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Activated cortical states: Experiments, analyses and models

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Abstract

In awake animals, the cerebral cortex displays an "activated" state, with distinct characteristics compared to other states like slow-wave sleep or anesthesia. These characteristics include a sustained depolarized membrane potential (V_m) and irregular firing activity. In the present paper, we evaluate our understanding of cortical activated states from a computational neuroscience point of view. We start by reviewing the electrophysiological characteristics of activated cortical states based on recordings and analysis performed in awake cat association cortex. These analyses show that cortical activity is characterized by an apparent Poisson-distributed stochastic dynamics, both at the single-cell and population levels, and that single cells display a high-conductance state dominated by inhibition. We next overview computational models of the "awake" cortex, and perform the same analyses as in the experiments. Many properties identified experimentally are indeed reproduced by models, such as depolarized V_m , irregular firing with apparent Poisson statistics and the conductance state of the membrane, suggesting that the network state displayed by models is not entirely correct. We also show how networks can approach a correct conductance state, suggesting ways by which future models will generate activity fully consistent with experimental data. © 2007 Elsevier Ltd. All rights reserved.

Keywords: High-conductance state; Cortex; Integrate-and-fire neurons; Neural networks; Poisson; Stochastic; Self-organized criticality

1. Introduction

Several experimental preparations show the propensity of cerebral cortex to generate spontaneous activity without any specific stimulus. For example, a high level of ongoing activity was reported in visual cortex in vivo, and remarkably, it was of the same order of magnitude as visuallyevoked responses (Arieli et al., 1996). Isolating the cortical tissue in vivo by creating cortical "slabs" first lead to a silent network, but activity recurs after a few days (Burns and Webb, 1979; Timofeev et al., 2000). In vitro cortical networks can also display self-sustained activity, as found in cortical slices (Sanchez-Vives and McCormick, 2000; Cossart et al., 2003) or in organotypic cultures of cortical neurons (Plenz and Aertsen, 1996).

Models of cortical networks have attempted to generate activity comparable to experiments, and several types of models were proposed, ranging from integrate and fire net-

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works (Amit and Brunel, 1997; Brunel, 2000) up to conductance-based network models (Compte et al., 2000; Timofeev et al., 2000; Vogels and Abbott, 2005; Kumar et al., in press). In particular, a recent study (Vogels and Abbott, 2005) provided relatively small networks (\simeq 10,000 neurons) displaying self-sustained activity, which were used to investigate the effect of "internal dynamics" on signal propagation.

In the present paper, we evaluate our understanding of cortical activated states from a computational neuroscience point of view. We start by reviewing the electrophysiological characteristics of activated cortical states based on recordings and analyses performed in awake cat association cortex. We next turn to models and evaluate to which extent these models can reproduce all experimental measurements.

2. Experimental characterization of activated cortical states

The term "activated" state refers to cortical activity in states of vigilance corresponding to the awake animal.

The electroencephalogram (EEG) during such activated states is typically "desynchronized", i.e., of low amplitude and irregular activity dominated by fast frequencies (15-60 Hz; see Fig. 1, Awake, EEG). Intracellularly, neurons are depolarized and fire tonic and irregular discharges (Fig. 1, Awake, Intra). This level of irregularity is also apparent in multiunit activity (Fig. 1, Awake, Units). During slow-wave sleep (SWS), the activity consists in up- and down-states which are in register with EEG slow waves (Fig. 1, SWS). Locally, the up-states are associated with desynchronized EEG, and thus can be considered as network states very close to activated states. Indeed, network activity is very similar during up-states compared to wakefulness (Fig. 1, SWS, Units). This similarity extends to various measurements, such as the patterns of discharges, patterns of correlation and relations between EEG and unit activity (Destexhe et al., 1999, 2007).

Note that, in contrast to the "global" up-states observed in vivo, "local" up-states have also been observed in vitro (Cossart et al., 2003). In this case, only a subset of the neurons enter simultaneously into firing activity. These local up-states have been connected to attractor dynamics and give additional constraints on dwell time and on activity levels. They last for several hundred milliseconds and include about 0.5-2% of the population. Such local upstates will not be considered here.

Activated states were characterized experimentally both from extracellular and intracellular recordings in order to provide constraints for models. The first type of characterization are the statistics of firing rates, which were evaluated from intracellular recordings to insure that only single neurons are considered (Fig. 2A). During wakefulness, there is a large diversity of spontaneous firing rates in different cells with inhibitory cells having larger rates of discharge (around 30 Hz on average) compared to excitatory cells (around 10 Hz on average). Another characteristic of the single-cell discharge is its irregularity. The interspike interval (ISI) distributions computed from single cells are exponentially distributed beyond a minimal refractory value (Fig. 2B), which is a characteristic property of Poisson stochastic processes (with a refractory period in this case).

In order to check for collective behavior, we have calculated the "clustering" of spikes simultaneously recorded at different sites, and in particular if the collective dynamics can be associated to neuronal "avalanches", as found in vitro (Beggs and Plenz, 2003). To perform such an analysis, the avalanches are detected as clusters of temporally contiguous spikes separated by silences, and the sign of self-organized critical state is a power-law behavior of the distribution of avalanche sizes (see Beggs and Plenz, 2003, and references therein). Such an avalanche analysis was performed from multielectrode recordings in awake cats (Bedard et al., 2006), and did not reveal the typical power-law scaling behavior of critical states, but rather exponential distributions (Fig. 2C). Such distributions are identical to those obtained using Poisson stochastic processes, compatible with the apparent Poisson statistics of single-cell firing patterns. Thus, it is unlikely that the network dynamics evolves according to a critical state; if the system would be near a phase transition, the dynamics would follow power-law behavior.



Fig. 1. Cortical activity during activated states and up/down-states during slow-wave sleep. Top traces: EEG and intracellular activity during wakefulness (left) and slow-wave sleep (right; modified from Steriade et al. (2001)). Bottom traces: raster plots of multiunit spiking activity at eight extracellular electrodes (modified from Destexhe et al. (1999)). During SWS, the down-states are indicated by vertical gray bars. All recordings were obtained from cat association cortex (area 5–7).



Fig. 2. Analysis of cortical activity during activated states. (A) Statistics of firing rates during wakefulness in cats. The left panel shows the relationship between the average V_m and the firing rate of different excitatory and inhibitory cells during wakefulness. The middle panel shows the distribution of firing rates obtained for presumed excitatory neurons, while that of inhibitory neurons is shown in the right panel. (B) Interspike interval (ISI) distributions computed from extracellularly recorded neurons in wakefulness (natural logarithms). (C) Avalanche analysis of extracellular recordings in the awake cat (natural logarithms). (D) Conductance measurements in awake cat. The distribution of relative excitatory (top) and inhibitory conductances (bottom) measured from intracellular recordings (conductances are shown relative to the leak conductance). Modified from Bedard et al. (2006) (B and C) and Rudolph et al. (2007) (A and D).

Another characterization is to measure the total synaptic conductance due to synaptic background activity. Such measurements were done from intracellular recordings in awake cats (Rudolph et al., 2007). These measurements also revealed a large diversity in different cells. Plotting the relative conductance (absolute conductance divided by the leak conductance) revealed that excitation is on average close to unity, while inhibition is larger, around 1.5 on average (Fig. 2D).

These features were confirmed recently by relating those conductance measurements to a spike-triggered average (STA) conductance analysis (Pospischil et al., 2007; Rudolph et al., 2007; Piwkowska et al., in press). It was found that the main synaptic conductance pattern associated to spikes in cortical neurons was a decrease of total conductance, which was due to a decrease of inhibitory conductance (Fig. 3). This analysis therefore shows that in awake or naturally sleeping cats, most spikes are evoked by fluctuations of inhibitory conductances. More specifically, it was shown recently that it is the ratio of variances between inhibitory and excitatory conductances that determines the exact conductance pattern associated to spikes (see details in Piwkowska et al., in press).

3. Single-cell model of activated states

The first type of model was directly linked to experimental data and was aimed at evaluating the plausibility of

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Fig. 3. Spike-triggered average conductance analysis from intracellular recordings in awake cats. (A) STA analysis during wakefulness. The time course of the excitatory and inhibitory conductances, as well as total membrane conductance, is shown in a 50 ms window prior to spikes. For most cells analyzed, the total membrane conductance dropped before the spike, which was associated with a drop of inhibitory conductance. (B) STA analysis during the up-states of slow-wave sleep. The general conductance patterns was similar as in the waking state. Modified from Rudolph et al. (2007).

conductance measurements. The conductance measurements during wakefulness (Fig. 2D) were integrated into a single-compartment model with Hodgkin–Huxley kinetics (Rudolph et al., 2007). The type of model considered was the point-conductance model (Destexhe et al., 2001), which consists in a single-compartment neuron subject to fluctuating conductances:

$$C\frac{dV}{dt} = -G_{\rm L}(V - E_{\rm L}) - g_{\rm e}(V - E_{\rm e}) - g_{\rm i}(V - E_{\rm i}) + S(t),$$
(1)

where C denotes the membrane capacitance, G_L the leak conductance and E_L the leak reversal potential. S(t) represents the spiking mechanism, which was here given by the Hodgkin–Huxley (HH) model (see Section 4.2). $g_e(t)$ and $g_i(t)$ are stochastic excitatory and inhibitory conductances, with respective reversal potentials E_e and E_i . These synaptic conductances were described by the following Ornstein-Uhlenbeck model (Destexhe et al., 2001):

$$\frac{\mathrm{d}g_{\mathrm{e}}}{\mathrm{d}t} = -\frac{1}{\tau_{\mathrm{e}}}[g_{\mathrm{e}} - g_{\mathrm{e}0}] + \sqrt{\frac{2\sigma_{\mathrm{e}}^2}{\tau_{\mathrm{e}}}}\xi_{\mathrm{e}}(t) \tag{2}$$

$$\frac{\mathrm{d}g_{\mathrm{i}}}{\mathrm{d}t} = -\frac{1}{\tau_{\mathrm{i}}}[g_{\mathrm{i}} - g_{\mathrm{i}0}] + \sqrt{\frac{2\sigma_{\mathrm{i}}^{2}}{\tau_{\mathrm{i}}}}\xi_{\mathrm{i}}(t), \qquad (3)$$

where g_{e0} and σ_e^2 are, respectively, the mean value and variance of the excitatory conductance, τ_e is the excitatory time constant, and $\xi_e(t)$ is a Gaussian white noise source with zero mean and unit standard deviation. The inhibitory conductance $g_i(t)$ is described by an equivalent equation (Eq. (3)) with parameters g_{i0} , σ_i^2 , τ_i and noise source $\xi_i(t)$.

The " $V_{\rm m}$ distribution" (VmD) method used for conductance analysis is directly derived from this model, and enables the extraction of the parameters g_{e0} , σ_e^2 , g_{i0} and σ_i^2 from experimental data (see details in Rudolph et al., 2004). The values obtained by VmD analysis of intracellular recordings in awake cats (Fig. 2D; Rudolph et al., 2007)



Fig. 4. Hodgkin–Huxley model of cortical activity during activated states and up/down-states. Top: simulated intracellular activity corresponding to measurements in the wake state (based on conductance values shown in Fig. 2D). Bottom: simulated up- and down-state transitions during slow-wave sleep (based on the values given in Rudolph et al., 2007). Right panels: $V_{\rm m}$ distributions obtained in the model (solid lines) compared to that of the experiments (gray) in the same conditions (DC injection of -0.5 and -0.43 nA, respectively). Note that the distribution in bottom right panel was calculated only from up-states. Modified from Rudolph et al. (2007).

were integrated in this model. This simulation (Fig. 4, Awake), allows us to verify that these conductance measurements led the model to generate $V_{\rm m}$ activity in excellent agreement with the intracellular recordings (see details in Rudolph et al., 2007). Similarly, integrating conductance measurements during up-states (not shown) generated $V_{\rm m}$ activity consistent with the up-down-state transitions seen experimentally (Fig. 4, SWS). These results show that the conductance estimates are consistent with the $V_{\rm m}$ activity recorded experimentally during activated states.

4. Network models of activated states

We now turn to network models that autonomously generate active states. We consider here a model derived from the Vogels and Abbott (2005) study of self-sustained irregular activity states in networks of spiking neurons with conductance-based synapses. The model consisted of 4000 neurons, which were separated into two populations of excitatory and inhibitory neurons, forming 80% and 20% of the neurons, respectively. All neurons were connected randomly using a connection probability of 2%.

The membrane equation of cell *i* was given by:

$$C_{\rm m} \frac{{\rm d}V_i}{{\rm d}t} = -g_{\rm L}(V_i - E_{\rm L}) + S_i(t) + G_i(t), \tag{4}$$

where $C_{\rm m} = 1 \,\mu\text{F/cm}^2$ is the specific capacitance, V_i is the membrane potential, $g_{\rm L} = 5 \times 10^{-5} \,\text{S/cm}^2$ is the leak conductance density and $E_{\rm L} = -60 \,\text{mV}$ is the leak reversal potential. Together with a cell area of 20,000 μm^2 , these parameters give a resting membrane time constant of 20 ms and an input resistance at rest of 100 M Ω . The function $S_i(t)$ represents the spiking mechanism intrinsic to cell *i* and $G_i(t)$ stands for the total synaptic current of cell *i* (see Section 4.3). Note that in this model, excitatory and inhibitory neurons have the same properties.

4.1. Integrate and fire (IF) models

In addition to passive membrane properties, IF neurons had a firing threshold of -50 mV. Once the Vm reaches threshold, a spike is emitted and the membrane potential is reset to -60 mV and remains at that value for a refractory period of 5 ms. This model was inspired from a previous publication reporting self-sustained irregular states (Vogels and Abbott, 2005).

4.2. Hodgkin–Huxley models

We also considered a Vogels-Abbott type network but using spike generating mechanisms described by the Hodgkin and Huxley (HH) (1952) model. HH neurons were modified from Traub and Miles (1991) and were described by the following equations:

$$S(t) = -\bar{g}_{Na}m^{3}h(V - E_{Na}) - \bar{g}_{Kd}n^{4}(V - E_{K})$$

$$\frac{dm}{dt} = \alpha_{m}(V)(1 - m) - \beta_{m}(V)m$$

$$\frac{dh}{dt} = \alpha_{h}(V)(1 - h) - \beta_{h}(V)h$$

$$\frac{dn}{dt} = \alpha_{n}(V)(1 - n) - \beta_{n}(V)n,$$
(5)

where $\bar{g}_{Na} = 100 \text{ mS/cm}^2$ and $\bar{g}_{Kd} = 30 \text{ mS/cm}^2$ are the maximal conductances of the sodium current and delayed rectifier with reversal potentials of $E_{Na} = 50 \text{ mV}$ and $E_K = -90 \text{ mV}$. *m*, *h*, and *n* are the activation variables whose time evolution depends on the (voltage-dependent) rate constants α_m , β_m , α_h , β_h , α_n and β_n . The voltage-dependent expressions for the rate constants were modified from the model described by Traub and Miles (1991):

$$\begin{split} &\alpha_m = 0.32(13 - V + V_T) / [\exp((13 - V + V_T)/4) - 1] \\ &\beta_m = 0.28(V - V_T - 40) / [\exp((V - V_T - 40)/5) - 1] \\ &\alpha_h = 0.128 \exp((17 - V + V_T + V_S)/18) \\ &\beta_h = 4 / [1 + \exp((40 - V + V_T + V_S)/5)] \\ &\alpha_n = 0.032(15 - V + V_T) / [\exp((15 - V + V_T)/5) - 1] \\ &\beta_n = 0.5 \exp((10 - V + V_T)/40), \end{split}$$

where $V_{\rm T} = -63 \text{ mV}$ adjusts the threshold (which was around -50 mV for the above parameters). The inactivation was shifted by $V_{\rm S} = 10 \text{ mV}$ toward hyperpolarized values to match the voltage dependence of Na⁺ currents in neocortical pyramidal cells (see Destexhe and Paré, 1999).

This version of the HH model is very convenient because it was matched to cortical pyramidal neurons (Destexhe and Paré, 1999), and its threshold can be easily adjusted using parameter $V_{\rm T}$. Using $V_{\rm T} = -63$ mV gives IF and HH models with approximately the same voltage threshold.

4.3. Synaptic interactions

Synaptic interactions were conductance-based, according to the following membrane equation for neuron *i*:

$$G_{i}(t) = -\sum_{j} g_{ji}(t)(V_{i} - E_{j}),$$
(6)

where V_i is the membrane potential of neuron *i*, $g_{ji}(t)$ is the synaptic conductance of the synapse connecting neuron *j* to neuron *i*, and E_j is the reversal potential of that synapse. E_j was 0 mV for excitatory synapses, or -80 mV for inhibitory synapses.

Synaptic interactions were implemented as follows: when a spike occurred in neuron *j*, the synaptic conductance g_{ji} was instantaneously incremented by a quantum value ($q_e = 6 \text{ nS}$ and $q_i = 67 \text{ nS}$ for excitatory and inhibitory synapses, respectively) and decayed exponentially with a time constant of $\tau_e = 5 \text{ ms}$ and $\tau_i = 10 \text{ ms}$ for excitation and inhibition, respectively.



Fig. 5. Network models of self-generated active states. (A) Two different network models are compared, and for each the activity of 10 cells randomly chosen in the network is displayed. Left: HH model, Right: IF model (see text for details). The two networks had the same (random) connectivity and the same 10 cells are shown. IF model based on the COBA model of Vogels and Abbott (2005). (B) Raster of spiking activity in the Vogels-Abbott model. The spiking activity is shown here for 400 cells chosen among the 4000 neurons of the network (excitatory neurons in black; inhibitory neurons in gray). All simulations were run under the NEURON simulation environment (Hines and Carnevale, 1997).

4.4. Behavior of the models

These two types of models simulate a self-sustained irregular state of activity, in which all cells fire irregularly and are characterized by important subthreshold voltage fluctuations (Fig. 5A). The similarity of activity in both IF and HH models shows that the spiking mechanism is not critical, and suggests that the irregular activity is due to the sparse connectivity in this model, as well as the balance between excitation and inhibition. Another characteristic of this model is that the firing activity is similar in excitatory and inhibitory cells (Fig. 5B). This feature is due to the fact that in this model, excitatory and inhibitory neurons have the same parameters and afferent connectivity.

5. Comparison of models to experimental data

We analyzed the model similarly to experimental data (see Section 2). First, we computed the spontaneous firing rates which were around 15 Hz on average (Fig. 6A). This value is similar to the experimental data. However, there was no significant difference between excitatory and inhibitory cells in this model because both cell types had similar parameters and connectivity. Second, we analyzed the statistics of interspike intervals (ISI), which are exponentially distributed (Fig. 6B), exactly as in the data (Fig. 2B). Third, we performed a similar avalanche analysis as performed for the experimental data (Bedard et al., 2006). This analysis also failed to evidence power-law scaling behavior but rather indicates exponential distributions (Fig. 6C), consistent with the Poisson type dynamics evidenced above. This avalanche analysis was performed by choosing eight cells in the network which had statistics identical to the data (Fig. 6C), but was also valid for eight randomly chosen cells (Fig. 7, left) or for larger sets of cells (Fig. 7, right). These data show that the apparent Poisson statistics and absence of avalanche dynamics observed in cat association cortex (Bedard et al., 2006) is also found in network models.

We also estimated the total synaptic conductance in all cells of the network, and displayed the values relative to the leak (Fig. 6D). These patterns of conductance revealed a major difference between the model and the experiments: both mean excitatory and inhibitory conductances are significantly stronger in the model compared to the experiments. The difference was particularly strong for the total inhibitory conductance, which was about 10-fold larger in the model compared to the estimates in real cells.

As for the data, we realized an STA conductance analysis from the model. Qualitatively, the pattern of conductance was the same in the model compared to



Fig. 6. Analysis of the network model of active states. (A) Distribution of firing rates during the simulated active state. (B) ISI distributions are exponential (noisy trace), as predicted by a Poisson process (straight line; inset: log–log representation using natural logarithms). (C) Absence of avalanche dynamics in this model (same description as Fig. 2C). (D) Distribution of relative synaptic conductance values computed from every cell in the network (conductances are shown relative to the leak conductance). (E) Spike-triggered conductance analysis in the model. The analysis was performed by recording the total excitatory and inhibitory conductances, as well as the V_m activity in a few randomly selected cells in the network. The spike-triggered conductances were then calculated and are shown here for one representative cell. There was a decrease of total membrane conductance, which was paralleled with a decrease of inhibitory conductance.

the data (Fig. 6E): spikes were correlated to a prior decrease of total membrane conductance, which was associated with a decrease of inhibitory conductance. However, the magnitude and time course of these changes were different to the ones seen in the data (compare with Fig. 3A). Nevertheless, the model shares with real neurons the fact that most spikes are caused by a decrease of inhibition.



Fig. 7. Avalanche analysis of the network model of active states. Left: analysis performed using eight randomly chosen cells in the network. Right: same analysis performed using 512 cells. In both cases, the distribution of avalanche size is approximately exponential, as predicted by a Poisson process. There is no power-law scaling (insets: log–log representation using natural logarithms), except for large sizes (gray line in right inset).

To check if conductance states closer to experiments can be obtained, we explored the parameter space (q_e, q_i) of the model. It has been shown (Kumar et al., in press) that synchrony can have a destructive effect on stability and lower conductance states are more likely to suffer from this phenomena. Therefore, we increased network size while freezing other properties, such as the number of synapses per neuron, to reduce correlations and synchrony. Thus, we considered networks up to sizes of N = 16,000, using a fixed synaptic strength ratio ($g = q_i/q_e = 10.333$), and a fixed number of synapses per neuron (k = 40). For each simulation, we searched for the lowest value of quantal conductances (q_e, q_i) for which stable self-sustained irregular activity can be observed, and measured the total excitatory and inhibitory conductances for each network state. The results of this exploration are shown in Fig. 8: the mean total excitatory and inhibitory conductances, as well as their standard deviations, decreased linearly with the quantal conductances. There was a boundary beyond which only the quiescent state is stable. This boundary seems to saturate to a finite value around N = 16,000 neurons. For this network configuration, smaller mean conductance values were obtained, but they were still larger compared to experimental data (see below). We also explored the network stability for different values of g, and the lowest value giving stable irregular network states, g = 2.88, was also reached for network sizes larger than N = 16,000. We also tried to modify the resting membrane potential, but no effect was noticeable on the mean conductances once the network settled into an active state (not shown).

The network configuration displaying states of irregular activity most in line with conductance measurements is shown in Fig. 9. This network of 16,000 neurons displays irregular states of activity (Fig. 9A) with mean conductance distributions in reasonable agreement with experimental data (Fig. 9B; compare with Fig. 6D): excitatory conductances were slightly lower than experimental measurements, while inhibitory conductance were about twice larger. This correspondence is much closer than the large differences evidenced above for networks of 4000 neurons. The lower conductance comes from two factors: the network has a lower overall firing rate compared to the N = 4,000 network (10.4 Hz vs. 18.7 Hz), and the quantal conductances are also lower ($q_e = 1.8 \text{ nS}$ and $q_i = 18 \text{ nS}$, compared to $q_e = 6 \text{ nS}$ and $q_i = 67 \text{ nS}$ in the N = 4,000 network). However, the activity of the network consisted of irregular bursts of spikes (see Fig. 9A), rather than tonic irregular firing as observed experimentally. The ISI distribution in such a case is affected and shows a more prominent peak for small ISIs (not shown). More exploration is necessary to find active states consistent with experiments, possibly using different network configurations. Ideally such an exploration should be performed in conjunction with mean-field approaches (work in progress).

6. Discussion

In this paper, we have provided a summary of analyses of activated states in cerebral cortex, both at the single-cell and network level (Section 2). We gave an overview of single-cell models of such states (Section 3) and a network model of self-sustained active cortical states (Section 4). In Section 5, we provided comparisons between these models and experimental data.

This analysis showed that many features of activated cortical states are well reproduced by models. These include the irregular firing activity as seen experimentally through raster plots and in the model. The range of firing of the neurons was within the experimental measurements, except that the significantly higher firing rate of inhibitory neurons (Fig. 2A) is not reproduced by the model (Fig. 6A), because excitatory and inhibitory cells have the same parameters and connectivity in this model. In reality,



Fig. 8. Scaling of total synaptic conductances with network size. (A) Total mean excitatory conductance (g_e) represented as a function of the quantal excitatory synaptic conductance (q_e) for different network sizes. Simulations have been done in networks of 16,000 neurons with 40 synapses per neuron and a fixed synaptic strength ratio $g = g_{inh}/g_{exc} = 10.333$ for which the dynamics is self-sustained and irregular. Mean values are indicated with gray points and standard deviations as bars. The lowest value corresponds to the limited available active state for those parameters. Beyond this value, the network is quiescent. (B) Same simulations, but representing the total mean inhibitory conductance (g_i) as a function of the quantal inhibitory synaptic conductance (q_i) . All simulations were performed with a fixed ratio of $q_i/q_e = 10.333$, $\tau_e = 10$ ms and $\tau_i = 20$ ms.

excitatory and inhibitory cells have a significantly different connectivity, and the inhibitory neurons are also more excitable. These properties may explain the high mean firing rate of interneurons, and should be incorporated in future models.

A remarkable property of the network model is that it reproduces very well the apparent Poisson statistics of spiking of individual neurons, as shown by the near exponential shape of ISI distributions (Fig. 6B). This Poisson statistics occurs despite the fact that this network model is completely deterministic (no external source of noise was used). The dynamics observed is similar to cortical neurons, not only for ISI distributions, but also at the level of collective dynamics: the network model did not display avalanche type of dynamics but exponentially-distributed avalanche sizes (Fig. 6C), similar to that predicted by a stochastic process. This result is in agreement with observations from neuronal dynamics in cat association cortex (Fig. 2C; Bedard et al., 2006). This provides evidence that the experimental observations of Poisson dynamics (exponential ISI distributions) and absence of avalanche dynamics, are all consistent with self-generated irregular states in cortical networks. Our interpretation is that these dynamics stem from deterministic chaos of very high dimension, which explains the apparent Poisson statistics, and that there is no need to invoke self-organized critical states to explain such dynamics.

A notable disagreement between data and models is the conductance state of the membrane. Model cells have about 10 times as much conductance as real cells (compare Fig. 6D with Fig. 2D). This difference is probably due to the small scale of the network, and the large synaptic conductances that were necessary to sustain irregular firing dynamics in such a network (Vogels and Abbott, 2005). It is interesting to note that the neurons have 10-fold too high conductances, which may explain the difficulty of observing propagating activity in this model. Quantal conductances had to be increased by a factor of 10–15 to sustain propagation (Vogels and Abbott, 2005). It will be interesting to re-evaluate such propagating properties in networks displaying the right conductance state.

Interestingly, despite the fact that the conductance state is incorrect in the model, we found that the STA of conductances in the model (Fig. 6E) qualitatively reproduces the patterns seen in the data (Fig. 3). This indicates that in both cases, most spikes are related to a prior decrease of inhibition (Rudolph et al., 2007) and that inhibitory fluctuations are therefore a determinant factor to evoke spikes in such states. It is surprising that despite the huge difference at the level of conductances, models and data converge on this point, indicating that the network state is not so dissimilar in the two cases.

We also explored the parameter space for networks of different sizes to obtain conductance states more in line with experimental measurements. We found that scaling down the quantal synaptic conductances also lead to selfsustained irregular activity states, but these states were possible only in sufficiently large networks. For too small sizes, the activity becomes too correlated and cannot be self-sustained. This rule, however, breaks down for a minimal value of the quantal conductance, beyond which no selfsustained activity state was possible even for very large sizes. Consistent with previous studies (Kumar et al., in press), we found networks displaying conductance states close to experimental observations, but such networks also displayed more "bursty" type of activity inconsistent with experimental observations. Thus, at present, our analysis did not lead to a unique network configuration consistent with all experimental measurements.

No such systematic analysis has been done on other computational models yet. For example, one recent model (Kumar et al., in press) reported self-generated active



Fig. 9. Large networks can display irregular activity states with conductances comparable to experimental measurements. (A) Raster of the activity showing the irregular dynamics in a network of 16,000 neurons (320 neurons are shown, regularly spaced across the network). (B) Distribution of excitatory and inhibitory conductances in the network (relative to the leak conductance). The conductance distributions were close – although not identical – to experimental data (compare with Fig. 6D).

cortical states, but in much larger network sizes (>100,000 neurons) than those reported in the Vogels and Abbott (2005) model (>4,000 neurons). In the Kumar et al. (in press) model, the connectivity is much closer to real values in number of synapses and quantal conductances. Measurements of the conductance state in a smaller-scale version of this network (with external noisy inputs) indicates values much more in line with the data, but the other analyses as done here have not been done on such networks, so it is difficult to tell which model is presently closest to reality.

We conclude that many features identified experimentally are present in models, and some of these features are non-trivial, such as the spiking dynamics and STA of conductances. However, there are strong disagreements, mostly about the level of inhibitory firing rates and the conductance state of the neurons. Such disagreements call for building better models fully consistent with experimental data. In turn, models can point to interesting variables to be measured experimentally. This was the case for example for avalanche dynamics, which was first studied theoretically before being investigated in experiments. It is only through such bidirectional interactions between experimental and computational approaches that we will be able to understand the genesis of activated cortical states and their computational roles.

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