Estimation of synaptic conductances and their variances from intracellular recordings of neocortical neurons *in vivo*

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Abstract

During intense network activity, neocortical neurons are in a "high-conductance" state. To estimate the respective contributions of excitatory and inhibitory conductances in generating such states, we combined computational models with intracellular recordings obtained in cat parietal cortex *in vivo*. Fitting a fluctuating-conductance model to the recordings revealed that inhibitory conductances are dominant (about 3-5 times larger than excitation). Conductance variance (i.e., the "noise") was also larger for inhibition, indicating that inhibitory dynamics has a pronounced impact on membrane potential fluctuations. We conclude that the synaptic bombardment of neocortical neurons *in vivo* is not excitatory, but mostly determined by inhibitory conductances.

Key words: cerebral cortex, synaptic noise, subthreshold activity, stochastic systems

Extended abstract

1. We combined computational models with intracellular recordings of morphologically-identified pyramidal neurons in cat parietal cortex to estimate the conductance due to background synaptic activity *in vivo*. Experiments were conducted using ketamine-xylazine anesthesia, which generates recurrent periods of activity similar to the wake state: neurons fire tonically at 5-20 Hz and the electroencephalogram (EEG) is characterized by low-amplitude fast activity [1,2]. These periods of

intense activity will be referred to as "active periods". In some experiments, stimulating electrodes were placed in the pedonculopontine tegmental nucleus (PPT). PPT stimulation evoked active periods of 20 to 30 s duration which were always paralleled with low-amplitude fast-frequency EEG. Both type of active periods display similar electrophysiological characteristics as neurons recorded in awake animals [2,3].

2. In previous work [4,5], we measured the effect of network activity on the input resistance (R_{in}) by comparing intracellularly-recorded cells in active periods and after microperfusion of tetrodotoxin (TTX) to the cortex. This analysis revealed that active states are characterized by a dramatically larger (about 500%) total conductance (5 times smaller R_{in}) compared to the resting state obtained after TTX. Synaptic activity was also responsible for an important depolarization (average V_m of $< V_m > = -65$ mV $\pm$ 2 mV, compared to -80 mV after TTX) and large amplitude V_m fluctuations (V_m standard deviation of σ_V=4 $\pm$2 mV). We report here similar values during active states following PPT stimulation. However, the R_{in} tended to be higher (up to 40% difference) and the V_m more hyperpolarized (a few millivolts) than during ketamine-xylazine anesthesia. Because the PPT participates to the ascending activating system during wakefulness, these states are electrophysiologically close to aroused states.

3. To estimate the respective contribution of excitatory and inhibitory conductances, we integrated these measurements in a passive membrane equation:

$$C_m \frac{dV_m}{dt} = -g_{leak}\,(V_m - E_{leak}) - g_{exc}\,(V_m - E_{exc}) - g_{inh}\,(V_m - E_{inh})\,,$$

which leads to estimates of

$$g_{exc}/g_{leak} = 0.73 \qquad g_{inh}/g_{leak} = 3.27\,.$$

The ratio g_{inh}/g_{exc} is therefore of 4.45 on average (ketamine-xylazine) and 4.7 for PPT stimulation.

To check for consistency, we used the above conductance values in the passive equation to predict the average V_m in conditions of reversed inhibition (chloride-filled pipettes; measured E_{inh} of -55 mV). The predicted $< V_m >$ was of -51.9 mV, which is remarkably close to the measured value of $< V_m >= -51$ mV [4,5]. This analysis therefore shows that for all experimental conditions (ketamine-xylazine anesthesia, PPT-induced active states, and reversed inhibition experiments), inhibitory conductances are several-fold larger than excitatory conductances. This conclusion is also in agreement with the strong inhibitory conductances measured in voltage-clamped cortical neurons during visual responses *in vivo* [6].

4. To determine the absolute values of conductances and their variance, we used a method consisting in fitting the experimental V_m distributions with the analytic

solution obtained from the above membrane equation when g_{exc} and g_{inh} are described by random walk processes [7]:

$$\frac{dg_u}{dt} = -(g_u - < g_u >)/\tau_u + \sqrt{D_u}\,\xi_u(t)\,,$$

where $< g_u >$ denotes the mean (static) and $2\sigma_u = \sqrt{D_u\,\tau_u}$ the standard deviations for excitatory and inhibitory synaptic conductances ($u = \{exc, inh\}$; ξ_u are independent Gaussian white noise processes, D_u the noise diffusion coefficients and τ_u the noise time constants). The explicit form of the membrane potential probability distribution at steady-state, which can be deduced by solving the stochastic membrane equation, yields analytic expressions for the mean $< g_u >$ and standard deviations σ_u of the synaptic conductances as functions of the mean and standard deviation of the membrane potential distribution at two different injected constant currents (see details of the method, as well as *in vitro* applications, in jointly submitted contribution [8]).

Applying this procedure to the active states of ketamine-xylazine anesthesia led to the following values for the synaptic conductances:

$$< g_{exc} >= 0.036\ \mu S \qquad < g_{inh} >= 0.127\ \mu S$$

(ratio g_{inh}/g_{exc} of 3.52), and for their standard deviation:

$$\sigma_{exc} = 0.013\ \mu S \qquad \sigma_{inh} = 0.021\ \mu S\,.$$

These values therefore confirm the above estimation that inhibitory conductances are several-fold larger than excitatory contributions. Inhibitory conductances also display the largest variance and have a determinant influence on V_m fluctuations. These predictions should be testable by dynamic-clamp experiments (see also [8]).

In summary, combining computational models with intracellular recordings of cortical neurons during active states *in vivo* allowed us to estimate that these neurons are in a high-conductance state dominated by inhibitory conductances. This conclusion is reached by using two different methods and is also consistent with recordings with reversed inhibition. The standard deviation of the conductance was also large for inhibition, suggesting that inhibitory conductances provide a major contribution to setting the high levels of fluctuations characteristic of active states. We therefore conclude that the "synaptic bombardment" of neocortical neurons during active states is not excitatory (as often assumed), but is mainly determined by the dynamics of inhibitory conductances.

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