

# Reconstructing synaptic background activity from conductance measurements *in vivo*

Q.Zou\*<sup>a</sup> M.Rudolph<sup>a</sup> N.Roy<sup>b</sup> M.Sanchez-Vives<sup>c</sup> D.Contreras<sup>b</sup>  
A.Destexhe<sup>a</sup>

<sup>a</sup>UNIC, CNRS, Gif-sur-Yvette, France

<sup>b</sup>Dept. Neurosci., University of Pennsylvania, Philadelphia, USA

<sup>c</sup>Inst. Neurosci., Universidad Miguel Hernandez-CSIC, Alicante, Spain

---

## Abstract

To reconstruct synaptic background activity, we combined computational models with intracellular recordings *in vivo*. A new conductance analysis method applied to intracellular recordings in the somatosensory cortex of anesthetized rats revealed mirror changes of excitation and inhibition during the up and down states of slow waves, but concerted changes in conductance variances. We then used these measurements to constrain the patterns of random release at excitatory and inhibitory synapses in computational models. We show that measurements of the mean and variance of conductances are sufficient constraints to design models fully consistent with *in vivo* recordings.

*Key words:* somatosensory cortex, subthreshold activity, synaptic noise, computational model

---

## 1 Introduction

During active states, neocortical neurons display intense background activity which is characterized by high-amplitude membrane potential ( $V_m$ ) fluctuations and a large overall conductance [1]. Models are needed to investigate the impact of background activity on the integrative properties of cortical neurons. Ideally, these models should be matched to intracellular measurements, but there exists very few quantitative methods to perform such a matching.

In the present paper, we propose such a method based on a new procedure for extracting conductances from intracellular recordings [2,3]. We apply this method to recordings of slow waves in rat somatosensory cortex *in vivo*, then build computational models based on the conductance parameters provided by this analysis.

## 2 Methods

Combined intracellular and local EEG recordings were performed in the barrel cortex of rats anesthetized with urethane. In this preparation, cortical neurons display spontaneously occurring slow-wave oscillations, which are characterized by periods of low-amplitude fast-frequency EEG activity lasting a few hundred milliseconds. During this activity, the membrane shows a transition between a down-state (characterized by a relatively hyperpolarized  $V_m$ , small fluctuations and absence of discharge activity) to an up-state (characterized by a depolarized  $V_m$  with large fluctuation amplitude and spontaneous discharge activity) back to a down-state.

Based on intracellular recordings at two different clamped currents, we characterized the conductance variations during slow waves by using a recent method based on computing membrane probability distributions (see details in ref. [3]).

Numerical simulations were performed using a 3-compartment model with morphological and electrophysiological properties described in [4,5]. A large amount of synapses (16,898 glutamatergic and 3,576 GABAergic synapses), described by two-state kinetic models [6], were distributed in all compartments. The total conductance contribution for different release statistics (characterized by the release rate  $\nu_{AMPA}$ ,  $\nu_{GABA}$  and temporal correlation  $c_{AMPA}$ ,  $c_{GABA}$  of AMPA and GABA synapses, respectively) were accessed using an ideal voltage-clamp (series resistance of 1 M $\Omega$ ) and were constrained by the values measured from experiments.

## 3 Results

We first characterized the time course of intracellular and network activity during slow-wave oscillations by estimating the mean and variance of the  $V_m$  and total synaptic conductances. The population activity (local EEG, Fig. 1A) was used for the alignment (dashed lines) of individual intracellular recordings to the start and end of the up-states (Fig. 1, left and right, respectively). During the up-state, cells discharge at higher rate and showed a marked depolarization and increase in the  $V_m$  variance compared to the down-state (Fig. 1B). Surprisingly, in this preparation, up and down states were characterized by a similar input conductance for all cells analyzed (n=6).

Estimating synaptic conductances from subthreshold membrane potential fluctuations (see Methods) revealed that the transition to up-states is associated with an increase in the mean excitatory and decrease in the mean inhibitory conductance. The variances of both inhibitory and excitatory conductances increased and show high-frequency fluctuations with periods around 50 ms (Fig. 1C, left). The termination of the up-state showed the opposite pattern of synaptic conductance changes

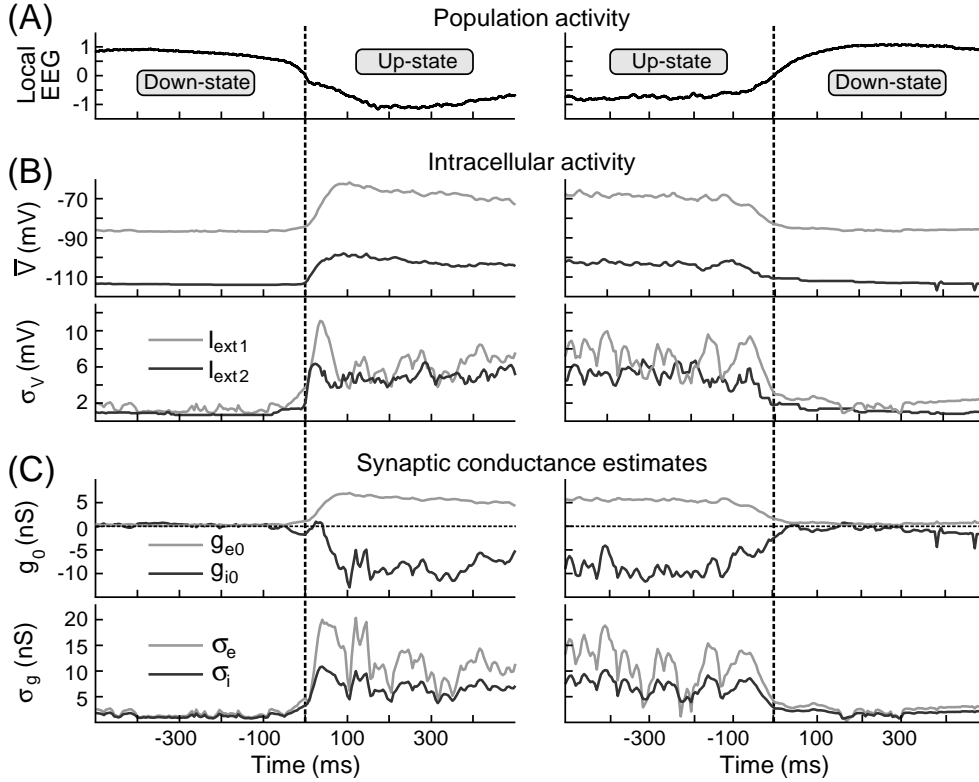


Fig. 1. Characterization of intracellular activity during slow-wave oscillations *in vivo*. A: The population activity (local EEG) is used to align individual intracellular recordings (dashed lines) corresponding to the start (left) and end (right) of the up-states characterizing slow-wave oscillations. B: Gaussian approximations of the membrane potential distributions yield the mean  $\bar{V}$  and standard deviation  $\sigma_V$  as function of time during slow-wave oscillations. Corresponding values for  $\bar{V}$  and  $\sigma_V$  at two different currents ( $I_{ext1} = 0.014$  nA,  $I_{ext2} = -0.652$  nA) are shown. C: With the characterization of the subthreshold membrane potential time course describing intracellular activity during slow waves, the mean  $g_{e0}$ ,  $g_{i0}$  and standard deviation  $\sigma_e$ ,  $\sigma_i$  of excitatory and inhibitory conductances can be estimated as a function of time.

(Fig. 1C, right). The time of the maximum slope of changes in the conductance mean shows a slight precedence for excitation at the beginning of the up-state in a slow-wave oscillation. Up-states terminate with a slight precedence of the decrease in the excitatory mean observed in the onset. No temporal precedence is observed in the variance of synaptic conductance changes. Similar results were obtained in all cells ( $n=6$ ), in which local EEG recordings allowed an alignment of the intracellular traces during slow-wave oscillations.

We next used these conductance measurements to build computational models. In a first step, we determined the correspondence between the release parameters of the model and global conductance properties (Fig. 2). To this end, we performed voltage-clamp simulations on a 3-compartment model with distributed synaptic inputs (see Methods). By varying the release rates at glutamatergic and GABAergic synapses ( $v_{AMPA}$  and  $v_{GABA}$ , respectively), the mean of the excitatory and inhibitory

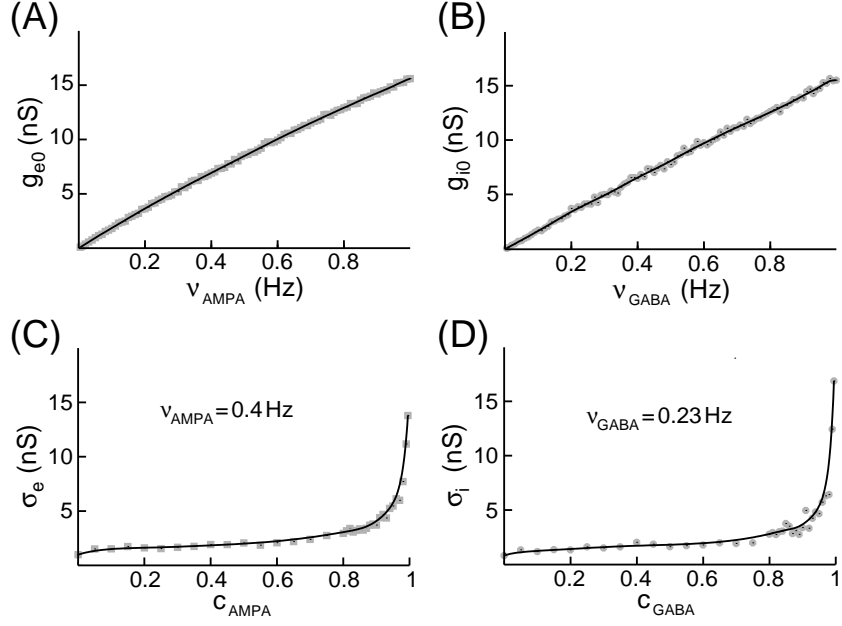


Fig. 2. Computing the correspondence between release parameters and global conductance properties. A. Relation between mean conductance ( $g_{e0}$  or  $g_{i0}$ ) and mean rate of release ( $v_{AMPA}$  or  $v_{GABA}$ ) at excitatory (left) and inhibitory (right) synapses. B. Relation between conductance variance ( $\sigma_e$  or  $\sigma_i$ ) and the temporal correlation ( $c_{AMPA}$  or  $c_{GABA}$ ) between excitatory (left) and inhibitory (right) synapses. The mean and variance of conductances were estimated by a somatic voltage-clamp (at 0 mV and -80 mV, to estimate inhibition and excitation, respectively).

conductances were changed and adjusted to the experimental estimates (Fig. 2A). Similarly, the dependence of the standard deviation of the total synaptic conductances on the temporal correlation in the release activity at synaptic terminals was used to confine  $c_{AMPA}$  and  $c_{GABA}$  (Fig. 2B).

In a second step, we simulated slow-wave oscillations using this 3-compartment model. Here, synaptic activity corresponding to the measurements of the up-states of slow waves led to a depolarized and highly fluctuating  $V_m$ , accompanied by an irregular discharge activity. In contrast, during the down-state the cell rested with low fluctuations at a hyperpolarized value (Fig. 3A). A more detailed statistical analysis showed that the  $V_m$  distribution obtained for up-states and down-states (Fig. 3B) matched those found in corresponding experiments. This suggests that the simplified computational model describing the time course of conductance during a slow-wave oscillation by fast sigmoidal changes yield slow waves with characteristics consistent with *in vivo* recordings.

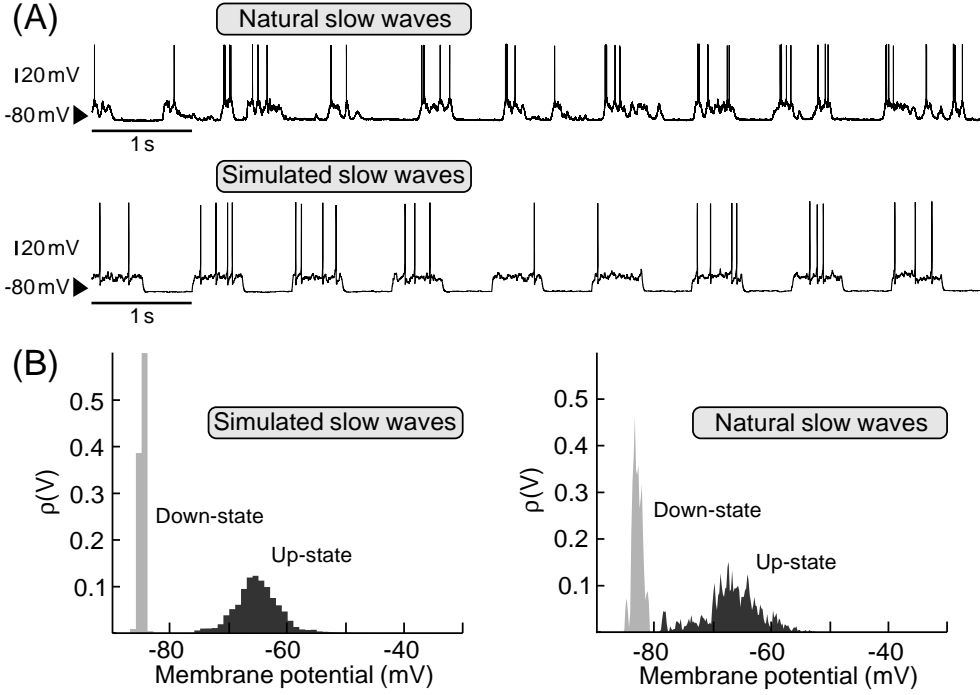


Fig. 3. Model of synaptic bombardment during slow-wave oscillations. A: For the down-state ( $R_{in} = 38 \text{ M}\Omega$ ), none of the excitatory neurons fires, whereas the release rate at GABAergic synapses was  $v_{GABA}=0.67 \text{ Hz}$  ( $g_i=11.85 \text{ nS}$ ). For upstate,  $g_i$  decreased by about 8 nS, corresponding to  $v_{GABA}=0.226 \text{ Hz}$ , whereas  $g_e$  increases by about 6 nS, corresponding input frequency  $v_{AMPA}$  between 0.3 and 0.4 Hz.  $\sigma_i$  increases by 3 to 4 nS during the transition to the up-state (corresponding to  $c_{GABA}=0.8$ ), whereas  $\sigma_e$  increases by 2 nS (corresponding to  $c_{AMPA}=0.4$ ). The periods of slow wave were 1 s. The slopes of changes in the mean and variance of synaptic conductances were fitted to experimental data. B:  $V_m$  distribution for up and down-state. The mean membrane potential was -64.80 mV and -84.90 mV, respectively, in accordance with experimental data.

#### 4 Conclusions

We showed that the conductance variations extracted from intracellular recordings are sufficient constraints to obtain a computational model fully consistent with those recordings. Using a novel method for extracting conductance parameters [2,3], we characterized the temporal pattern of the mean and variance of excitatory and inhibitory synaptic conductances in single cortical cells during slow-wave oscillations *in vivo*. This analysis showed that the transition between hyperpolarized (down) and depolarized (up) states is not accompanied by a significant change of the total input conductance due to synaptic inputs, but rather triggered by a change in the relative contribution of excitatory and inhibitory synaptic conductances. We next showed that in models there is a one-to-one correspondence between the release parameters and the global conductance parameters. Therefore, one can constrain computational models based on the conductance parameters extracted from intracellular recordings, as we showed here for slow-wave oscillations.

It is worth noting that the observation of a similar input resistance in up and down states can also be explained in terms of  $K^+$  currents. It may be that there are strong  $K^+$  currents activated during the down state, such that their total conductance is approximately equal to the conductance of background activity during the up state. This hypothesis would be more in line with previous studies in cats, showing that the down state is disfacilitation [7] and is not mediated by  $GABA_A$  inhibition [8]. However, in this preparation there is a large difference of input resistance between up and down states [1,7] unlike what we find here in rat somatosensory cortex. Moreover, the I-V relation was linear in all cells examined here, which does not indicate dominant voltage-dependent  $K^+$  conductances. Further experiments, such as reversing inhibition, or blocking  $K^+$  currents, are needed to verify which mechanism is correct, as well as to understand why the cortical state seems fundamentally different between these two preparations.

Research supported by CNRS and HFSP.

## References

- [1] A.Destexhe, M.Rudolph and D.Paré, The high-conductance state of neocortical neurons in vivo. *Nature Rev. Neurosci.* **4** (2003) 739-751.
- [2] M.Rudolph and A.Destexhe, Characterization of subthreshold voltage fluctuations in neuronal membranes. *Neural Comput.* **15** (2003) 2577-2618.
- [3] M.Rudolph, Z.Piwkowska, M.Badoual, T.Bal and A.Destexhe, A method to estimate synaptic conductances from membrane potential fluctuations. *J. Neurophysiol.* submitted (2003).
- [4] A.Destexhe. Simplified models of neocortical pyramidal cells preserving somatodendritic voltage attenuation. *Neurocomputing* **38** (2001) 167-173.
- [5] A.Destexhe and D.Paré, Impact of network activity on the integrative properties of neocortical pyramidal neurons in vivo. *J. Neurophysiol.* **81** (1999) 1531-1547.
- [6] A.Destexhe, Z.F.Mainen and T.J.Sejnowski, An efficient method for computing synaptic conductances based on a kinetic model of receptor binding. *Neural Comput.* **6** (1994) 14-18.
- [7] D.Contreras, I.Timofeev and M.Steriade, Mechanisms of long lasting hyperpolarizations underlying slow sleep oscillations in cat corticothalamic networks. *J. Physiol.* **494** (1996) 251-264.
- [8] M.Steriade and F.Amzica, Intracellular study of excitability in the seizure-prone neocortex in vivo. *J. Neurophysiol.* **82** (1999) 3108-3122.