Point-conductance models of cortical neurons with high discharge variability

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Abstract

Recent in vivo intracellular measurements indicate that cortical neurons operate in a high-conductance state mainly caused by intense network activity. Biophysical models of morphologically-reconstructed neocortical neurons with thousands of random synaptic events successfully reproduce intracellular measurements and the high discharge variability. Here we compare several classes of simplified models. Experimental findings are reproduced when the high-conductance component is explicitly taken into account. In contrast to integrate-and-fire models, the high discharge variability does not depend on the balance between excitation and inhibition. We suggest that basic electrophysiological properties and irregular activity of cortical neurons in vivo can be optimally captured by high-conductance models.

Keywords: Cerebral cortex; Point conductance; Synaptic background activity; Spontaneous discharge variability; Computational models

1. Introduction

Cortical neurons in vivo generate action potentials with highly irregular interspike intervals (ISI), both during sensory stimuli and during spontaneous activity. The coefficient of variation ($C_V$), the standard measure for the variability of a spike train, was measured in cat and macaque V1 and MT neurons [11] and reported to be higher than 0.5.

Much theoretical work has since been done to construct modeling frameworks which could account for this observed high irregularity. Softky and Koch [11] showed that

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neither the integration of random EPSPs by a simple leaky integrate-and-fire (IAF) neuron model, nor a more biophysical model of a layer V cell with passive dendrites were able to generate the high $C_V$ observed in vivo. In other contributions [1,10,13] it was argued that a balancing of conductances could generate a high $C_V$ in IAF models.

In this paper we construct two conductance-based neuron models, a biophysical multi-compartment model of a neocortical pyramidal neuron with active dendrites subject to Poisson-like synaptic background activity, constrained by recent experimental data obtained from cat parietal cortex in vivo [2,4,8], and a simple one-compartment “point-conductance” model, described by stochastic random-walk processes. We show that these models successfully describe in vivo like activity of neocortical neurons, and reproduce the high $C_V$ observed in vivo. The results are compared with another type of simplified models, where spontaneous discharge activity is produced by injection of noisy current.

2. Methods

Detailed biophysical model: A computational model was designed based on a morphologically-reconstructed layer VI neocortical pyramidal of a cat, obtained from a previous study [2] (Fig. 1A), with passive parameters as described in [4,8]. Active ionic currents (sodium current, delayed-rectifier and $V_m$-dependent potassium currents) were simulated by inserting Hodgkin–Huxley type conductances, with kinetics as well as somatic and dendritic densities based on measurements in neocortical pyramidal neurons [4].

Synaptic currents were incorporated by using two-state kinetic models [5] of AMPA and GABA_A receptors. Quantal conductances were estimated by matching the model to recordings of miniature synaptic events [4]. A total of 16,563 glutamatergic and 3,376 GABAergic synapses were used [3]. Synaptic background activity was simulated by the firing of inhibitory and excitatory synapses according to a Poisson-like process with average rates of $v_{inh} = 5.5$ Hz for GABA_A and $v_{exc} = 1.0$ Hz for AMPA synapses (see [4,7,9] for details).

Simplified models: Four simplified models were constructed to approximate synaptic background activity. In the point-conductance model [6], the total synaptic current was decomposed into a sum of inhibitory ($g_i$) and excitatory ($g_e$) conductances, described by a one-variable stochastic process similar to the Ornstein–Uhlenbeck process [12]. In the fluctuating current model, a membrane current described by an Ornstein–Uhlenbeck process was injected into the cell. In two other models, the total synaptic current was represented by a constant current with a fluctuating conductance, and a constant conductance with a fluctuating current, respectively. All resulting models were inserted in a single compartment with a total membrane area equivalent to that of the layer VI cell used in the biophysical model. Voltage-dependent conductances matching that used in the detailed model were incorporated in the simplified model. See [6] for details about the model settings.
3. Results

In the detailed biophysical model, high-frequency synaptic release conditions due to background activity with a weak correlation at a level evidenced previously between pairs of neurons in the monkey cerebral cortex [14], lead to a spontaneous spiking activity of the cell between 5 and 20 Hz (Fig. 1B). The cell displays a depolarized $V_m$, an about 5-fold lower input resistance (Fig. 1C), and high-frequency $V_m$ fluctuations with standard deviation between 2 and 4 mV, consistent with recent in vivo measurements [4].

Correlated synaptic background activity in conjunction with active dendrites leads to spontaneous discharge patterns, characterized by a $C_V$ around unity (Fig. 1D), in excellent agreement with experimental results [11]. Various cellular parameter settings show only a minimal impact on the $C_V$ (see Fig. 1D for different membrane
Fig. 2. Fluctuating point-conductance model of synaptic background activity. (A) Fit of the free model parameters using the conductance power spectral densities obtained from the detailed model (upper panel: excitatory, lower panel inhibitory). (B) Fluctuating $V_m$ in the presence of synaptic background activity represented by two fluctuating conductances. Under quiescent conditions the $V_m$ was resting at $-80 \text{ mV}$. (C) A hyperpolarizing pulse of $-0.1 \text{ nA}$ injected at $-65 \text{ mV}$ under active conditions leads to a marked decrease in the input resistance compared to the quiescent case (average of 100 pulses). (D) The coefficient of variation $C_V$ for different membrane excitability (equivalent to settings in Fig. 1D). (E) The $C_V$ as a function of the average excitatory and inhibitory conductances.

Excitability, and Fig. 1E for different excitatory and inhibitory conductances). In all simulated cases the model preserves the high $C_V$ of the distributed Poisson-distributed synaptic input trains. An independent change in the release frequencies for excitatory and inhibitory terminals within a range of 50–200% around the optimal value of 1 Hz, and 70–150% around the optimal value of 5.5 Hz established previously [4], respectively, impacts directly on the balance between excitation and inhibition. However, a $C_V$ higher than 0.5 could be evidenced in a broad range of frequency settings, in contrast to the necessary fine-tuning of the balance between inhibitory and excitatory conductances in IAF neuron models [1].

Similar results were obtained for the point-conductance model after fitting the free parameters (Fig. 2A). The model correctly reproduced experimental measurements in vivo [8] (Fig. 2B) and captured the effect of background activity on input resistance (Fig. 2C) as well as on the amplitude of $V_m$ fluctuations [6]. The spontaneous discharge
Fig. 3. Comparison of different simplified models of synaptic background activity. In the point-conductance model \((g_0 + \text{fluctuating } g)\), excitatory and inhibitory conductances were changed around a mean according to an Ornstein–Uhlenbeck process, leading to a high \(C_V\) around unity. In the fluctuating current model \((i_0 + \text{fluctuating } i)\), random currents around a mean described by an Ornstein–Uhlenbeck process, lead to a much lower variability of the spontaneous discharge activity. In two other models (constant current with fluctuating conductance around a zero mean, and a constant conductance with fluctuating current around a zero mean) higher \(C_V\) values were obtained, showing that high conductance states account for the high discharge variability.

activity showed a high variability with a \(C_V\) around unity for a variety of cellular (see Fig. 2D for membrane excitability) and background (Fig. 2E) properties. On the other hand, the fluctuating current model leads to considerably lower \(C_V\) values (Fig. 3, white dots), whereas the model with background activity described by a constant conductance and fluctuating current lead to a discharge variability comparable to that found in the point-conductance model.

4. Conclusion

We have presented two conductance-based neuron models which successfully reproduce in vivo activity of pyramidal cells. The background activity causes a highly fluctuating intrinsic cellular activity and high conductance states, whose resulting spontaneous discharge patterns show a high variability (\(C_V\) around unity). We have shown that this variability is only minimally effected by cellular properties and remains stable even for a high disturbance of the balance between inhibitory and excitatory inputs, in contrast to results obtained with simple IAF neuron models.

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References