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Gating Information by Two-State Membrane Potential Fluctuations

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Kepecs A, Raghavachari S. Gating information by two-state membrane potential fluctuations. J Neurophysiol 97: 3015–3023, 2007. First published February 27, 2007; doi:10.1152/jn.01242.2006. Two-state voltage fluctuations between a hyperpolarized down-state and a depolarized up-state have been observed experimentally in a wide variety of neurons across brain regions. Using a biophysical model, we show that synaptic input by NMDA receptors can cause such membrane potential fluctuations. In this model, when a neuron is driven by two input pathways with different AMPA/NMDA receptor content, the NMDA-rich input causes up-state transitions, whereas the AMPA-rich input generates spikes only in the up-state. Therefore the NMDA-rich pathway can gate input from an AMPA pathway in an all-or-none fashion by switching between different membrane potential states. Furthermore, once in the up-state, the NMDA-rich pathway multiplicatively increases the gain of a neuron responding to AMPA-rich input. This proposed mechanism for two-state fluctuations directly suggests specific computations, such as gating and gain modulation based on the distinct receptor composition of different neuronal pathways. The dynamic gating of input by up- and down-states may be an elementary operation for the selective routing of signals in neural circuits, which may explain the ubiquity of two-state fluctuations across brain regions.

INTRODUCTION

The N-methyl-D-aspartate (NMDA) subtype of glutamate receptors are widely expressed (Monyer et al. 1994) and make large contributions to synaptic transmission across a range of brain areas (Feldmeyer et al. 1999; Gil and Amitai 2000; Jones and Baughman 1988; Kumar and Huguenard 2003). There are two important properties that differentiate them from other ionotropic glutamate receptors: first NMDA receptors are slow (τNMDA ≈ 100 ms) and, second, they are uniquely voltage dependent, requiring the postsynaptic neuron to be depolarized in addition to the binding of glutamate for the channel to open. As a consequence of this dual activation requirement, NMDA receptor (NMDAR)–mediated synaptic transmission satisfies the associativity property of Hebbian learning and in fact plays a critical role in its cellular model, long-term synaptic plasticity. Based on this evidence, NMDARs are thought to support long-term memory storage. Nevertheless, pharmacological agents that block NMDARs impair a variety of brain processes (Adler et al. 1998), suggesting that NMDAR transmission also plays an important role beyond long-term memory and participates in shaping the dynamic activity of neural networks (Daw et al. 1993; Schiller et al. 2000).

To explore this, previous theoretical work sought to clarify what other computational functions might the unique properties of NMDARs support. The long time constant of NMDARs at recurrent synapses was found to be necessary for the reverberation of activity leading to sustained firing, which is thought to be the substrate of short-term memories (Koulakov 2001; Seung et al. 2000; Wang 1999). Another class of models exploited the voltage dependency of NMDAR receptors in recurrent networks for short-term memory storage (Koulakov et al. 2002; Lisman et al. 1998). These studies converged on the hypothesis that sustained neural activity requires NMDA receptors and therefore NMDAR transmission may be particularly strong in the prefrontal cortex to enable the sustained firing of neurons responsible for short-term memory traces (Wang 2001). However, in vitro experiments did not identify any gross differences in the amplitude or kinetics of NMDA currents between prefrontal and visual cortical areas in the rat (Myne et al. 2003). These observations leave open the possibility that local differences in NMDAR-mediated transmission across input pathways within a region play an important role in local circuit function. In fact, such pathway-specific differences in glutamate receptor composition were previously observed in the hippocampus (Otmahtova et al. 2002), neocortex (Kumar and Huguenard 2003), as well as in subcortical regions (Mooney and Konishi 1991). However, a potential computational role for these differences is lacking.

Therefore we reexamined the role of NMDA receptors in postsynaptic integration, focusing on the distinct computational functions that may be enabled by their unique voltage-dependent activation. Our modeling results suggest that NMDA receptors may serve to gate the flow of information as well as control the gain of information transfer, two elementary operations that are critical for the operation of neural networks.

METHODS

We modeled the neuron with two compartments (for Fig. 1): a lumped soma/axon hillock and an active dendrite (Lisman et al. 1998; Pinsky and Rinzel 1994). Next we present the reference set of parameters for the currents used in the model. The membrane potentials of the two compartments (Vs for the soma and Vd for the dendrite) obeyed the following current balance equations

\[
C_n \frac{dV_s}{dt} = -I_{Na} - I_K - I_{Loak} - I_{KA} - I_{KA} - g_e \frac{(V_s - V_0)}{\rho} - I_{GABA} \tag{1}
\]

\[
C_n \frac{dV_d}{dt} = -I_{CaL} - I_{KA} - I_{KU} - I_{LKA} - g_e \frac{(V_d - V_0)}{(1 - \rho)} - I_{NMDA} - I_{AMPA} \tag{2}
\]

The passive parameters were membrane capacitance, \(C_m = 1 \mu F/cm^2\); somatodendritic coupling, \(g_e = 0.1 mS/cm^2\); and somatic membrane...
area as a fraction of total area, $p = 0.3$. Absolute conductance values were calculated assuming a total area of 50,000 $\mu$m$^2$ for the neuronal membrane. The leak conductance was modeled as $g_l(V - V_l)$ with $g_l = 0.3$ mS/cm$^2$ [all conductance values are in units of milliSiemens per square centimeter (mS/cm$^2$)] and the reversal voltage, $V_l = -65$ mV. The spiking currents were modeled as given by Wang and Buzsáki (1996; with the activation voltages shifted to obtain a threshold of $-52$ mV) and $g_{Na} = 36$, $V_{Na} = 50$ mV and $g_K = 9$, $V_K = -90$ mV. The somatic compartment also contained transient potassium and inward rectifier currents (Nisenbaum and Wilson 1995). The dendritic compartment contained an L-type calcium current (Churchill and Maccabee 1998; Compte et al. 2003) that activated at depolarized voltages as well as transient and slow potassium currents (Hoffman et al. 1997; Johnston et al. 2000; Nisenbaum and Wilson 1995; Wolf et al. 2005). All active currents were modeled following the Hodgkin–Huxley formalism, with first-order kinetics for both activation and inactivation gating variables

$$\frac{dm}{dt} = [m_e(V) - m_f(V)]\tau_m(V)$$

(3)

with

$$m_e(V) = \frac{1}{1 + \exp\left(\frac{V - V_{m0}}{k}\right)}$$

as given in Table 1.

The geometric parameters of the neurons as well as the half-activation voltage and the slope of the dendritic potassium currents (the A-current and the slow current) were adjusted within a physiologically observed range (Nisenbaum and Wilson 1995; Nisenbaum et al. 1994) to ensure that the steady-state membrane potential in the soma remained subthreshold for a large range of NMDA activation. To simplify the analysis, we neglected the slow inactivation of the L-type calcium current. Inclusion of this results in up-states of slightly shorter duration.

The synaptic conductances were also explicitly modeled with first-order kinetics [for $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and $\gamma$-aminobutyric acid (GABA) synapses] and second-order kinetics (for NMDA) (Wang 1999). The AMPA synaptic current, $I_{AMPA} = g_{AMPA} \sum j x_j V_{\text{pre}}$, where $x_j$ is the fraction of AMPA channels activated at the jth input and the sum ranges over the different inputs, with $g_{AMPA}$ fixed at 0.02 for Fig. 1. The GABA synaptic current $I_{GABA} = g_{GABA} \sum j x_j (V_{\text{pre}} - V_{\text{inh}})$, where $x_j$ is the fraction of activated channels for the jth input and $g_{GABA} = 0.02$, $\alpha = 0.1$ ms, and $\beta = 4$ ms$^{-1}$; $V_{\text{inh}}$ is the chloride reversal potential, taken to be $-70$ mV. For both AMPA and GABA the synaptic gating variables obey

$$\frac{dx_j}{dt} = \alpha(V_{\text{pre}})(1 - x_j) - \beta x_j$$

The NMDA current, $I_{NMDA} = g_{NMDA} F(V_{\text{pre}}) \sum j s_j V_{\text{pre}}$, where the sum ranges over the different inputs, with $g_{NMDA} = 0.04$. The activation of the NMDA current was modeled as a second-order process

$$\frac{dx_{\text{act}}}{dt} = \alpha(V_{\text{pre}})(1 - x_{\text{act}}) - \beta x_{\text{act}}$$

and

$$\frac{dx_{\text{inh}}}{dt} = \alpha(V_{\text{inh}})(1 - x_{\text{inh}}) - \beta x_{\text{inh}}$$

with $[Mg^{2+}] = 0.5$ mM, $\alpha = 0.1$ ms, $\beta = 2$ ms, $\alpha = 2$ ms, and $\beta = 100$ ms. The voltage dependency of the NMDA current (Mayer et al. 1984) was modeled as

$$F(V) = \frac{1}{1 + 0.3[Mg^{2+}] \exp(-0.08V)}$$

Our choice of NMDA:AMPA maximal conductance ratio is broadly within the range observed in experiments (Myme et al. 2003), which varies from nearly 1:1 to even as high as 8:1 depending on the method of measurement or location of synapses (Myme et al. 2003; Ottomahovna et al. 2002).

Excitatory input to the neuron was modeled as Poisson spike trains delivered to by AMPA and NMDA synapses. For Fig. 1, we fixed the number of inputs to be 100. The hypothesized synchrony betweenafferent inputs (Kasanez et al. 2002) was included in the form of weak correlations between the afferents that create input fluctuations. Twenty afferents spiked synchronously at a rate $\lambda_{\text{syn}}$, as well as at a basal rate $\lambda_{\text{basal}}$, giving a total rate of $\lambda = \lambda_{\text{basal}} + \lambda_{\text{syn}}$. The remaining afferents were uncorrelated and spiked at the total rate $\lambda$. In all cases, $\lambda_{\text{basal}} = 1$ Hz for the NMDA inputs and 0.1 Hz for AMPA inputs. To avoid saturating the NMDA conduction, we also assumed that all excitatory synapses were probabilistic, with a release probability of 0.8 (Markram and Tsodyks 1996). Omitting the probabilistic release affected only the dynamic range of the input rates over which the two-state fluctuations were observed but not the qualitative phenomena in Figs. 1 and 2. GABAergic input was delivered by 25 afferents modeled as independent Poisson spike trains with a fixed rate of 20 Hz. The model in Fig. 2 uses a three-compartment neuron with the two input pathways segregated to the two different compartments. The NMDA-rich pathway was made up of 100 mixed inputs with high NMDA:AMPA ratio ($4:1$, $g_{NMDA} = 0.04$) delivered to the active dendritic compartment (with the currents as above and the area fraction $p = 0.35$). The AMPA-rich pathways contained 100 inputs with only AMPA receptors ($g_{AMPA} = 0.02$) delivered to a second dendritic compartment (area fraction $p = 0.35$). The output rates in Fig. 2 were computed over runs of 200 s. Similar results were obtained for a large number (2,000) of short runs of 1 s. All simulations were coded in C and numerical integration was performed using a modified second-order Runge–Kutta method that is stable for stochastic inputs (Greenside and Helfand 1981). To quantify the interaction between the AMPA and NMDA pathways on the output rates, we first used the singular value decomposition (SVD) of the matrix of output firing rates as a function of the input AMPA and NMDA rates. This technique calculates a generalized inverse of a nonsquare matrix and decomposes it into its generalized eigenvalues and eigenvectors. The squared magnitude of the first eigenvalue relative to the sum of all the squared eigenvalues is the fraction of the variance captured by approximating the data matrix as an outer product of two vectors. This technique is widely used to evaluate whether a data set of two variables can be approximated as a product of the two variables (Mitra and Pesaran 1999; Peña and

<table>
<thead>
<tr>
<th>Current</th>
<th>$g_{base}$ mS/cm$^2$</th>
<th>HH Form</th>
<th>$V_{1/2}$, mV</th>
<th>$k$, mV</th>
<th>$\tau$, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_s$ (soma)</td>
<td>10</td>
<td>$m_s h m$</td>
<td>-50</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td>$K_s$ (dendrite)</td>
<td>10</td>
<td>$m_s h m$</td>
<td>-80</td>
<td>-6</td>
<td>20</td>
</tr>
<tr>
<td>$K_{slow}$ (dendrite)</td>
<td>0.12</td>
<td>$h$</td>
<td>-27</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td>$K_{Na}$ (soma)</td>
<td>1</td>
<td>$n_a$</td>
<td>-76</td>
<td>15</td>
<td>2.5$[1 + e^{t(V-70)/\tau}]$</td>
</tr>
<tr>
<td>$K_{Na}$ (dendrite)</td>
<td>6</td>
<td>$n_a$</td>
<td>-34</td>
<td>2</td>
<td>$200 + [400e^{-t(V+35)/\tau}]$</td>
</tr>
<tr>
<td>$C_{Na}$ (dendrite)</td>
<td>0.15</td>
<td>$m^2$</td>
<td>-20</td>
<td>7</td>
<td>40</td>
</tr>
</tbody>
</table>

\[ J \text{ Neurophysiol} \quad \text{VOL 97} \quad \text{APRIL 2007} \quad \text{www.jn.org} \]
Konishi 2001). We found that 99.8% of the variance in the output firing rate could be accounted for by a multiplicative model. Although the two components recovered by SVD were linearly related to the inputs, small deviations from linearity may have led to an overestimation of the variance accounted for by multiplication. Therefore we directly fit the following multiplicative and additive models using a least-squares error criterion

\[
\langle \text{rate}_{\text{OUTPUT}} \rangle = \beta \text{rate}_{\text{AMPA}} \text{rate}_{\text{NMDA}}
\]

(4)

\[
\langle \text{rate}^{\text{add}}_{\text{OUTPUT}} \rangle = \beta_1 \text{rate}_{\text{AMPA}} + \beta_2 \text{rate}_{\text{NMDA}}
\]

(5)

\[
\text{rate}_{\text{OUTPUT}} = \beta_0 + \beta_1 \text{rate}_{\text{AMPA}} + \beta_2 \text{rate}_{\text{NMDA}}
\]

(6)

Because multiplicative scaling in the model requires the gating pathway to be above the up-state threshold, we first adjusted rate_{NMDA} by subtracting 6 Hz (approximately the threshold value). The multiplicative model required only a single parameter, \( \beta = 0.44 \), and accounted for 99.2% of the variance with a correlation value \( r^2 = 0.99 \).

The additive model with two parameters (\( \beta_1 = 1.2, \beta_2 = 1.9 \)) accounted for only 70% of the variance and gave \( r^2 = 0.83 \). The three-parameter additive model (\( \beta_0 = -16, \beta_1 = 2.2, \beta_2 = 3.2 \)) accounted for 84% of the variance and gave \( r^2 = 0.84 \).

RESULTS

Stochastic NMDA input leads to membrane voltage fluctuations

We examined the effect of NMDAR mediated excitatory inputs on the membrane potential using a biophysical model (see METHODS). Our initial observations showed that strong NMDA inputs can lead to large regenerative depolarizations similar to those seen in many neurons (Schiller et al. 2000). Neurons, however, also possess a variety of potassium currents that are able to limit these large excursions in voltage (Day et al. 2005; Johnston et al. 2000; Nisenbaum and Wilson 1995). Including these potassium currents in the neuron model with AMPA and NMDA receptor input shows that the membrane voltage alternates between two distinct subthreshold states (Fig. 1A). Visual inspection of the membrane potential and its histogram (Fig. 1B) reveals a striking resemblance to two-state membrane potential fluctuations recorded in vivo from cortical (Anderson et al. 2000; Lewis and O’Donnell 2000; Petersen et al. 2003; Steriade et al. 1993; Waters and Helmchen 2006) and subcortical regions (O’Donnell and Grace 1995; Stern et al. 1998; Wilson and Kawaguchi 1996).

The origin of two-state fluctuations in our model can be understood as follows. The hyperpolarized down-state is stable because NMDA receptors are almost completely blocked and the outward potassium currents dominate. For sufficiently large depolarizations, the Mg\(^2+\) block of the NMDA channel is relieved and this conductance dominates, producing a regenerative depolarization (Schiller et al. 2000). The activation of the transient potassium current \( I_K \) curbs the regenerative action of large NMDA input, whereas slower potassium currents active at depolarized potentials help maintain a balance that keeps the higher voltage state subthreshold. The membrane potential thus becomes conditionally bistable for a range of NMDA conductances. This conditional bistability can been seen in the bifurcation diagram [similar to the current–voltage (I–V) curve], which captures the steady-state behavior of the voltage with active NMDA input (Fig. 1C). The range of bistability \([g_{\text{NMDA}}, g_{\text{NMDA}}]\) depends not only on the NMDA input but also on the leak, the inward rectifier, \( I_A \), and \( C_{\text{L}} \) conductances. The inward calcium and outward potassium conductances are in balance and do not cause bistability on their own, but in the presence of glutamate they expand the range of bistability arising from the NMDA current. More generally, any outward current active near the resting membrane voltage that would resist depolarization, such as \( I_h \) would set the bistable range.

From Fig. 1A, we can see that time-varying NMDAR activation can cause membrane potential transitions between these up- and down-states. A transient fluctuation in NMDAR activation beyond the threshold of bistability \( g_{\text{NMDA}}^1 \) (see Fig. 1C)

![Figure 1](https://example.com/figure1.png)

**FIG. 1.** Stochastic N-methyl-D-aspartate (NMDA)–receptor-mediated inputs evoke 2-state membrane potential fluctuations. **A**: example membrane voltage trace from the model shows irregular alternation between a hyperpolarized (mean \( \approx -72 \) mV) down-state and a depolarized, subthreshold (mean \( \approx -53 \) mV) up-state. Spikes occur only during the up-states. **B**: histogram of the membrane potential showing 2 distinct peaks. **C**: bifurcation diagram [akin to a current–voltage (I–V) curve] demonstrating the conditional bistability that arises for a range of NMDA input relative to the outward currents. Diagram includes all the active conductances in the steady state (extrinsic and intrinsic currents, excluding spiking currents) with perfect somatic voltage clamp. Stable steady states are denoted by solid lines; unstable states are shown as dashed lines. Arrows mark the level of NMDA input at which the membrane potential must switch states. For the range of NMDA conductances between the arrows \((g_{\text{NMDA}}^1 < g_{\text{NMDA}} < g_{\text{NMDA}}^2)\), the membrane potential is bistable. Note that the stable states correspond to the 2 modes of the membrane potential histogram in **B**. To construct this, we have assumed that the mean NMDA activation is slower than any other timescale in the system. However, the 2 steady states are maintained even if we consider additional slow variables such as the slow inactivation of the calcium channels and the potassium current \( I_{KS} \). In this case, the steady states are parameterized as a multidimensional surface. **D**: histogram of the up-state durations for 3 different values of input rates (6, 10, and 14 Hz per afferent, from light to dark gray).
causes the membrane potential to jump to the up-state. Because of hysteresis, however, the membrane potential is maintained in this state until NMDAR activation falls below $g_{\text{NMDA}}$ (arising due to glutamate unbinding from receptors) at which point the membrane potential returns to the down-state. Additional input during the up-state increases NMDAR activation and prolongs the up-state. Note that the neuron is not bistable (i.e., cannot be reset) in the up-state if the rate and amplitude of the input are sufficiently large (Fig. 1C). The duration of up-states depends on the degree of NMDA receptor activation, mean AMPA drive, and the strength of potassium currents. As a result, randomly fluctuating inputs naturally generate a distribution of up-state durations whose mean increases with the firing rate of the afferent inputs (Fig. 1D). Because up-states are driven by synaptic input there is an increase in the net membrane conductance ($10 \pm 4 \mu S$) during the up-state compared with the down-state in the dendrite. This overall increase in input conductance can be attributed to the large increase in synaptic input conductance resulting from the NMDA channel opening, which is counteracted to some degree by a decrease in input conductance resulting from the closing of inward rectifier channels in the up-state. In contrast, we find that in the soma there is a small net increase in input resistance (equivalently, net decrease in conductance) during up-states compared with down-states ($34 \pm 3 \text{ vs. } 40 \pm 5 \text{ M}\Omega$), resulting from the closure of the inward rectifier channels. These observations show that large voltage fluctuations can be consistent with small changes in input resistance (Waters and Helmchen 2006) and the direction of change in input resistance can depend on the spatial balance between intrinsic and synaptic conductances.

Input gating and multiplication by two-state fluctuations

Beyond a plausible biophysical mechanism, this model directly suggests a computational role for two-state fluctuations. Segregating inputs based on their AMPA/NMDA receptor composition into distinct pathways located in different neuronal compartments will result in a powerful functional dissociation as well. Inputs delivered by NMDARs can bring the membrane potential into the depolarized up-state, as explained earlier. However, because of transient potassium currents active near the up-state and the slow time course of NMDA receptor activation relative to AMPA receptors, fluctuations of NMDA-rich inputs in the up-state are unable to bring the membrane potential above spike threshold (Fig. 2A, bottom left; Fig. 2B, bottom). On the other hand, fluctuations in inputs that are rich in AMPAR (Fig. 2A, top) cannot switch the membrane potential to the up-state in the absence of NMDA-rich inputs and are also unlikely to generate enough current to reach spike threshold from the down-state. Once in the up-state, however, these extremely fast inputs can bring the membrane potential above threshold and trigger an action potential. Note, that for both AMPA- and NMDA-rich inputs, transient potassium currents are activated and it is the difference in their rise time constants that results in the more selective suppression of NMDA-generated fluctuations.

If only AMPA-rich inputs are activated in the absence of NMDARs, even large increases in input (rates or maximal conductances) do not result in action potential generation (Fig. 2A, top). On the other hand, the same AMPA-rich inputs can trigger spikes once NMDA-rich inputs bring the membrane into the up-state (Fig. 2A, bottom). The rate of spiking in the up-state can be variable and depends on the rate and strength of inputs coming from the AMPA pathway. This demonstrates the ability of NMDA-rich inputs to gate spike generation by AMPA-rich inputs. Note that when either of the input pathways is inactive, the neuron does not fire spikes (Fig. 2, A–C) for a large range of input rates for the other pathway. Our model thus provides a biophysically plausible implementation of a “soft” AND gate, a logic operation that is fundamental for computation. The model overcomes a key difficulty with the biophysical realization of an AND gate or multiplication: mathematically, zero multiplied with a large number is still zero, but biophysically it has been unclear how a highly active input pathway might be unable to trigger spikes simply because of the lack of input from a second pathway.

What is the role of the NMDA-rich or gating pathway once the neuron is in the up-state? Changing either the rate (Fig. 2B) or maximal conductance (not shown) of the NMDA-rich pathway beyond the up-state threshold results in an approximately multiplicative modulation of the input–output relationship for the AMPA pathway. Similarly, increasing the input rate of the AMPA-rich pathway for a given NMDA input also multiplicatively scales the output rate of the neuron (Fig. 2C). To quantitatively examine this scaling relationship, we fitted the output rates in Fig. 2B to a simple multiplicative model. Fitting a single parameter, $\beta = 0.44$, in $\text{rate}_{\text{output}} = \beta \text{rate}_{\text{AMPA}} \text{rate}_{\text{NMDA}}$, accounted for >99% of the variance in the output firing rate (see METHODS for details and Supplemen-

**FIG. 2.** Gating and gain modulation with 2-state fluctuations. A: responses of the model neuron to 2 input pathways, one with low and high conductance NMDA inputs ($g_{\text{NMDA}}$ values of 25 and 50 $\mu$S/cm²) and another with low, medium, and high conductance $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) inputs ($g_{\text{AMPA}}$ values of 20, 40, and 80 $\mu$S/cm²). Same input pattern is simulated in all panels and only the NMDA/AMPA conductances are different. Model behaves as a “soft” AND gate, i.e., the neuron has an off or zero-state and a graded on-state. B: NMDA input acts as a gain control mechanism. Output spike rate is shown as a function of AMPA input rate for 4 different NMDA input rates (down-triangle: 4 Hz; square: 8 Hz; diamond: 12 Hz; circle: 16 Hz). Error bars denote SDs calculated from 10 runs of 20 s. C: AMPA pathway also multiplicatively scales in the NMDA input–output curves. Output spike rate as a function of NMDA input rate, for 4 different AMPA input rates (down-triangle: 0 Hz; square: 4 Hz; diamond: 8 Hz; circle: 12 Hz). Error bars denote SDs calculated from 10 runs of 20 s.
tary Fig. S1). In contrast, even a two-parameter additive model accounted for only 70% of the variance in firing rates. A multiplicative interaction between the input pathways can arise because they are statistically independent; thus the probability of spiking is proportional to the product of the probability of a large AMPA fluctuation and the probability that the neuron is in an up-state. Therefore the mean output spike rate is proportional to the product of the mean duration of an up-state and the rate of large AMPA fluctuations. This argument applies to timescales longer than the mean up-state duration. However, even for shorter periods the interaction of the two pathways during the up-state will still be supralinear as a consequence of depolarizing AMPA inputs that boost NMDA inputs resulting from their voltage dependency. Therefore we examined the modulation of the firing rate in the up-state alone as a function of input rates. Even during sustained up-states the firing rate modulation was multiplicative (99% of the variance was accounted for by multiplicative interaction as determined by singular value decomposition), suggesting a more general applicability of our mechanism (Peña and Konishi 2001). The multiplicative property of this regime likely depends on subtle features of the model such as the interaction of the voltage-dependent kinetics of NMDAR with other ion channels.

Model robustness

The model did not require fine-tuning of parameters to exhibit gating by two-state membrane fluctuation and it was robust to changes in maximal conductances as long as a rough balance was maintained between the inward NMDA currents and the outward potassium currents that defined the up-state. A key assumption of the model is a relatively high (4:1) NMDA/AMPA maximal conductance ratio in one pathway. This ratio is broadly within the experimentally observed range, which varies from nearly 1:1 to as high as 8:1 depending on the method of measurement and the location of synapses (Myeme et al. 2003; Ottmakova et al. 2002). We tested the range of NMDA/AMPA ratios over which gating occurred, with all other parameters held constant. Gating was defined as the ability to fire spikes when both pathways are active and stay silent while one pathway is silent even if the other one is highly active (Fig. 2A). Using these criteria and input patterns shown in Fig. 2, the NMDA/AMPA ratio could be varied from 4:1 (used in Fig. 2) down to 3:2 while preserving the gating functionality. We also varied the geometric parameters such as the somatodendritic coupling and the relative area fraction of the soma and dendrite (see METHODS) as well as the maximal conductances of various currents by ±10%. These variations left up- and down-states qualitatively intact.

These findings suggested that the basic phenomenon does not depend on the details of ion channel kinetics used, as long as there is sufficient NMDA input to trigger up-states and fast and slow potassium currents to stabilize them. We tested this by constructing another biophysical model based on ionic currents measured from medium spiny neurons in the striatum. These neurons have an extensive repertoire of potassium currents that have been well characterized (Mahon et al. 2000; Nisenbaum and Wilson 1995; Wolf et al. 2005) and exhibit two-state membrane potential fluctuations (O’Donnell and Grace 1995; Plenz and Aertsen 1996; Wilson 1993). We included the fast and slow A-like potassium currents (Nisenbaum and Wilson 1995), an inward rectifier current (Nisenbaum and Wilson 1995), an L-type calcium current (Churchill and Macvicar 1998), and a persistent sodium current in a three-compartment model of a medium spiny neuron (see supplementary information for details). Excitatory synapses were distributed on the dendritic compartments and GABAergic inhibition was restricted to the soma.

Similar to the previous model, the membrane voltage showed alternation between two subthreshold voltage states (Supplementary Fig. S2A). Next, we tested whether the interactions between the two pathways remained multiplicative. Increasing the rate of the NMDA-rich pathway beyond the up-state threshold increased the gain of the AMPA-pathway input–output function (Supplementary Fig. S2, B and C). To quantify this we fitted a single parameter multiplicative and a two-parameter additive model to the firing rates as done previously (see METHODS for details). The multiplicative model accounted for >92% of the variance in the output firing rate compared with 65% for the additive model. These findings illustrate that not only the basic two-state phenomenon, but also the gating and gain operations are robust to changes in maximal conductances, ion channel kinetics, and even some channel types.

DISCUSSION

We explored the computational implications of the voltage dependency of NMDA receptors in synaptic integration using a biophysical neuron model. Our simulations showed that synaptic input delivered by AMPA and NMDA receptors can generate robust two-state membrane potential fluctuations in a model neuron (Fig. 1) with properties broadly consistent with experimental observations. First, the membrane potential histograms are clearly bimodal with peaks separated by about 10–20 mV (Cossart et al. 2003; Shu et al. 2003; Steriade et al. 2001; Stern et al. 1998; Wilson and Kawaguchi 1996). Second, the transitions between the two states are rapid (tens of milliseconds) compared with the durations of the individual states (hundreds of milliseconds) (Shu et al. 2003; Wilson and Kawaguchi 1996). Third, blockade of intrinsic inward currents leaves the phenomenon qualitatively intact (Wilson and Kawaguchi 1996). Fourth, blockade of cortical activity or inactivation of synaptic transmission blocks two-state fluctuations (Cossart et al. 2003; Plenz and Aertsen 1996; Shu et al. 2003; Wilson 1993). Blockade of inhibition, however, does not prevent the fluctuations (Wilson 1993; but see Shu et al. 2003). Finally, hyperpolarization or depolarization by current injection in the soma changes only the voltage of the up- and down-states and rarely causes state transitions, as observed in the striatum (Wilson and Kawaguchi 1996) and neocortex (Cowan and Wilson 1994).

The model exhibits a small increase in input resistance during up-states in the soma consistent with some experimental observations in cortical neurons (Waters and Helmchen 2006). In contrast, there is a decrease in input resistance in the dendrite that could be attributed to the high synaptic drive (Destexhe et al. 2003) that is not fully counteracted by the closure of the inward rectifier conductances. These observations show that the direction of change in input resistance can
depend on the spatial balance between intrinsic and synaptic conductance, which may account for contradicting experimental observations (Paré et al. 1998; Sachdev et al. 2004; Shu et al. 2003; Waters and Helmchen 2006). Therefore our model suggests that the role of inward rectifier conductances may be to equalize the total input conductance of neurons across different voltage states.

Previous experimental observations suggested that NMDARs participate in two-state fluctuations in striatal medium spiny neurons (Vergara et al. 2003) and cortical neurons (Milojkovic et al. 2005; Sanchez-Vives and McCormick 2000; Steriade et al. 1993), but it was not clear what mechanisms allow NMDA plateau potentials to remain sub-threshold and generate a range of durations observed both in vitro and in vivo. Our model suggests that the balance between NMDA and $K^+$ currents leads to the stabilization of the up-state voltage to subthreshold levels.

Previous biophysical models (Compte et al. 2003; Wilson 1992; Wolf et al. 2005) showed the ability to generate up-states that either directly reflected the input timescale or were purely rhythmic as a result of the nature of the intrinsic currents. In contrast, our model generates a range of up-state durations that is observed experimentally (Anderson et al. 2000; Stern et al. 1998). The duration of up-states in our model depends not only on the strength of inputs (Fig. 1D) but also on the balance between the inward and outward currents. One class of models for two-state fluctuations assumed that the neuron is intrinsically bistable because of the interaction of an inward calcium current and the inward rectifier (Gruber et al. 2003). However, previous experiments showed that current injection in the soma changes only the amplitude of the up- and down-state voltages, but does not lead to a change of state (Wilson and Kawaguchi 1996), suggesting that intrinsic bistability may not be responsible for the up- and down-states. By contrast, our model exhibits conditional bistability in the dendrite, i.e., the dendritic voltage is bistable for an intermediate range of NMDA input. For large fluctuations outside this range, however, the up-state becomes monostable (Fig. 1C). Thus current injections that coincide with periods of high or low excitatory inputs will not be able to trigger or reset up-states (Cowan and Wilson 1994; Wilson and Kawaguchi 1996). As noted, two-state voltage fluctuations occur in a wide range of cell types across different brain areas, which are unlikely to all rely on the same biophysical mechanism. On the other hand, the core mechanism in our model consists of the interaction between NMDA input and transient potassium currents, both of which are present in all these cell types, suggesting that this mechanism could potentially contribute to the genesis of two-state fluctuations across brain regions.

One challenge for our proposed mechanism may be based on the fact that two-state membrane potential fluctuations were observed under ketamine anesthesia in several regions (Haider et al. 2006; Paré et al. 1998; Sachdev et al. 2004; Steriade et al. 1993; Wilson and Kawaguchi 1996). Although ketamine is known to block NMDARs, it is not clear by what mechanisms its anesthetic effects arise because ketamine also has strong effects on monoamine levels (Kari et al. 1978) by directly inhibiting transporters (Nishimura et al. 1998) and it blocks D2 and 5-HT2 receptors (Kapur and Seeman 2002). Furthermore, most NMDAR antagonists have differential effects on different NMDAR subunits (Cull-Candy et al. 1998) and, because our proposed mechanism involves primarily the voltage-dependent property of NMDARs, it may rely on a subset of NMDARs with distinct subunit composition.

A computational function for two-state fluctuations

The NMDA-based mechanism for two-state fluctuations directly leads to a computational function. When pathway-specific differences exist in the expression of NMDA receptors, the input pathway with high NMDAR content can gate spike generation elicited by the other, AMPAR-rich input. Figure 3 shows a schematic of this process, where the gating pathway acts to switch the neuron from a “disabled” down-state to an “enabled” up-state in which the signal pathway is able to generate spikes. Therefore, independent of the specific biophysical mechanisms proposed, the model highlights how two-state membrane fluctuations can serve to gate signals (MacLean et al. 2005; O’Donnell and Grace 1995), which is a fundamental operation for selective routing of information across brain areas, and may explain the ubiquity of the phenomenon across brain regions.

Possible relevance to the striatum and the bird song system

The gating function of two-state fluctuations may be relevant for the striatum and, in particular, for the nucleus accumbens (NAcc), a region implicated in the context-dependent selection of motor plans (Grace 2000). NAcc combines input from the limbic system and the neocortex to drive the motor nuclei of the basal ganglia. Because individual medium spiny neurons receive inputs from both the hippocampus and the prefrontal cortex (French and Totterdell 2002), the context-dependent selection of particular action plans could be accomplished by the selective gating of cortical inputs by the hippocampal pathway bringing contextual cues. Consistent with this, the up-states of NAcc neurons are driven largely by hippocampal input and, in contrast, cortical input can generate spikes only when the neuron is in the up-state (O’Donnell and Grace 1995). Thus our model makes a testable prediction: hippocam-
The gating pathway in our model has an additional function: once in the up-state, further increasing the input will change the gain of the neuron. The gating/gain pathway creates a multiplicative increase in the output of a neuron without changing its selectivity resulting from the signal pathway. Similar modulation in the gain of receptive fields has been widely observed across different brain areas. For instance, in the parietal cortex, gaze direction (Andersen et al. 1985), and in the visual cortex, attention (Connor et al. 1996; McAdams and Maunsell 1999; Reynolds et al. 2000) scales up responses without changing the selectivity of neurons. Gain modulation is recognized as a powerful computational operation for mixing signals (Pouget et al. 2002; Salinas and Sejnowski 2001) but the neuronal mechanisms underlying it are not known. Recent studies showed that a balanced configuration of correlated excitation and inhibition is able to change neuronal gain (Chance et al. 2002; Mitchell and Silver 2003; Prescott and De Koninck 2003). Our model presents an alternative biophysical mechanism for input-specific modulation of neuronal gain. An important difference is that the gain pathway in our model mediates multiplicative increases and not divisive decreases in neuronal responses and it also has the ability to completely shut off or gate the signal pathway.

Experimental evidence about the functional role of up- and down-states during wakefulness is sparse and mixed. Some observations indicated that up-states are the only awake state of cortex (Steriade et al. 2001); however, recent experiments demonstrated up- and down-state fluctuations during quiet wakefulness as well (Crochet and Petersen 2006). Indeed, it may be that intentional movements (such as whisker twitching) may lock the membrane voltage in the up-state, which could be interpreted as an increase in the top-down or gating input in our model. Awake recordings of behaviorally engaged animals will be necessary to resolve this controversy. Note, however, that our model can also generate multiplicative firing-rate modulation during sustained up-states.

**Possible relevance to neocortex and gain modulation**

In the neocortex, some studies found an increase in the responsiveness of neurons during up-states (Shu et al. 2003; Steriade et al. 2001), whereas others found that up-states reduce the ability of a stimulus to evoke firing despite the fact that the membrane potential is closer to threshold (Petersen et al. 2003; Sachdev et al. 2004). Our model could reconcile these different observations by assuming that these studies probed the effects of input pathways with different AMPA/NMDA ratios. By bringing the neuron closer to spike threshold, up-states enhance the effects of a signaling pathway dominated by AMPA receptors. However, if whisker stimulation is carried not only by a signaling pathway, but also by synapses with large NMDAR content then its impact will be reduced if the neuron is already in the up-state. Consistent with this, in vitro recordings show that thalamic stimulation evokes up-states in cortical neurons similar to those that occur spontaneously (MacLean et al. 2005).

The gating pathway in our model has an additional function: once in the up-state, further increasing the input will change the gain of the neuron. The gating/gain pathway creates a multiplicative increase in the output of a neuron without changing its selectivity resulting from the signal pathway. Similar modulation in the gain of receptive fields has been widely observed across different brain areas. For instance, in the parietal cortex, gaze direction (Andersen et al. 1985), and in the visual cortex, attention (Connor et al. 1996; McAdams and Maunsell 1999; Reynolds et al. 2000) scales up responses without changing the selectivity of neurons. Gain modulation is recognized as a powerful computational operation for mixing signals (Pouget et al. 2002; Salinas and Sejnowski 2001) but the neuronal mechanisms underlying it are not known. Recent studies showed that a balanced configuration of correlated excitation and inhibition is able to change neuronal gain (Chance et al. 2002; Mitchell and Silver 2003; Prescott and De Koninck 2003). Our model presents an alternative biophysical mechanism for input-specific modulation of neuronal gain. An important difference is that the gain pathway in our model mediates multiplicative increases and not divisive decreases in neuronal responses and it also has the ability to completely shut off or gate the signal pathway.

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**Receptor composition and computational function of neuronal pathways**

The key feature of the model—pathway-specific differences in NMDAR content—was previously observed in several brain regions, for instance in the striatum of songbirds discussed earlier (Mooney and Konishi 1991), and in the hippocampus between the perforant path and Schaffer collaterals (Otmak-hova et al. 2002). In layer 5 pyramidal cells the basal but not the apical dendrites can generate NMDA spikes (Schiller et al. 2000) and there are also differences in NMDAR subunits between intracortical and callosal inputs (Kumar and Hugue-nard 2003). Nonetheless, more data are needed to understand the diversity and distinctness of receptor composition across different neuronal pathways. Our results suggest that the AMPA/NMDA receptor ratio at different classes of synapses can determine their computational role, extending the classification of “driver” and “modulator” pathways to “gating/gain control” pathways (Abbott and Chance 2005; Sherman and Guillery 1998).

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