

A novel method for characterizing synaptic noise in cortical neurons

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Abstract

Cortical neurons *in vivo* are subject to intense synaptic noise that has a significant impact on various electrophysiological properties. Here we characterize the subthreshold activity of cortical neurons using an explicit solution of the passive membrane equation subject to independent inhibitory and excitatory conductance noise sources described by stochastic random-walk processes. The analytic expression for the membrane potential distribution can be used to estimate the average and variance of synaptic conductances from intracellular recordings obtained under current clamp. We demonstrate the application of this method to neuronal models of various complexity as well as to *in vitro* intracellular recordings.

Key words: cerebral cortex, membrane equation, subthreshold activity, Ornstein-Uhlenbeck, Fokker-Planck,

1 Introduction

Intracellular recordings of cortical neurons *in vivo* consistently display a highly complex and irregular activity [1,2] which results from an intense and sustained discharge of presynaptic neurons in the cortical network. Computational models suggest that this tremendous synaptic activity, or synaptic “noise” [3], may have important consequences on the integrative properties of these neurons [4], as well as on the subthreshold behavior [5].

Here we focus on the interplay between network activity and subthreshold dynamics of individual neurons in the cortex. We approached this issue in the context of stochastic calculus by explicitly solving the stochastic passive membrane equation. This approach provides a novel method for characterizing

synaptic noise based on intracellular recordings obtained under current stimuli, aiming at extracting information about the underlying network activity.

2 Methods

Effective models of subthreshold *in vivo* neuronal dynamics were constructed using the stochastic passive membrane equation subject to two independent colored Ornstein-Uhlenbeck (OU) multiplicative synaptic noise processes describing inhibitory and excitatory conductances $g_e(t)$ and $g_i(t)$ [6]: $C_m a \dot{V}(t) = -g_L(V(t) - E_L) - g_e(t)(V(t) - E_e) - g_i(t)(V(t) - E_i) + I$, where $V(t)$ denotes the membrane potential, I a stimulating current, C_m the specific membrane capacity, a the membrane area, g_L and E_L are the leak conductance and reversal potential, E_e and E_i the reversal potentials for $g_e(t)$ and $g_i(t)$, respectively. Using the stochastic differential calculus, the governing Fokker-Planck equation was solved, yielding an analytic expression for the membrane potential (V_m) probability distribution $\rho(V)$ at steady-state [7].

The question to which extend the analytic approach captures the stochastic dynamics of neuronal models subject to distributed noise sources was addressed by using computational one- and multi-compartment models (incorporated into the NEURON simulation environment [8]) with synaptic noise described by thousands of independent (Poisson-distributed) excitatory and inhibitory random synaptic inputs [4,6]. In some cases, voltage-dependent membrane currents for spike generation were included into the models.

In vitro experiments were performed in slices of the ferret visual cortex. These slices display spontaneously generated recurrent waves of robust action potential and synaptic activity that travel throughout the extent of the slice and resemble the slow oscillation during slow-wave sleep [9]. In intracellular recordings, this network activity manifests as a depolarized state (*up-state*). To characterize synaptic noise, intracellular recordings were collected at several different membrane potentials maintained by injection of steady currents through the recording micropipette (current clamp).

3 Results

Intracellular recordings at two constant stimulating currents I_1 and I_2 yield two steady-state V_m distributions which can be described by their means \bar{V}_1 , \bar{V}_2 and standard deviations σ_{V1} , σ_{V2} . From these, together with the analytic expression for $\rho(V)$ [7], the mean and variance of the excitatory and inhibitory synaptic noise (g_{e0} , g_{i0} and σ_e , σ_i , respectively) can be explicitly estimated:

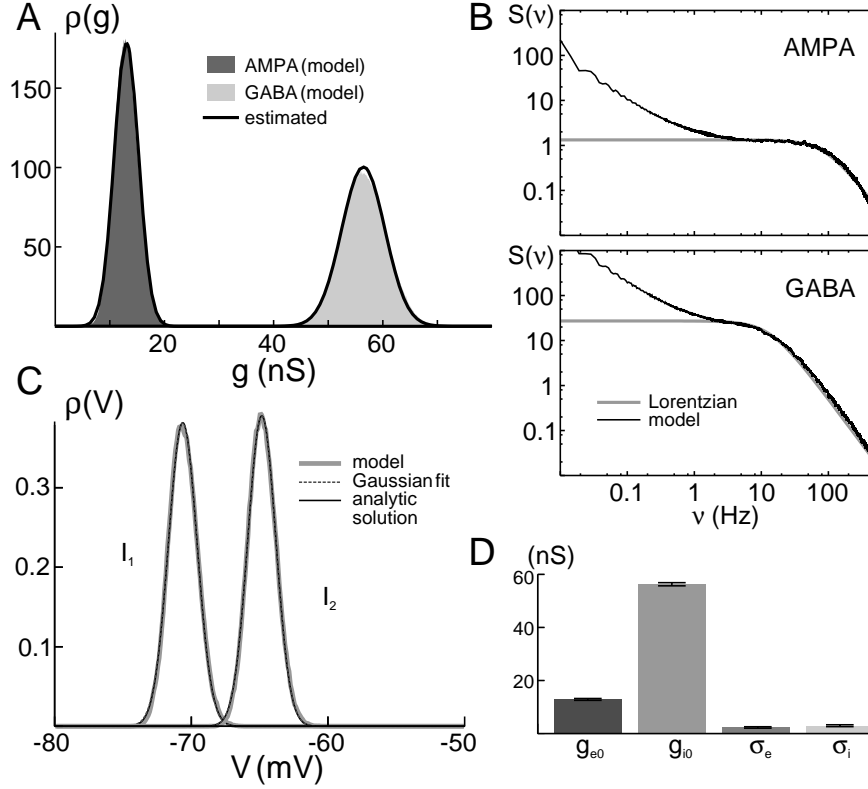


Fig. 1. Estimation of synaptic noise parameters in a one-compartment model subject to random synaptic inputs (4472 excitatory and 3801 inhibitory synapses releasing according to independent Poisson processes). The latter yield nearly Gaussian distributions $\rho(g)$ (A, grey) whose power spectral density $S(\nu)$ deviates only for low frequencies $\nu < 1$ Hz from a Lorentzian $S(\nu) = \frac{2D\tau^2}{1+(2\pi\tau\nu)^2}$ expected for OU noise (B). V_m distributions $\rho(V)$ (C, grey) obtained at two different constant currents ($I_1 = -0.5$ nA, $I_2 = 0$ nA) allowed to deduce synaptic noise parameters (D). The latter led to conductances distributions (A, black) and analytic V_m distribution $\rho(V)$ (C, black), which were in excellent agreement with the numerical simulations.

$$\sigma_{\{e,i\}}^2 \tau_{\{e,i\}} = \frac{2aC_m \Delta I_{12} [\sigma_{V1}^2 (\Delta E_{\{i,e\}2})^2 + \sigma_{V2}^2 (\Delta E_{\{i,e\}1})^2]}{(\Delta E_{e1} \Delta E_{i2} + \Delta E_{e2} \Delta E_{i1}) \Delta E_{\{ei,ie\}} (\Delta \bar{V}_{12})^2},$$

$$g_{\{e,i\}0} = \frac{\sigma_{\{e,i\}}^2 \tau_{\{e,i\}}}{2aC_m} - \frac{\Delta I_{12} \Delta E_{\{i,e\}2} + (I_2 - g_L a \Delta E_{\{i,e\}L}) \Delta \bar{V}_{12}}{\Delta E_{\{ei,ie\}} \Delta \bar{V}_{12}}.$$

Here, $\Delta E_{e1} = E_e - \bar{V}_1$, $\Delta E_{e2} = E_e - \bar{V}_2$, $\Delta E_{i1} = E_i - \bar{V}_1$, $\Delta E_{i2} = E_i - \bar{V}_2$, $\Delta E_{ei} = -\Delta E_{ie} = E_e - E_i$, $\Delta \bar{V}_{12} = \bar{V}_1 - \bar{V}_2$ and $\Delta I_{12} = I_1 - I_2$.

This method was first tested by characterizing the excitatory and inhibitory conductances distributions in simplified one-compartment models with synaptic noise described by thousands of independent Poisson-distributed inputs (Fig. 1A, grey). The estimation of noise parameters (Fig. 1D) based on $\rho(V)$ obtained at two constant current stimulations (Fig. 1C, grey) yielded conductance distributions (Fig. 1A, black) which closely matched the distributions

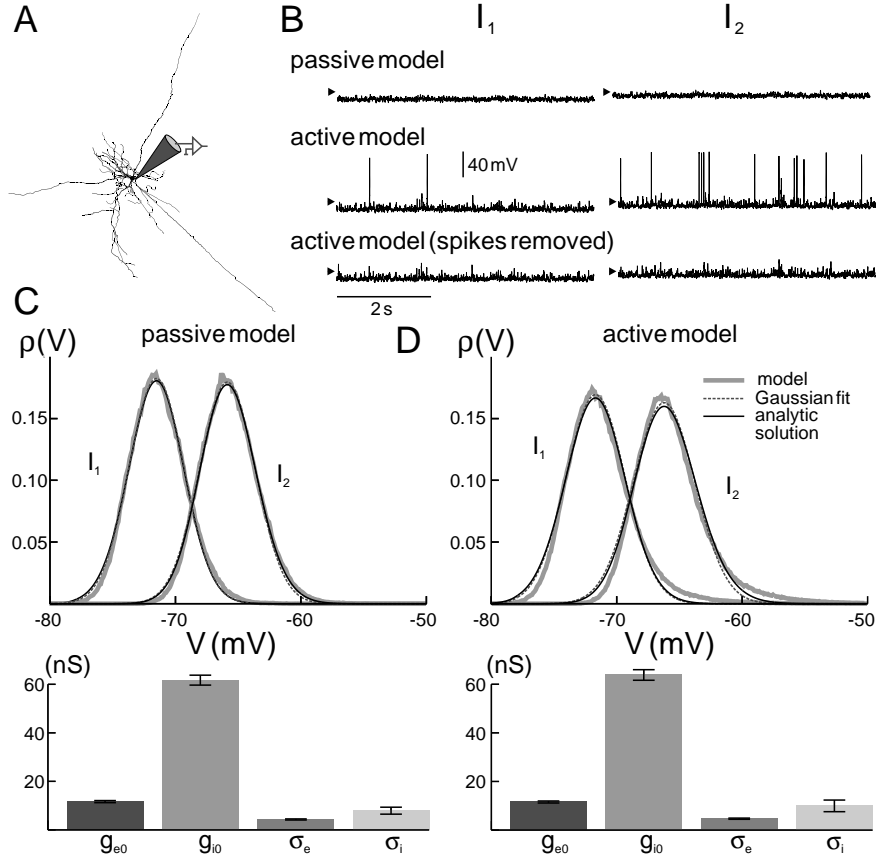


Fig. 2. Estimation of synaptic noise parameters in (passive and active) biophysical multi-compartment models of cortical neurons (A) subject to distributed excitatory and inhibitory synaptic noise. The cellular activity at two different injected currents ($I_1 = -0.5$ nA, $I_2 = 0$ nA; B) yielded V_m distributions $\rho(V)$ (C,D, top, grey) from which synaptic noise parameters were deduced (C,D, bottom). The corresponding analytic solutions for $\rho(V)$ (C,D, top, black) closely matched the distributions obtained from numerical simulations. No major differences were found between the passive (C) and active (D) model. The arrows in B denote a V_m of -60 mV.

due to Poisson inputs. Differences between the computational and stochastic model were minimal and observed only for low frequencies < 1 Hz in the power spectrum (Fig. 1B), thus validating the OU process as an effective model of synaptic noise. The corresponding analytic V_m distributions (Fig. 1C, black) were also in excellent agreement with those from the numerical simulations.

The approach was further tested using detailed biophysical models of morphologically reconstructed cortical neurons (Fig. 2A) with random synaptic inputs distributed in dendrites (Fig. 2B; for models see e.g. [4]). The obtained synaptic noise parameters (Fig. 2C and D, bottom) yielded analytic V_m distributions which were in excellent agreement with distributions obtained from numerical simulations (Fig. 2C and D, top). The characterization of synaptic noise was also in agreement with estimations obtained under voltage-clamp (e.g. [6]; data not shown), and only minimal differences were found when active mem-

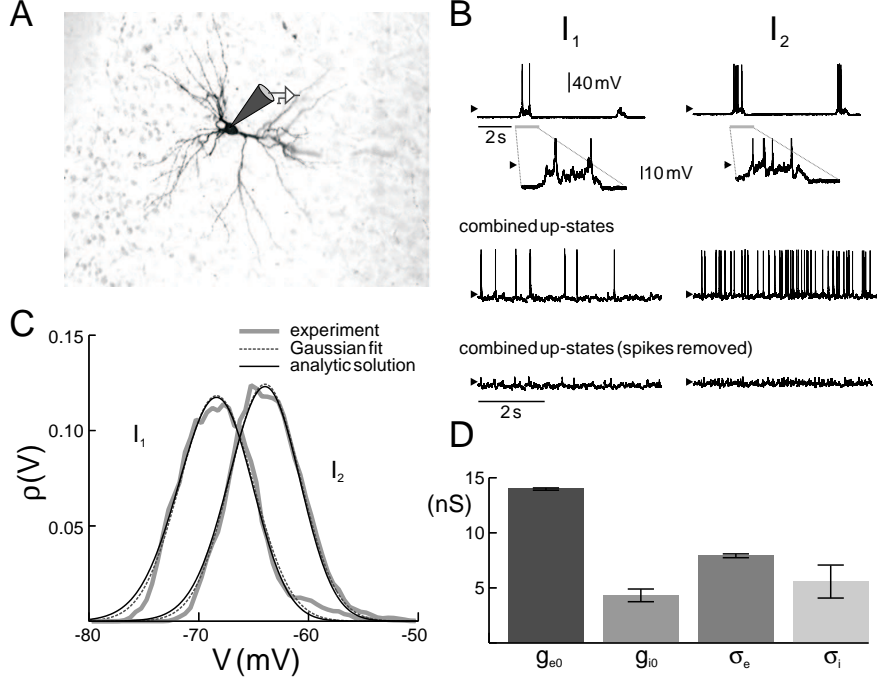


Fig. 3. Characterization of synaptic noise in specific network states (up-states) from *in vitro* intracellular recordings (A). The V_m profiles (B, upper traces) show periods of spontaneous network activity (up-states). After combining such states from recordings at two different injected constant currents ($I_1 = -0.3257$ nA, $I_2 = -0.01$ nA) and removing of spikes (B, bottom traces), the resulting V_m distributions (C, grey) were used to estimate synaptic noise parameters (D). The resulting analytic V_m distributions $\rho(V)$ (C, black) were found to nearly match the experimental ones. The arrows in B denote a V_m of -60 mV.

brane currents for spike generation were incorporated into the model (compare Fig. 2C and D). These results suggest that even for spatially extended dendritic structures and in the presence of active membrane conductances, the proposed method may allow an estimation of the statistical properties of excitatory and inhibitory conductances in different network states.

Finally, we applied the method for estimating synaptic noise parameters to intracellular recordings *in vitro* (Fig. 3A). Network activity during spontaneous up-states [9] (Fig. 3B) was characterized using recordings at two injected constant currents. After collecting appropriate up-states (Fig. 3B, bottom), V_m distributions were obtained (Fig. 3C) from which synaptic noise parameters were estimated (Fig. 3D). Using these estimates for g_{e0} , g_{i0} , σ_e and σ_i , the resulting analytic V_m distributions $\rho(V)$ were shown to nearly match the experimental ones. We also injected the estimated stochastic conductances into the same cell at rest using the dynamic-clamp protocol. This way, artificial active states were created, whose V_m distribution and discharge activity resembled those observed during the “natural” up-states, thus further validating the method (data not shown).

4 Conclusions

We constructed and analytically solved effective stochastic models of cortical neurons subject to multiplicative synaptic noise using the Fokker-Planck approach. The explicit expression for the V_m distribution allows to estimate synaptic noise parameters from intracellular recordings, thus yielding an effective characterization of cortical network activity. The proposed method was successfully applied to various models of cortical neurons and *in vitro* intracellular recordings. In all cases, the estimated synaptic noise parameters yielded analytic V_m distributions, which were in excellent agreement with those obtained numerically or from experimental recordings. The evaluation of this method from experimental data, the assessment of its sensitivity, and the application to issues like gain modulation or differences between synaptic noise models will be the subject of forthcoming studies.

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