMPA and 0.6 nS for $GABA_A$ [3]. Synaptic densities were estimated from morphological studies of neocortical pyramidal cells.

Synaptic background activity was simulated by random (Poisson-distributed) release events at all synapses with average rates between 0.1 to 1 Hz at glutamatergic, and 0.55 to 5.5 Hz at GABAergic synapses. The release statistics was altered by including a correlation between release events [3].

For stimulation, a supplementary set of AMPA synapses was placed at different locations in the dendritic tree. Stimulation intensity was adjusted by varying the number of colocalized synchronously activated AMPA-mediated synapses.

3 Results

We first compared the effect of synaptic background activity on action potential (AP) initiation and propagation in dendrites. In quiescent conditions, superthreshold stimulation either by somatic current injection or synaptic stimulation evoked action potentials first in the axon, followed by a somatic spike which propagated back into the dendrites with declining amplitude, in accordance with experimental studies [5]. Although *in-vivo*-like conditions did not

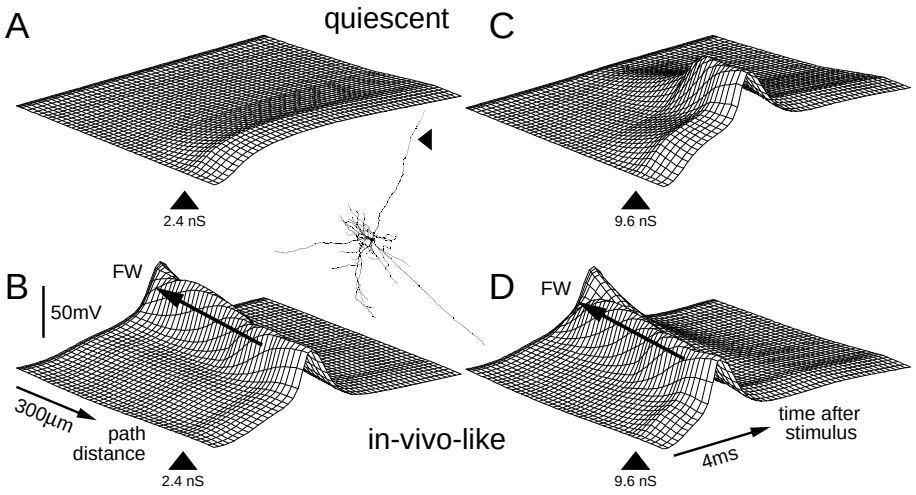

Fig. 1. Somatodendritic membrane voltage profiles for synaptic stimulation (A, B: amplitude 6 nS; C, D: amplitude 12 nS) in the distal apical dendrite of a layer V neuron (path distance 800 μm, see inset) under quiescent (A,C) and *in vivo*-like (B,D) conditions. Initiation and active forward-propagation of dendritic spikes evoked in the distal region is favored under *in-vivo*-like conditions (FW: forward propagating dendritic spikes).

impact on temporal order of axonal/somatic spike initiation, the distance of robust backpropagation of APs was smaller and often failed to reach more distal parts of the dendrites.

Under quiescent conditions, the threshold for AP initiation in the dendrites was high (Fig.1A) compared to states with network activity (Fig.1B). Forward-propagation of dendritic APs initiated by strong synaptic stimulation occured in the quiescent state only over limited distances (Fig.1C), and was sensitive to morphological or electrophysiological peculiarities, such as branch points, passive properties or distribution of active conductances. In contrast, under *in-vivo*-like conditions, at equivalent voltages, dendritic APs could forward-propagate over large distances and reach the soma (Fig.1D).

We next investigated the consequences of forward-propagating dendritic APs on the cellular response by computing the post-stimulus time histogram (PSTH) over long periods of time with repeated stimulation of single or groups of colocalized excitatory synapses. Under *in vivo* conditions, PSTHs obtained for stimuli occurring at different distances from the soma revealed a roughly location independent impact of synaptic stimulation (Fig.2A). The "efficacy" of synaptic stimulation, quantified by the probability that a somatic spike is specifically evoked by a synaptic stimulus, was found to be roughly independent of synapse location for a broad range of stimulus amplitudes subthreshold under quiescent conditions (Fig.2B), and was robust against changes in the background intensity (Fig.2D).

To show how this location-independent mode depends on forward-propagating

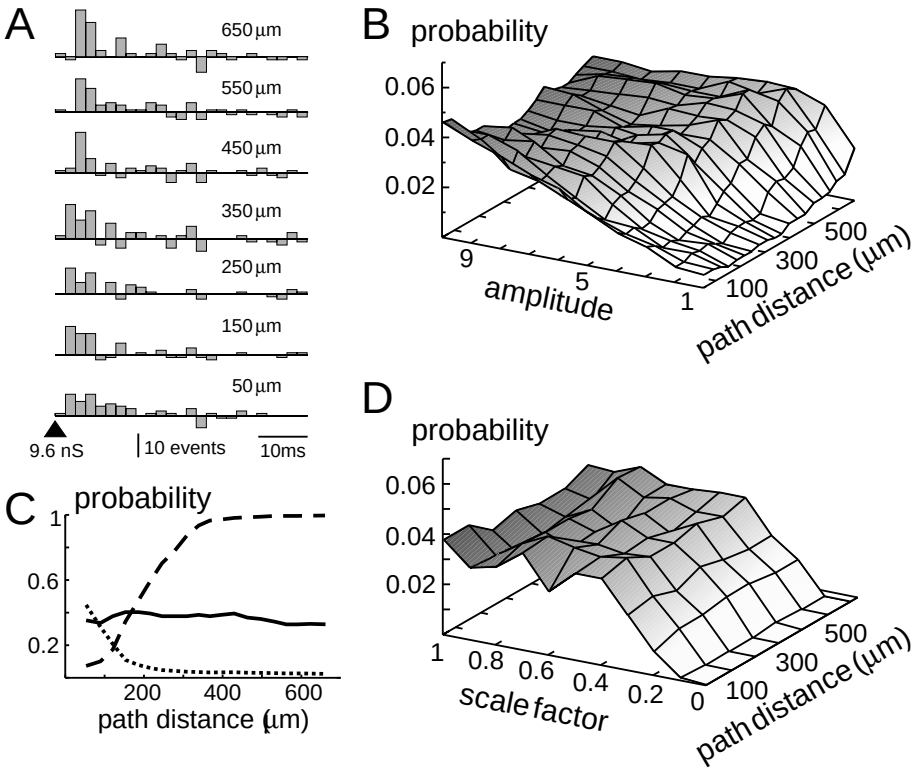

Fig. 2. Independence of the somatic response to the location of synaptic stimulation under *in-vivo*-like conditions. **A.** Post-stimulus time histograms (PSTHs) of responses to identical AMPA-mediated synaptic stimuli (9.6 nS) at different dendritic locations. **B.** Integrated PSTH (probability that a somatic spike was specifically evoked by the stimulus) as a function of stimulus amplitude (number of synchronously activated colocalized synapses with quantal conductance 1.2 nS) and distance to soma. **C.** Comparison of the probability of evoking a dendritic spike (dashed) and the probability that an evoked spike translated into a somatic/axonal spike (dotted), represented as a function of the location of the stimulus (stimulus amplitude 9.6 nS). The solid line represents the multiplication of this two probabilities ($\times 10$), leading to the probability of somatic spike specifically evoked by the stimulus. **D.** Integrated PSTH for various intensities of background activity obtained by scaling the release frequencies at all terminals (stimulus amplitude 12 nS).

dendritic APs, we selected all stimulation trials which evoked dendritic spike and found that the probability for stimulus evoked dendritic spikes increases with path distance from the soma for fixed stimulation amplitude (Fig.2C, dashed). On the other hand, the probability that a stimulus evoked dendritic spike propagates all the way down to the soma and triggers a somatic spike was found to decrease with path distance due to the higher chance of interference with background induced fluctuations along the path (Fig.2C, dotted). Remarkably, these two opposing effects nearly compensated such that the probability of evoking a soma/axon AP was approximately independent on the distance to soma (Fig.2C, solid).

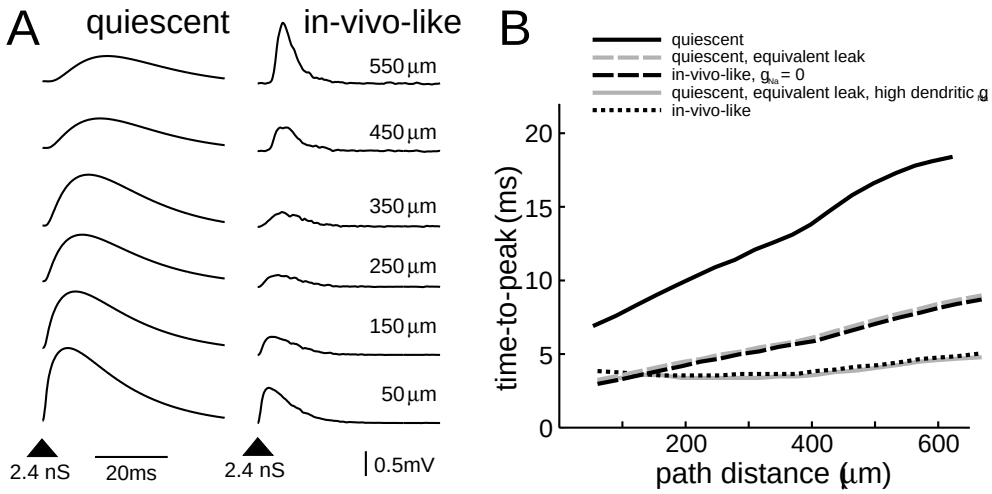

Fig. 3. **A.** Somatic voltage deflections of EPSPs following synaptic stimulation (subthreshold at the soma) at different dendritic sites in the quiescent and under *in-vivo*-like conditions. **B.** Time-to-peak for somatic voltage deflections for both conditions (dashed), and mechanism underlying fast dendritic conduction. Replacing background activity by an equivalent (light grey), or suppressing dendritic Na^+ channels (light grey dashed) led to an intermediate location-dependence of EPSP time-to-peak. High dendritic excitability together with strong synaptic stimuli evoked reliable dendritic APs and yielded a reduced location dependence of the time-to-peak in quiescent conditions (black solid), comparable to *in-vivo*-like conditions (black dotted).

Active network conditions also impacted on the somatic voltage deflections of dendritic EPSPs (Fig.3A), yielding an increase of the peak height for distal stimulations under *in-vivo*-like conditions due to the presence of stimulation triggered forward-propagating dendritic spikes. In contrast, in quiescent conditions, the amplitude monotonically declined with increasing path distance of the stimulus. Surprisingly, the presence of dendritic spikes also showed an impact on the timing of synaptic events, yielding a marked reduction of the location dependence of the time-to-peak compared to quiescent conditions (Fig.3B, compare black solid and black dotted). Both the synaptic background induced high-conductance state as well as the intense fluctuating activity were found to be the determining factors of this fast-conducting state *in vivo* (Fig.3B).

4 Conclusions

We have investigated the impact of synaptic background activity at a level present *in vivo* on the dendritic integration of synaptic inputs using computational models of neocortical pyramidal neurons. The results suggest that the synaptic background activity present *in vivo* sets pyramidal neurons into a qualitatively different integrative mode, determined by the intensity of net-

work activity, which is fast-conducting and in which the impact of inputs is roughly location-independent. This mode was found for different morphologies without fine-tuning the model, and was also robust to changes in active channels kinetics and distribution, passive settings as well as to the intensity of background activity.

The proposed mechanism suggests that in active states in the intact brain the integration of synaptic inputs is not constrained by cellular morphology, but instead must be viewed as a state and activity-dependent dynamic property. The impact of the proposed mechanism on the spatial and temporal integration of more complex synaptic inputs, such as paired events, will be the subject of future investigations (research supported by CNRS and NIH).

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