Dynamic Spatiotemporal Synaptic Integration in Cortical Neurons: Neuronal Gain, Revisited

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Azouz, Rony. Dynamic spatiotemporal synaptic integration in cortical neurons: neuronal gain, revisited. J Neurophysiol 94: 2785–2796, 2005. First published June 29, 2005; doi:10.1152/jn.00542.2005. Gain modulation is a ubiquitous phenomenon in cortical neurons, providing flexibility to operate under changing conditions. The prevailing view is that this modulation reflects a change in the relationship between mean input and output firing rate brought about by variation in neuronal membrane characteristics. An alternative mechanism is proposed for neuronal gain modulation that takes into account the capability of cortical neurons to process spatiotemporal synaptic correlations. Through the use of numerical simulations, it is shown that voltage-gated and leak conductances, membrane potential, noise, and input firing rate modify the sensitivity of cortical neurons to the degree of temporal correlation between their synaptic inputs. These changes are expressed in a change of the temporal window for synaptic integration and the range of input correlation over which response probability is graded. The study also demonstrates that temporal integration depends on the distance between the inputs and that this interplay of space and time is modulated by voltage-gated and leak conductances. Thus, gain modulation may reflect a change in the relationship between spatiotemporal synaptic correlations and output firing probability. It is further proposed that by acting synergistically with the network, dynamic spatiotemporal synaptic integration in cortical neurons may serve a functional role in the formation of dynamic cell assemblies.

INTRODUCTION

Cortical neurons possess multiple mechanisms that dynamically regulate their output. These mechanisms regulate the transformation of synaptic inputs into trains of action potentials, thus enabling neurons with a limited dynamic range to combine and process multifaceted dynamic information (for a review, see Salinas and Thier 2000). Generally, these processes are involved in modulation of neuronal gain, i.e., changing the sensitivity of the output to variations in the input, and appear in a wide range of contexts, including maximization of sensory information transfer (Brenner et al. 2000; Wainwright 1999), center-surround organization of receptive field (Heeger 1992), the effects of attention (McAdams and Maunsell 1999), invariant object recognition (Salinas and Abbott 1997), and coordinate transformations (Salinas and Abbott 1995; Zipser and Andersen 1988).

What neural mechanisms might underlie this striking capacity for gain modulation? One attractive model posits that the transfer function of neurons can be described by a linear relationship between mean input current and output firing rate ($I/I$ curve; Koch 1999). According to this paradigm, gain modulation reflects a change in this relationship, brought about by variation in membrane conductance, potential, and variance. Although this model received ample experimental and theoretical support recently (Chance et al. 2002; Fellous et al. 2003; Grande et al. 2004; Mitchell and Silver 2003; Moreno et al. 2002; Prescott and Konick 2003; Rudolph and Destexhe 2001; Shu et al. 2003), it assumes that neurons obeying these simple principles are thought to transmit information in their mean firing rates (Shadlen and Movshon 1999; Shadlen and Newsome 1998 and references therein). This view neglects both the well-established fact that cortical neurons can synchronize their firing on a millisecond timescale (Gray 1994, 1999; Reyes 2003; Singer and Gray 1995; Usrey and Reid 1999), and the complexity and sophistication by which a single neuron can process synaptic information (Ariav et al. 2003; Azouz and Gray 2003; Konig et al. 1996; Larkum et al. 1999; Léger et al. 2005; Polsky et al. 2004).

Cortical neurons are in fact very different from the simplistic view, in which irregular synaptic inputs are transformed into output discharge rates. They are sensitive to both the timing and location of their synaptic inputs (Ariav et al. 2003; Azouz and Gray 1999, 2000, 2003; Bair and Koch 1996; Buracas et al. 1998; Konig et al. 1996; Mainen and Sejnowski 1995a; Margulis and Tang 1998; Nowak et al. 1997; Polsky et al. 2004; Singer and Gray 1995; Softky and Koch 1993; Usrey and Reid 1999; Williams and Stuart 2002, 2003). Thus, gain modulation may not be reflected solely as a change of the relationship between mean input and output firing rate. Rather, it may be manifested as a modification of the relationship between the timing and location of synaptic inputs and response probability (Destexhe and Pare 1999; Hö and Destexhe 2000; Santamaria and Bower 2005).

This study attempts to provide a broad framework within which the impact of input correlations on cortical neurons can be better understood. By the use of theoretical models, the probability of spike generation is shown to be dependent on the degree of temporal correlation and distance between synaptic inputs to the cells. This dependency is dynamically modulated by the density of voltage-gated conductances, changes in membrane leak conductance, potential, variance, and input firing rate. The results suggest that cortical neurons can be described as devices that dynamically transmit the spatiotemporal correlations in their synaptic inputs.

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METHODS

Compartmental model

The aim of the simulation was to determine the relations between the degree of temporal correlation and the distance between synaptic inputs and the probability of spike generation and whether changes in membrane leak conductance, potential, noise, input firing rate, and voltage-gated conductances influence this relationship. Numerical simulations were conducted with NEURON (Hines 1989) by using a 10-µs time step and simulated temperature of 37°C. Compartmental models were constructed from layers V and II/III cortical pyramidal neurons described in Mainen and Sejnowski (1996) (Fig. 1A). An Axon morphologically identical to that in Mainen et al., 1995b was attached to the soma. The dendritic surface was corrected for spines, assuming that spines represent about 40% of the dendritic surface area (DeFelipe and Farina 1992). A passive leak conductance reversing at -70 mV was inserted at 0.03 mS cm⁻² giving an input impedance of 30 MΩ. Axial resistivity was set to 200 Ωcm, and membrane capacitance was set to 1 μF cm⁻².

The study used four types of model neurons: 1) passive compartmental models with integrate-and-fire (I&F) mechanisms in the soma; 2) an otherwise identical model neurons endowed with passive dendrites and Hodgkin and Huxley (H-H)–like voltage-gated Na⁺ and K⁺ conductances in the soma and axon; 3) H-H voltage gated conductances were inserted in different densities depending on the compartment (Na⁺ and K⁺ in mS cm⁻²): Soma and dendrites, 12; 10; Axon, 120; 100; and 4) voltage-gated Na⁺ and hyperpolarization-activated (Ih) K⁺ conductances. The densities of Na⁺ conductances were the same as in C while Ih were varied spatially. It increased linearly from 0.1 mS cm⁻² in the soma to 0.7 mS cm⁻² in the distal dendrites (Desjardins et al. 2003).

In the I&F neuron, as long as the voltage is subthreshold, \( v(t) < V_{\text{thres}} \) the voltage in the soma is given by

\[
\tau \frac{dv(t)}{dt} = -[v(t) - V_{\text{rest}}] + I_{\text{syn}}(t)R_{\text{n}}
\]

where \( I_{\text{syn}} \) is the synaptic current driving a leaky integrator with a time constant \( \tau \) and a threshold \( V_{\text{thres}} \). \( R_{\text{n}} \) is the input resistance and \( V_{\text{rest}} \) is the resting potential. At an instant the voltage reaches the threshold \( V_{\text{thres}} \), the neuron generates a spike, and resets to some level \( V_{\text{reset}} < V_{\text{thres}} \). The spike threshold for the integrate-and-fire (I&F) model (-55 mV) was adjusted to correspond to the spike threshold level in a Hodgkin–Huxley model injected with a 5-ms depolarizing pulse at the resting \( V_{\text{rest}} \).

The voltage in the H-H model neuron was described by

\[
\frac{dv}{dt} = \frac{G_m}{C_m} (v + h(E_n - v) + G_{E_k}(E_k - v) + G_{E_E}(V_{\text{rest}} - v))
\]

where \( m, h, \) and \( s \) are the activation, inactivation, and slow inactivation variables for the voltage-gated Na⁺ current; \( n \) is the activation variable for the voltage-gated K⁺ current; \( G \) and \( E \) are the peak conductance and the equilibrium potential for each current, respectively. Voltage-gated Na⁺ and K⁺ conductances were implemented using the Hodgkin–Huxley equations (Hodgkin and Huxley 1952a,b; Noble 1966). The maximal conductances and the activation and inactivation variables were derived from the experimental data (Beluzzi and Sacchi 1991; Fleidervish et al. 1996; Hamill et al. 1991; Huguenard et al. 1988; see Azouz and Gray 2003 for detailed parameters).

The model for \( I_{\text{f}} \) obtained from Huguenard and McCormick (1992), was

\[
\frac{dv}{dt} = \tilde{G}_k h(E_k - v)
\]

where \( h \) is the activation variable. \( \tilde{G} \) and \( E_k \) (-45 mV) are the peak conductance and the equilibrium potential, respectively.

Synaptic inputs

The model neurons received excitatory synaptic inputs of the voltage-independent α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) [non-N-methyl-D-aspartate (NMDA)] type (\( V_{\text{rest}} = 0 \) mV) and inhibitory synaptic inputs of the γ-aminobutyric acid type A (GABA_A) (\( V_{\text{rest}} = -70 \) mV). The synaptic input was modeled as nonsaturating currents with a dual-exponential time course of the form \( 1 - \exp(-t/\tau_{\text{rise}}) \exp(-t/\tau_{\text{decay}}) \), where for excitatory inputs \( I_{\text{max}}, \tau_{\text{rise}}, \tau_{\text{decay}} \) were 1 pA, 1 ms, and 5 ms, respectively, whereas for inhibitory inputs \( I_{\text{max}}, \tau_{\text{rise}}, \tau_{\text{decay}} \) were 0.4 pA, 4 ms, and 20 ms, respectively (Haussler and Roth 1997; Markram et al. 1997; Salin and Prince 1996).

The excitatory synapses were distributed uniformly and randomly on the apical dendrites, whereas inhibitory inputs were placed on the dendrites, soma, and axon initial segment. The densities of synapses in different regions of the cell were estimated from morphological studies in cortical pyramidal cells (DeFelipe and Farina 1992; White 1989). The number of synapses per 100 µm² of membrane were: 15 (GABA_A, soma), 50 (GABA_A, axon initial segment), 10 (GABA_A, dendrites), and 60 (AMPA–NMDA, dendrites), leading to a total of approximately 15,000 glutamatergic and 3,000 GABAergic synapses for the layer II/III and V neurons shown in Fig. 1A.

To determine the relations between input convergence and the probability of spike generation, a subset of the synapses was stimulated synchronously. This was achieved by generating a template pseudorandom excitatory spike train that consisted of Poisson-distributed spikes with minimal interspike interval (ISI) of 1 ms. The excitatory spike trains in the synchronous group were generated such that the arrival times of their spikes were distributed according to a Gaussian function around the times of the template spike train (Fig. 1B). The temporal distribution and the degree of correlation between presynaptic spikes were defined by SD (\( \sigma_{\text{input}} \)). The remaining excitatory spikes were distributed with \( \sigma_{\text{input}} = 100 \) ms. The inhibitory inputs consisted of independent Poisson-distributed spike trains with similar minimal ISI and firing rates as of the excitatory inputs.

These simulations lasted 3 s and were repeated 500 times with different template spike trains. To determine whether this procedure generates temporal structure in each of the presynaptic spike train both the ISI distribution and the autocorrelation function were calculated. It was found that presynaptic spike trains were highly irregular, the distribution of ISIs approximated an exponential probability density function, and no structure was detected in the autocorrelation function (not shown). Modulation of the passive leak conductance, membrane potential, and noise was established 1 s before synaptic stimulation.

To estimate the effects of input temporal correlation on output spike probability the number of synchronous synaptic inputs was set to 300 (the number of synaptic input that gave output spike probability of 0.5 with \( \sigma_{\text{input}} = 7 \) ms). These inputs were placed in random location on the apical dendrites and were restricted to a volume with a diameter of 100 µm (Fig. 1A, smaller circle). The influence of synaptic distance on spatiotemporal synaptic integration was studied by keeping the number of synchronous synaptic inputs constant while changing both the radius of dispersion as well as their \( \sigma_{\text{input}} \) (Fig. 1A, bigger circle). To ensure that the results were not ascribed to the choice of number of synchronous synaptic inputs, the influence of population size on the cumulative probability distribution was studied (Fig. 3).

The probability of output spike generation was defined by

\[
P_{\text{out}} = \frac{SP}{SP_{\text{max}}}
\]

where \( SP \) and \( SP_{\text{max}} \) are output spike count and output spike count at \( \sigma_{\text{input}} = 0 \) ms, respectively.

J Neurophysiol • VOL 94 • OCTOBER 2005 • www.jn.org
The results of these simulations (all figures) show that response probability depends on the degree of temporal correlation between afferent synaptic inputs. This relationship may be described by the slope, onset, and median point. In the following, these measures were used to characterize the responsiveness of cortical neurons in different conditions (Hô and Destexhe 2000).

To determine the effect of membrane conductance and variance on response probability in the model neuron, each of these parameters was independently varied. Increasing the leak membrane conductance by 10 nS resulted in a shift of the spike probability curve to the right and an increase of the slope (Fig. 2A, High shunt). These changes reduced only slightly the probability of responding to a higher degree of input correlation, whereas the response to the medium and smaller degrees of correlation was considerably decreased. Alternatively, decreasing the leak membrane conductance by the same amount resulted in a shift of the spike probability curve to the left and a steeper slope, such that a smaller degree of input correlation was needed to reach spike threshold (Fig. 2A, Low shunt). To quantify these effects, the slope and the shift in the curve as a function of leak membrane conductance were plotted (Fig. 2B). The graph in Fig. 2B shows that increasing leak membrane conductance results in a rightward shift in the curve and an increase of the slope. Conversely, decreasing leak membrane conductance results in a shift of spike probability curve to the left and a steeper slope.

These results appear counterintuitive at first glance because both increasing and decreasing leak membrane conductance resulted in an increase of the slope. However, they may be consistent with the notion that membrane conductance affects both the magnitude and the time course of synaptic inputs. Thus increased membrane conductance will result in a reduction of response magnitude and time window for synaptic integration, whereas reduction of membrane conductance will result in an increase of response magnitude and time window.
for synaptic integration. Consequently, increasing the leak membrane conductance will have only a moderate effect on highly synchronized inputs with higher probability for spike generation while resulting in a steep decline of response probability to smaller degrees of correlation. Similarly, decreasing the leak membrane conductance will have only a modest effect on response probability to smaller degrees of input correlation.

To determine the effect of membrane variance on response probability, $I_{\text{max}}$ for the noncorrelated excitatory and inhibitory inputs (a change of about 8% was needed) were modulated to attain a change of 2 mV in the $V_m$ variance, while keeping the mean $V_m$ constant. Increasing membrane potential variance by 2 mV resulted in a decrease in the slope, such that the probability of responding to smaller and higher degrees of input correlation was enhanced and reduced, respectively (Fig. 2C. High noise). Conversely, decreasing membrane potential variance by the same amount resulted in an increase of the slope, which led to a reduction in the probability of responding to smaller degree of input correlation, while increasing the probability of responding to higher degree of input correlation (Fig. 2C. Low noise). These effects pivoted on the 50% spike probability point, as predicted by others (Destexhe et al. 2001).

To quantify these effects, the slope and the shift in the curve as a function of membrane variance were plotted (Fig. 2D). The graph in Fig. 2D shows that increasing membrane variance results in a decrease of the slope, whereas decreasing leak membrane conductance results in a steeper slope.

Combining the effects of membrane conductance and variance on input–output relation led to a response curve shown in Fig. 2E. Increasing membrane conductance and variance resulted in a rightward shift in the curve and an increase of the slope that mainly led to a decrease in the response to the medium and smaller degrees of input correlation (Fig. 2E, High shunt, noise). Decreasing these parameters led to a steeper slope, thus increasing the probability of responding to medium and larger input correlations (Fig. 2E, Low shunt, noise).

To estimate the effects of synchronous population size on output spike probability, the number of synchronous synaptic inputs was varied. Variation in the number of synchronous synaptic inputs affects mostly the probability of responding to medium and higher degrees of input correlation, whereas the response to smaller degrees of correlation is only moderately affected (Fig. 3A). To quantify these effects, the slope and the shift in the curve as a function of synchronous input size were plotted (Fig. 3B). The graph in Fig. 3B shows that increasing the number of synchronous inputs results in a shift of the spike probability curve to the left and an increase of the slope. Alternatively, decreasing the number of synchronous inputs.
results in a shift of spike probability curve to the right and a reduction in the slope.

It has been shown recently that both input correlation and firing rate can influence neuronal output firing rate (Salinas and Sejnowski 2000), but the influence of input firing rate on the relation between input correlation and output spike probability has not been demonstrated. To determine the influence of input synchrony and firing rate on response probability in the model neuron, these parameters were simultaneously varied. Variation in firing rate affects mostly the probability of responding to lower and medium degrees of input correlation, whereas the response to medium and higher degrees of correlation is only moderately modulated (Fig. 4A). To quantify these effects, the slope and the shift in the curve as a function of firing rate were plotted (Fig. 4B). The graph in Fig. 4B shows that increasing input firing rate results in a leftward shift in the curve and a decrease of the slope. Conversely, decreasing input firing rate results in a shift of spike probability curve to the right and a steeper slope. Taken together, these results suggest that membrane conductance, variance, number of synchronous inputs, and firing rate may change the relation between output spike probability and input correlation by changing both the temporal window for synaptic integration and the range, defined as the temporal correlation range over which response probability was graded.

The contribution of voltage-gated conductances to dynamic coincidence detection

In previous studies, we have shown that spike threshold in cortical neurons is sensitive to the rate of rise of the rapid depolarizations preceding it (Azouz and Gray 2000). Moreover, we found that slow membrane depolarization reduces the overall cellular sensitivity by elevating spike threshold while simultaneously increasing the relative sensitivity to rapid depolarizations (Azouz and Gray 2003). These results suggest that somatic spike generation mechanisms may dynamically change the temporal window for synaptic integration as a function of membrane potential.

To understand the relationship between $V_m$ and the sensitivity to input correlation, the contribution of membrane potential on response probability in a model neuron endowed with H-H–like conductances in the soma was investigated. Depolarization of 2 mV resulted in a shift of the spike probability curve to the left and an increase of the slope (Fig. 5A, Depolarization). These changes increased only slightly the probability of responding to smaller degrees of input correlation, whereas the response to the medium and higher degrees of correlation was considerably enhanced. In contrast, hyperpolarizing the neuron by the same amount resulted in a shift of the spike probability curve to the right and a reduction of the slope (Fig. 5A, Hyperpolarization). This led to a reduction in response probability to all inputs, which was more pronounced for the higher degree of input correlation.

Combining the effects of membrane potential, shunt, and variance on input–output relation in a model neuron endowed with somatic H-H–like conductances led to a response curve shown in Fig. 5B. Membrane depolarization and increased shunt and variance resulted in a leftward shift and an increase...
of the slope. These changes increased only slightly the probability of responding to smaller degrees of input correlation, whereas the response to medium and higher degrees of correlation was considerably enhanced. Membrane hyperpolarization and decrease in shunt and variance resulted in a rightward shift and increased slope, such that a higher degree of input correlation was needed to reach spike threshold. Taken together, these results suggest that both passive and voltage-gated mechanisms in the neuronal membrane act synergistically to change the relation between output spike probability and input synaptic correlation. This is accomplished mainly through changing both the temporal range and window for synaptic integration.

The contribution of leak membrane conductance and noise to spatiotemporal synaptic integration

Processing of synaptic inputs by cortical neurons occurs mostly in dendrites and is influenced by dendritic morphology, membrane characteristics, and the properties of synaptic inputs. To determine the effect of membrane conductance change on spatiotemporal integrative properties of cortical neurons a compartmental model was used, constructed from layers V and II/III cortical pyramidal neurons with passive dendrites and I&F mechanism in the soma. The correlated synaptic inputs were placed on the dendrites and the synaptic dispersion was modified (Fig. 1A, dashed circles). The minimal $\sigma_{\text{input}}$, needed to evoke a response in the soma as well as spike probability curve slope while increasing the distance between the correlated synaptic inputs, was then measured. Increasing the distance between correlated synaptic inputs reduced exponentially the minimal $\sigma_{\text{input}}$ needed for spike generation (i.e., a higher degree of temporal correlation between synaptic inputs was needed to evoke a spike in the soma) (Fig. 6A, Control). Moreover, increasing the distance increased the slope of the probability curve, thus decreasing the temporal input range for synaptic integration (Fig. 6B, Control).

Increasing the leak membrane conductance by 10 nS resulted in a downward shift of the probability threshold curve (Fig. 6A, High shunt), such that a higher degree of input correlation was needed to reach spike threshold in the soma. Moreover, this increase reduced the slope of the spatial dependency curve (from 0.0033 to 0.0025), thereby reducing the spatial gradient of $\sigma_{\text{input}}$ needed for spike generation. Conversely, decreasing the leak membrane conductance by the same amount resulted in an upward shift of the probability threshold curve, such that a lesser degree of input correlation was needed to reach spike threshold. Reduction in leak conductance also resulted in an increase in the spatial dependency slope (Fig. 6A, Low shunt; from 0.0033 to 0.0034 ms/$\mu$m), thus increasing the spatial gradient of $\sigma_{\text{input}}$ needed for spike generation.

Modification in membrane leak conductance also changed the spike probability curve slope at each distance. Increasing the leak conductance shifted upward the normalized slope curve (Fig. 6B, High shunt) such that the slope of the spike probability curves became steeper with a steeper spatial gradient (from 0.33 to 1.22). Reducing the leak conductance by the same amount resulted in shallower slopes of spike probability curves, which resulted in an increase in the range of input temporal correlation. This was expressed in small downward shift of the normalized slope curve at small distances (Fig. 6B, Low shunt).

Also tested was whether the probability distribution of output spike generation as a function of $\sigma_{\text{input}}$ is influenced by the proximity of synaptic inputs to the soma. Placing the correlated excitatory synaptic inputs close to the soma ($<200 \mu$m from the soma) led to a leftward shift of spike probability curve and an increase of the slope (Fig. 6C). This resulted in an increase in response probability to all inputs, which was more pronounced for medium and higher degrees of input correlation as well as decreasing the range of input range. Together these findings indicate that temporal integration of synaptic inputs also depends on the distance between these inputs. This interplay of space and time may be modulated by changing the leak membrane conductance.

Although these findings confirm previous model predictions that network activity can change the passive cable properties of neurons (Bernander et al. 1991; Holmes and Woody 1989; Rapp et al. 1992), voltage-gated conductances in the dendrites can completely alter synaptic integration. To determine the influence of nonlinear processes on the relationship between spatiotemporal synaptic correlations and response probability, voltage-gated $\text{Na}^+$ conductance was placed in the dendrites.

**FIG. 5.** Separate effects of membrane polarization, shunting, and noise on response probability in an H-H model neuron. *A*: probability distribution of output spike generation as a function of $\sigma_{\text{input}}$ in control condition (●: thick line), 2 mV depolarization (△: thin line), and 2 mV hyperpolarization (●: thin line). Result is a leftward shift of the curve and an increase of the slope when the cell was depolarized ($\gamma$: $b = 0.73$, $c = 5.4$; $\Delta$: $b = 0.35$, $c = 7.6$) vs. a rightward shift and a reduction in the slope when the cell was hyperpolarized ($\bullet$: $b = 0.93$, $c = 3.4$). *B*: membrane depolarization in combination with increased shunt and noise resulted in leftward shift of the curve and an increase of the slope ($\Box$: $b = 0.33$, $c = 7.5$), whereas hyperpolarization in combination with reduced shunt and noise resulted in rightward shift of the curve and an increase of the slope ($\bullet$: $b = 0.11$, $c = 4.2$).
FIG. 6. Shunting regulates the spatial dependency of response probability on input correlation in passive dendrites. A: minimal $\sigma_{\text{input}}$ for spike generation as a function of the distance between the populations of synaptic inputs for an I&F model neuron in control condition (○: Control), additional 10 nS of leak conductance (□: High shunt), and a reduction of leak conductance by 10 nS (●: Low shunt). Data were fit by the equation $y = a \exp(-bx)$ (○: $a = 15.08, b = 0.0033$; □: $a = 5.72, b = 0.0034$; ●: $a = 18.27, b = 0.0025$). Inset: onset (the minimal $\sigma_{\text{input}}$ for spike generation) and slope of response probability curve. B: slope of response probability curve as a function of the distance between the 2 populations of synaptic inputs. Data were fit by the equation $y = a + b \exp(cx)$ (○: $a = 0.71, b = 0.19, c = 0.33$; □: $a = 1.29, b = 0.43, c = 0.46$; ●: $a = 0.57, b = 0.0016, c = 1.2$). C: placing excitatory synaptic inputs <200 μm from the soma lead to a leftward shift of spike probability curve and an increase of the slope (●: $b = 0.51, c = 10.1$).

D I S C U S S I O N

The impact of voltage-gated and leak membrane conductances, potential, noise, and input firing rate on the transmis-
sion of correlated synaptic inputs was studied using theoretical models. The results suggest that cortical neurons do not act solely by transforming the mean firing rate in their synaptic inputs to output firing rate. Rather, for a given firing rate they can transmit the spatiotemporal correlations in their synaptic inputs. Cortical networks can regulate this transformation through synaptically activated conductances and modulation of membrane potential and variance, which in turn will influence voltage-gated conductances.

The probability of spike generation is dependent on the degree of temporal correlation between afferent synaptic inputs. During states of high network activity, the input impedance of the cells decreases, the cells depolarize, and the membrane potential and variance, which in turn will influence voltage-gated conductances.

The results further suggest that the relationship between the degree of input correlation and spike generation is dependent on the spatial arrangement of these inputs. The farther the synaptic inputs are from each other, the higher degree of input correlation and spike generation is dependent on input correlation, respectively. D: onset as a function of the distance between the populations of synaptic inputs in control condition (○: Control), additional 10 nS of leak conductance (□: High shunt) and a reduction of leak conductance by 10 nS (●: Low shunt; □: a = 15.65, b = 0.0009; □: a = 10.80, b = 0.0011; ○: a = 21.37, b = 0.0008). To compare to passive dendrites, the control condition from Fig. 6A is depicted as a dashed line. E: introduction of voltage-gated Na+ and K+ conductances in the dendrites decreases the minimal $\sigma_{input}$ for spike generation and reduces the spatial dependency of response probability on input correlation.

Methodological considerations

Before discussing the underlying mechanisms and implications of these findings, it is important to consider the assumptions on which the interpretations are based. The first concerns the nature of input correlation to the model neuron. The method that was used to generate the temporal correlation in the synaptic inputs covers a specific case in which input...
correlations are generated by a common drive, and thus the probability of firing of one input is not independent of the probabilities of the rest of the inputs. Second, the conclusions also rest on the assumption that all presynaptic spikes result in synaptic potentials. However, transmission at individual synaptic contacts on pyramidal neurons has been found to be very unreliable and subject both to release failures and quantal fluctuations. Moreover, release probability changes in a history-dependent manner during short-term plasticity (Abbott et al. 1997; Markram and Tsodyks 1996). Again, the inclusion of detailed stochastic behavior of synaptic transmission is beyond the scope of this study and no attempt has been made herein to explore the potentially important consequences of such use-dependent effects. Third, to determine the separate effects of membrane conductance and variance on response probability in the model neuron, each of these parameters was independently varied. Therefore, the synaptic inputs in this study were modeled as current sources, whereas their impact on the input impedance of the cell was modeled as a uniform shunt. How-ever, network synaptic inputs onto the neuron will exert dynamic influences on the variance in the $V_m$ and membrane shunt. Both of these influences will affect the integrative properties of the neuron. These effects may depend on the distances between the synchronized synchronized synaptic inputs and their firing rates. Although the implications of these processes were not dealt in the current study, they fall within the framework within which the relationship between input correlation and output spike generation can be better understood.

Finally, the study generally assumes that the temporal pattern of synaptic inputs is reflected fully in the soma. Although this interpretation is fully consistent with the properties of synaptic integration (Alonso et al. 1996; Azouz and Gray 1999, 2000; Destexhe and Paré 1999; Reyes 2003; Usrey and Reid 1999), it neglects the fact that it occurs mostly in dendritic trees that contain a large variety of spatially inhomogenous active conductances (for reviews, see Johnston et al. 1996; Magee et al. 1998, 2000). These conductances, when activated, change the biophysical properties of dendrites and endow them with rich nonlinear computational capabilities (Archie and Mel 2000; Segev and London 2000). Thus synaptic inputs can be processed along multiple integrative modes that range from attenuation, through a linear integration mode within a single compartment encompassing the entire dendritic tree to nonlinear integration within a dendritic tree composed of multiple nonlinear integrative compartments, capable of parallel independent processing (Ariav et al. 2003; Golding and Spruston 1998; Larkum et al. 1999; Poirazi et al. 2003; Polsky et al. 2004; Schiller and Schiller 2001; Schiller et al. 2000). Although the implications of these processes are beyond the scope of the current study, they fall within the broad framework within which the impact of input correlations on a cortical neuron can be better understood. Thus, both the size of the “nonlinear integration compartment” and the time window for supralinear summation can be modulated by the network activity by changing membrane conductance, potential, and noise (Fig. 8).

Related work

Two recent theoretical studies (Destexhe and Paré 1999; Hô and Destexhe 2000) have used a somewhat similar methodology to that used here: analyzing the spike probability in response to synaptic inputs distributed in time and space with a Gaussian envelope of varying width. The results in the current study are largely consistent with the aforementioned papers. However, because the interest herein is focused on the basic operating mode of a cortical neuron, the results are based on an analysis of the entire parameter space of spatiotemporal synaptic integration. This expansion of parameter space also ensured that synaptic integration could be described as a continuum of operating modes rather than an all-or-none phenomenon.

Recent study has shown that both input correlation and firing rate can influence neuronal output firing rate (Salinas and Sejnowski 2000). The interplay between these parameters may contribute to a change in neuronal gain (ibid.), but the relationship between input correlation and output spike probability has not been demonstrated. In fact, the majority of studies that examined the effect of input correlation on neuronal input–output relation treat it as a by-product of cortical architecture and not as the chief carrier of sensory information (Bernander et al. 1991; Hô and Destexhe 2000; Salinas and Sejnowski 2000; Shadlen and Newsome 1998; Zohary et al. 1994). A determination of the effect of network activity on the transmission of correlated synaptic inputs in this investigation indicated that changing input firing rate within the range of 5–60 Hz may change the temporal window for spike initiation and the temporal correlation range over which response probability was graded. However, these changes did not qualitatively change the effect of membrane properties on cumulative probability distribution (not shown).

Dynamic spatiotemporal synaptic integration in cortical neurons

The manner by which neurons integrate their incoming synaptic inputs is a fundamental problem in cortical physiology. The common view in much of cortical physiology and neural computation considers the cortical neuron as a threshold
element that performs a simple linear sum over irregular synaptic inputs to produce the output in the form of action potentials (Shadlen and Newsome 1998 and references therein). An alternative view that takes into account the complexity and sophistication by which a single neuron can process synaptic information suggests that transformation of synaptic inputs into trains of action potentials can be defined by three basic elements: the manner in which synaptic inputs add in time (temporal summation), the amplitude of these synaptic inputs, and the integration of synaptic inputs occurring in separate regions of the dendritic tree (spatial summation). Recent support for this view comes from several studies showing the spike initiation and synaptic summation in the soma are dependent on the timing and distance between synaptic inputs (Ariav et al. 2003; Azouz and Gray 2003; Larkum et al. 1999; Margulis and Tang 1998; Polsky et al. 2004). Thus it is most likely that these elements of synaptic integration cannot be separated and the end result at the site of spike initiation depends both on spatial and temporal characteristics of synaptic inputs. These in turn will be shaped by dendritic morphology and the passive and active properties of the membrane.

In an attempt to provide a broad framework within which the influence of membrane characteristics on input–output transformation can be better understood a model of synaptic integration is used herein that relates the probability of output spike generation to the temporal correlation between synaptic inputs and their relative distance. The behavior of the cell is shown in Fig. 8, which depicts the sigmoid-shape cumulative probability distribution of output spike generation as a function of $\sigma_{\text{input}}$ at different distances between synaptic inputs. Increasing the distance between inputs decreases and increases the range and the temporal constraints on $\sigma_{\text{input}}$ for generating a spike, respectively. Changing the leak membrane conductance, variance, and potential in the cell will result in a change of the input/output relations, which may be expressed in temporal range change, change in the temporal constraints for generating a spike, and spatial dependency of these parameters (dashed lines in Fig. 8). Thus, the cortical neuron can be described as a device that dynamically transmits the spatiotemporal correlations in its synaptic inputs.

**Implications for the formation of dynamic cell assemblies**

Distributed coding is a concept by which the activity of large and spatially distributed populations of neurons is responsible for representing the attributes of incoming sensory stimuli (Hebb 1949; von der Malsburg 1995). According to this paradigm, neurons that constitute the assembly cooperate with one another, thereby forming dynamic functional circuits that represent distinct attributes or features of a unitary stimulus. One theory postulates that the forming of these cell assemblies may be defined by the synchronous firing of the participating neurons on a millisecond timescale (Gray 1994, 1999; Singer and Gray 1995; von der Malsburg 1981). In this scenario, the continual adjustment of the spatiotemporal constraints of synaptic integration is likely to have dramatic effects on the formation of cell assemblies and the membership of the constituent cells. Thus the characteristics of cortical neurons—and therefore the networks within which they operate—are constantly changing on various temporal and spatial scales in accordance with the properties of the sensory stimuli and the state of the network. This may be mediated through variation in membrane characteristics that change the relationship between output spike probability and input synaptic correlation by changing both the temporal range and window for synaptic integration. This effect of the network can be described as a control mechanism determining the operating point of neurons and thereby the efficacy of information transmission (Aertsen et al. 1989).

This conjecture meshes well with experimental and theoretical findings showing that synaptic activity present in intact networks dramatically modifies the integrative properties of cortical neurons (Azouz and Gray 2003; Destexhe and Paré 1999; Léger et al. 2005; Paré et al. 1998). This synaptic activity is tightly linked to the state of the cortical network that is likely to regulate the generation of synchronous activity by changing the spatiotemporal window of synaptic integration. Support for this comes from a recent study demonstrating that the strength of response synchronization covary with the amount of $\gamma$ power in the EEG, indicating a dynamic and direct relationship between synchronization of visual responses and the state of cortical activation (Herculano-Houzel et al. 1999). Such mechanisms may also participate in top-down processing of incoming sensory information in which attention to behaviorally relevant stimuli regulates the degree of synchronized oscillation (Fries et al. 2001; Steinmetz et al. 2000). Thus changing neuronal input–output relationship by modulating the transmission of synchronized activity might therefore be a fundamental neuronal mechanism for controlling signals that represent behaviorally relevant stimuli.

**Experimental predictions**

The proposed model describes the capability of cortical neurons to process spatiotemporal synaptic correlations, leading to several experimental predictions. First, the model suggests that dendritic voltage-gated conductances may modulate the relationship between spatiotemporal synaptic correlations and output firing probability. These results mesh well with numerous studies showing that several types of synaptic and voltage-gated conductances can control the temporal summation properties as well as spatial attenuation of postsynaptic potentials in cortical cell (Berger et al. 2001; Nettleton and Spain 2000; Polsky et al. 2004; Schwindt and Crill 1997; Williams and Stuart 2000, 2003). Thus the model predicts that by modulating these currents one will be able to control the relationship between spatiotemporal synaptic correlations and output firing probability.

Second, it has been suggested that during development, the cortical network is organized using rules that involve correlated activity between the neurons on the postsynaptic target (Shatz 1990). Using these rules combined with the characteristics of active dendrites, Poirazi and Mel (2001) suggested that during development, inputs carrying related information terminate onto functional integration compartments such as the same dendritic branch. Thus it becomes imperative to determine whether inputs carrying functionally related information cluster in space and time onto the same dendritic compartment. By combing two-photon laser scanning microscopy with intracellular recording in vivo, it will become possible to find whether stimuli of similar visual properties, for example position on the
receptive field, will activate nearby afferents, whereas afferents that are activated by stimuli of different attributes will activate distant compartments on the dendritic tree.

Third, it has been shown recently that cortical neurons are composed of multiple functional integration compartments capable of performing nonlinear amplification of spatiotemporal clustered inputs (Polsky et al. 2004). The model predicts that the size of the “integration compartment” and the time window for summation can be modulated by changing leak membrane conductance, potential, and noise. To examine this prediction one line of experiment would be to correlate the level of network activity by monitoring the local field potential in vivo or the level of spontaneous synaptic inputs in vitro and the spatiotemporal constraints on afferent synaptic inputs.

Fourth, the question of whether cortical neurons encode and process information by using precise spike timings (i.e., coincidence detectors) or spike rates (i.e., temporal integrators) has been highly debated. The results suggest the ongoing synaptic activity may change the temporal constraints on synaptic integration, and thus the network may modulate the operating mode of the neuron and shift the mode between temporal integration and coincidence detection (Rudolph and Destexhe 2003). This prediction can be tested by using intracellular recording in vivo and determining the relationship between the state of the network and temporal constraints on synaptic integration.

Finally, the model hypothesizes that the continual adjustment of the spatiotemporal constraints of synaptic integration is likely to have dramatic effects on the formation of cell assemblies and the membership of the constituent cells. Thus, ongoing network activity is likely to regulate the generation of synchronous activity by changing the spatiotemporal window of synaptic integration (see Herculean-Houzel et al. 1999 for an experimental validation of this prediction).

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References


Williams SR and Stuart GJ. Site independence of EPSP time course is mediated by dendritic I(h) in neocortical pyramidal neurons. *J Neurophysiol* 83: 3177–3182, 2000.


