Integration of Broadband Conductance Input in Rat Somatosensory Cortical Inhibitory Interneurons: An Inhibition-Controlled Switch Between Intrinsic and Input-Driven Spiking in Fast-Spiking Cells

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Tateno T, Robinson HPC. Integration of broadband conductance input in rat somatosensory cortical inhibitory interneurons: an inhibition-controlled switch between intrinsic and input-driven spiking in fast-spiking cells. J Neurophysiol 101: 1056–1072, 2009. First published December 17, 2008; doi:10.1152/jn.91057.2008. Quantitative understanding of the dynamics of particular cell types when responding to complex, natural inputs is an important prerequisite for understanding the operation of the cortical network. Different types of inhibitory neurons are connected by electrical synapses to nearby neurons of the same type, enabling the formation of synchronized assemblies of neurons with distinct dynamical behaviors. Under what conditions is spike timing in such cells determined by their intrinsic dynamics and when is it driven by the timing of external input? In this study, we have addressed this question using a systematic approach to characterizing the input–output relationships of three types of cortical interneurons (fast spiking [FS], low-threshold spiking [LTS], and nonpyramidal regular-spiking [NPRS] cells) in the rat somatosensory cortex, during fluctuating conductance input designed to mimic natural complex activity. We measured the shape of average conductance input trajectories preceding spikes and fitted a two-component linear model of neuronal responses, which included an autoregressive term from its own output, to gain insight into the input–output relationships of neurons. This clearly separated the contributions of stimulus and discharge history, in a cell-type dependent manner. Unlike LTS and NPRS cells, FS cells showed a remarkable switch in dynamics, from intrinsically driven spike timing to input-fluctuation–controlled spike timing, with the addition of even a small amount of inhibitory conductance. Such a switch could play a pivotal role in the function of FS cells in organizing coherent gamma oscillations in the local cortical network. Using both pharmacological perturbations and modeling, we show how this property is a consequence of the particular complement of voltage-dependent conductances in these cells.

INTRODUCTION

The cortical network contains a variety of distinct inhibitory neuron types, differing in electrical response properties, morphology, and expression of peptides and calcium-binding proteins (Kawaguchi 1995). Over the last ten years, it has been shown that interneurons of a specific functional type, such as fast-spiking (FS) or low-threshold spiking (LTS) neurons, form gap junctional connections specifically with other neurons of the same type (Connors and Long 2004; Hestrin and Galarreta 2005). Thus there are multiple electrically coupled assemblies of neurons, each with its own specific dynamical characteristics. This can lead to tight synchrony of firing among coupled neurons (Mancilla et al. 2007) and suggests that the intrinsic dynamics of the neurons in each electrical network may directly represent one particular motif or pattern in the repertoire of network activity. For example, we have shown that FS neurons have a hard, “type 2” threshold firing frequency at a low gamma frequency (20–30 Hz), when driven by synaptic-like conductance inputs (Tateno et al. 2004). This strongly suggests that an electrically coupled network of FS neurons—because of the shared intrinsic integrative properties of the connected neurons—would show stable synchronous and periodic firing at this frequency, when sufficiently excited. Such periodic FS firing could underlie locally generated gamma-frequency oscillations (Hasenstaub et al. 2005; Morita et al. 2008). Furthermore, recent studies show that, in layer 2/3 barrel cortex of awake mice, electrical activity of adjacent neurons is asynchronous during an active (whisking) state, whereas the neurons show synchronous oscillations during quiet states (Poulet and Petersen 2008). Understanding the neural mechanisms of such brain state transitions is a key to understanding sensory perception, sensorimotor functions, and learning (Gilbert and Sigman 2007). It is therefore important to ask: Under what conditions is spike timing in such cells determined by their intrinsic dynamics and when is it dominated by input fluctuations? What causes an electrically coupled network to exert its intrinsic dynamics on the rest of the network or, conversely, to be driven by activity in the network?

Herein, we have used a fluctuating conductance stimulus, with a high variability resembling that of natural synaptic input (Destexhe et al. 2001; Harsch and Robinson 2001; Softky and Koch 1993), and computed average spike-triggered conductance trajectories (ASTCTs), in fast-spiking (FS), low-threshold spiking (LTS), and nonpyramidal regular-spiking (NPRS) neurons. The use of a conductance stimulus gives a much more realistic spiking dynamics than does a fluctuating current input, by reproducing the shunting, saturating behavior of actual synaptic conductance inputs and a greatly shortened, dynamic membrane time constant, as well as spike-shape variations in certain classes of cells (de Polavieja et al. 2005). Intracellular recordings in vivo have revealed that cortical neurons are subjected to an intense synaptic bombardment, resulting in the resting conductance being generally much higher in the intact brain than that in in vitro preparations (Destexhe et al. 2003). Thus neocortical networks most likely operate in a “high conductance state,” which must have profound effects on the...
Conductive injection

For conductive injection (dynamic-clamp) stimulation (Robinson and Kawai 1993; Sharp et al. 1993), an SM-1 or SM-2 conductance injection system (Cambridge Conductance, Cambridge, UK) was used. The opening of a population of receptor channels at synapses is modeled by an excitatory (α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid [AMPA]) receptor synaptic conductance \( g_E(t) \) and an inhibitory (γ-aminobutyric acid type A [GABA_A]) receptor synaptic conductance \( g_I(t) \). Depending on the changing membrane voltage \( V(t) \), an injected current is described by

\[
I(t) = g_E[V(t) - E_E] + g_I[V(t) - E_I]
\]

where \( E_E \) and \( E_I \) are the reversal potentials for the AMPA- and GABA_A-type conductances, respectively. For each cell, \( E_I \) was set at the membrane resting potential (Connors et al. 1988) and \( E_E = 0 \) mV (Hollmann and Heinemann 1994; MacDermott and Dale 1987).

Current and conductance stimulation waveform

The standard injected current or conductance stimuli of broadband noise was 10–15 s in duration, repeated in sessions of 30 trials for each fixed parameter set. The broadband noise component was defined by the Ornstein–Uhlenbeck process \( X(t) \) with the relationship

\[
\frac{dX(t)}{dt} + \frac{X(t)}{\tau} = \sigma \xi(t)
\]

where \( \xi(t) \) is the standard white Gaussian noise, \( \tau \) is the filtering time constant, and \( \sigma \) is noise intensity. The broadband noise was actually synthesized by filtering white Gaussian noise with the following recursive formula

\[
X_n = \frac{1}{1 + K} \left( \frac{1}{\tau_n} X_{n-1} + \sigma \sqrt{\Delta t} \xi_n \right)
\]

where \( X_n \) is the \( n \)th point of the noise waveform, \( \xi_n \) is the standard Gaussian noise at the \( n \)th point, \( \Delta t \) is the sampling interval in milliseconds, and \( K = \Delta t/\tau \). We varied the noise realizations from trial to trial by choosing different initial random number seeds. For all trials in sessions, the filtering time constant was fixed at a time constant between 1 and 5 ms. For all trials of current stimulation, the noise intensity \( \sigma \) was 20–300 pA and for those of conductance injection stimuli, it was 1.0–4.0 nS. For each stimulus, the noise component was superimposed on a constant-step component, which was 0–500 pA for current injection and 0–3.0 nS for conductance injection. For the conductance injection stimuli, the sign of the membrane resting potential (Connors et al. 1988) and \( \sigma \) is noise intensity. The broadband noise was actually synthesized by filtering white Gaussian noise with the following recursive formula

\[
X_n = \frac{1}{1 + K} \left( \frac{1}{\tau_n} X_{n-1} + \sigma \sqrt{\Delta t} \xi_n \right)
\]

where \( X_n \) is the \( n \)th point of the noise waveform, \( \xi_n \) is the standard Gaussian noise at the \( n \)th point, \( \Delta t \) is the sampling interval in milliseconds, and \( K = \Delta t/\tau \). We varied the noise realizations from trial to trial by choosing different initial random number seeds. For all trials in sessions, the filtering time constant was fixed at a time constant between 1 and 5 ms. For all trials of current injection stimuli, the noise intensity \( \sigma \) was 20–300 pA and for those of conductance injection stimuli, it was 1.0–4.0 nS. For each stimulus, the noise component was superimposed on a constant-step component, which was 0–500 pA for current injection and 0–3.0 nS for conductance injection. For the conductance injection stimuli, the sign of the composed signal should be nonnegative, so that occasional negative values in the input signal were truncated to zero. Similar types of stimuli were used in Destexhe et al. (2001) and Hasenstaub et al. (2005).

Spike statistics

Spike times were measured as the times of upward zero crossing of the membrane potential. Instantaneous frequency (reciprocal of each interspike interval [ISI]) was computed from trains of action potentials evoked by 600-ms-duration pulses for the first, second, fourth, and last ISIs. Steady-state (SS) firing frequency was computed as the average of instantaneous frequency for the last three intervals of a train. Current or conductance strength was usually progressively increased or decreased in small (10- or 20-pA) steps. Instantaneous frequency and steady-state firing rate were plotted as a function of the injected current strength, to construct frequency–current (\( f-I \)) relationships. The maximum firing rate of a neuron was computed from the number of spikes per trial at the highest current strength before depolarization block. Results are reported as means ± SD.
Membrane time constants were obtained by fitting a single-exponential function to the initial part of >10 time-averaged voltage responses to small (~20 or ~10 pA), 600-ms-long hyperpolarizing current pulses. Input resistance was calculated from Ohm’s law by dividing the maximal average voltage deflection by the amplitude of the applied current pulses. Action potential shape parameters were measured from action potentials evoked by just-suprathreshold 200-ms current steps from a membrane potential near ~60 mV. Current strength was increased in 20-pA increments to determine the threshold. Spike amplitude was measured as the difference between the peak and the threshold of the action potential. Spike threshold was determined by finding the potential at which the second derivative of the voltage waveform exceeded threefold its SD in the period preceding spike onset (Erisir et al. 1999). The afterhyperpolarization (AHP) was measured as the difference between the spike threshold and voltage minimum following the action potential peak. Spike width was measured at half the spike amplitude.

Data analysis

To characterize stochastic properties of spike trains, we first calculated the mean, SD, and coefficient of variation (CV) of the ISIs, the ISI histogram, and the hazard function. The ISI histogram represents an estimate of the underlying probability density function \( f(t) = \frac{f(t)}{f(t_1) - f(t_k)} \), where \( t = t_k - t_{k-1} \), and \( t_k \) and \( t_{k-1} \) are, respectively, the successive \( k \)th and \((k - 1)\)th spike times, under the assumption that the history dependence in the spike trains is Markov. The hazard function, which represents the instantaneous probability of a spike occurring in an infinitesimal time interval as a function of time since the previous spike, is defined as

\[
b(t) = \frac{f(t)}{1 - \int_0^t f(u)du}
\]

It is termed “hazard” because in analysis of survival times, the hazard \( h(t) \Delta t \) may be interpreted as the risk of a failure in time interval \( [t, t + \Delta t] \) given that the system has survived up to time \( t \) (Cox and Miller 1965). To calculate the hazard function, we approximate it as

\[
P_h = \frac{\ln \left( \frac{N_o}{N_i} \right)}{BW}
\]

where BW is the bin width in milliseconds and \( N_o \) and \( N_i \) are the sum of all subsequent bins in the simple interval histogram, with \( N_o \) including the bin whose \( P_h \) is being computed and \( N_i \) excluding it (Matthews 1996).

Average spike-triggered trajectories (ASTTs) of current or conductance were calculated by averaging the broadband injected current or conductance from 100 ms before spikes to 20 ms after spikes. We also calculated ASTTs for subsets of spikes defined on the basis of the length of the preceding ISI. We evaluated the statistical significance of ASTT properties by calculating 95% confidence limits for the average and SD of the current or conductance preceding spikes, as described by Bryant and Segundo (1976). For the average, we used the 98% band provided by \( \pm 2.326 \times \sigma_x / N \) on each side of the mean, where \( \sigma_x \) is the SD of the noise waveform and \( N \) is the number of spikes. For the SD about the average, the 98% confidence limits are given as (Dixon and Massey 1969)

\[
\sigma_m = \left[ 1 - 2/(9N) \right]^{1/2} \times 2.326 \times \sqrt{2/(9N)}
\]

Linear modeling

To examine the impact of spike history on spike generation, we estimated parameters of a linear model of spike generation, using the spike times obtained during broadband conductance inputs. The model, which is the same as that used in Powers et al. (2005), is based on the approach of Joeken et al. (1997) who extended the Wiener series approach to neuronal system identification (Marmarelis et al. 1986; Westwich and Kearney 2003), to incorporate the effects of prior neuronal activity. The model is described by the following equation

\[
Y_n - \mu = \sum_{i=1}^q a_i X_{n-i} + \sum_{i=1}^p b_i (Y_{n-i} - \mu) + R_n
\]

where \( \mu \) is the expected value of \( Y_n \), \( q \) and \( p \) are positive integers that determine the length of the kernels, \( a_i \) and \( b_i \) are unknown parameters representing the estimated values of the stimulus and feedback kernels respectively at each time lag \( \tau \), and \( R_n \) is an error term. In the model, we first defined the broadband conductance input \( X_n \) and the binary spike output \( Y_n \). After the time axis was divided into small time bins with width \( \Delta t \), \( X_n \) is a time series that represents the input to the neuron during the nth time interval \([n \Delta t, (n + 1)\Delta t)\), \( Y_n \) is a time series that is unity if there was a spike in the nth time interval; otherwise, it is zero.

This model describes neural spike responses in a simple but reasonably accurate fashion, separating a component of spike generation due directly to the input and a component that is due to recovery from refractoriness through the feedback kernel, both of which will in general be varying in time. Rather than predicting an exact binary spike train output, it determines the probability of a spike occurring in a given time bin. As described in Powers et al. (2005), this technique can be used to predict the spike probability or instantaneous firing rate on the basis of the stimulus kernel, the feedback kernel, or both of the kernels. Therefore we evaluated the performance of these different models by calculating peristimulus time histograms describing the effect of stimulus transients on firing probability. In addition, to reduce the number of parameters to estimate, we resampled the spike times and stimulus waveforms using a time interval of 0.2 ms rather than 0.05 ms. To estimate coefficient parameters \( \{a_i\} \) and \( \{b_i\} \) of the model, we used the method described in Powers et al. (2005). The basic idea of the method is to minimize the sum of square error \( R_n^2 \) in Eq. 7 using a least-squares approach. The calculation was performed by using MATLAB (The MathWorks, Natick, MA) on a PC. To characterize feedback kernels, we used several parameters: minimum rate, zero crossing time, and slopes at the initial time and at the half-time of zero crossing (see Fig. 6Cb). The minimum rate is the firing rate at which the feedback kernel gives a minimum value. The zero-crossing time is the time when the feedback kernel crosses zero for the first time. Finally, the two slopes at the initial time and the half-time of zero crossing represent steepness at these two time points.

Results

Cell types in layer 2/3 of rat somatosensory cortex

On the basis of responses to injected step currents, putative inhibitory neurons of nonpyramidal morphology with multipolar dendrites were recorded in layer 2 or layer 3 of somatosensory cortex and were classified into three groups: nonpyramidal regular-spiking (NPRS), low-threshold spiking (LTS), and fast-spiking (FS) cells (Beierlein et al. 2003; Connors and Gutnick 1990; Kawaguchi 1993; Kawaguchi and Kubota 1997; Tateno and Robinson 2007), as shown in Fig. 1. This study is based on recordings from 41 NPRS, 18 LTS, and 38 FS neurons. See Table 1 for basic firing statistics of the three cell types. As described previously (Tateno and Robinson 2006, 2007; Tateno et al. 2004), Fig. 1, A, B, and C, respectively, shows typical action potential waveforms for an NPRS cell, an LTS cell, and an FS cell at three levels of injected step current.
NPRS cells showed monophasic afterhyperpolarizations (AHPs) as seen in Fig. 1A, whereas LTS cells showed biphasic AHPs (Fig. 1B). FS cells (Fig. 1C) showed deep AHPs, with the trough occurring only a few milliseconds after the spike. NPRS cells and FS cells differed in their basic electrical parameters, particularly in maximum firing rate (see Table 1). We also used several other measures to distinguish NPRS and FS cells, as reported in Tateno et al. (2004). Notice that LTS cells were easily distinguished from the other two cell classes by low-threshold action potentials produced when stimulated from hyperpolarizations (Beierlein et al. 2003; Fig. 2Aa in Tateno and Robinson 2007). In addition, it is also notable that characteristically, RS and LTS cells have “type 1” threshold dynamics and FS cells have “type 2” threshold dynamics (Tateno and Robinson 2007; Tateno et al. 2004).

Average spike-triggered conductance trajectories

Figure 2A shows waveforms of evoked action potentials (Fig. 2Aa) and of an excitatory conductance stimulus (Fig. 2Ab) for an NPRS cell. Average spike-triggered conductance trajectories (ASTCTs) were calculated for all cells (Fig. 2Ca), by averaging the broadband noise/synaptic conductance inputs over an interval of from −100 to +50 ms with respect to the time of occurrence of each spike in 20–40 trials for each session (see METHODS). Similarly, Fig. 2, Ba and Bb shows an average action potential (AAP) and the SD about the average, respectively, computed for firing at 17.4 ± 3.2 spikes/s and total 5,329 spikes, driven by broadband excitatory conductance inputs as shown in Fig. 2Ab. The AAP shows a shallow trough followed by a rising phase lasting about 2 ms, leading into the spike proper. As shown in Fig. 2Bb, the SD about the AAP is reduced significantly, starting about 30 ms before the spike and reaches a local minimum around the time of the AAP peak after a rapid increase during the rising phase of spikes. The ASTCT also shows a shallow trough followed by a rising phase lasting about 2 ms, leading into the spike proper. As shown in Fig. 2Ca, the shape of the ASTCT was characterized by the duration of the trough and by its depth and the amplitude of the peak, expressed as percentages of the baseline of the injected conductance for firing rates at 11–20 Hz (see Tables 2, 3, and 4). In addition, the percentage depth of the prespike minimum in conductance SD was measured, as shown in Fig. 2Cb. The properties of ASTCTs for 12 NPRS, 8 LTS, and 15 FS cells are summarized in Table 2.

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

**FIG. 1.** Firing properties of 3 classes of neurons in layer 2/3 somatosensory cortex. A: repetitive firing of a nonpyramidal regular spiking (NPRS) cell for 3 different current steps of increasing amplitude (90–380 pA). B: repetitive firing of a low-threshold spiking (LTS) cell for 3 different current steps of increasing amplitude (20–200 pA). C: repetitive firing of a fast-spiking (FS) cell for 3 different current steps of increasing amplitude (70–300 pA). FS and LTS cells had larger afterhyperpolarizations than NPRS cells.

**TABLE 1. Summary of basic statistics on NPRS, LTS, and FS cells**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NPRS</th>
<th>LTS</th>
<th>FS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cells</td>
<td>41</td>
<td>18</td>
<td>38</td>
</tr>
<tr>
<td>Resting potential, mV</td>
<td>−75.2 ± 5.0</td>
<td>−67.3 ± 2.7</td>
<td>−73.1 ± 5.9</td>
</tr>
<tr>
<td>Input resistance, MΩ</td>
<td>419.0 ± 116.0</td>
<td>429.0 ± 84.0</td>
<td>306.0 ± 72.0</td>
</tr>
<tr>
<td>Maximum firing rate, spikes/s</td>
<td>35.8 ± 10.1</td>
<td>58.8 ± 12.9</td>
<td>88.0 ± 27.0</td>
</tr>
<tr>
<td>Time constant, ms</td>
<td>43.1 ± 7.2</td>
<td>46.1 ± 6.5</td>
<td>32.6 ± 10.3</td>
</tr>
</tbody>
</table>

Values are means ± SD. NPRS, nonpyramidal regular spiking; LTS, low-threshold spiking; FS, fast spiking.
**Input level dependence of ASTCTs: distinctive spike-generation dynamics of FS cells**

Figure 3, Aa and Ab shows examples of ASTCTs and AAPs, respectively, for an NPRS cell. As the level of excitatory synaptic input was increased (labeled “Low,” “Medium,” and “High” in Fig. 3, Aa and Ab), ASTCTs developed a deep trough (around −20 ms in Fig. 3Aa) followed by an increasingly large, rapid peak immediately preceding the spike at 0 ms (dotted line), as previously reported by Tateno and Robinson (2006) for cortical RS cells. Similar characteristics of the ASTCT are seen in LTS and FS cells (Tateno and Robinson 2006). For the same NPRS cell, the excitatory input level determines spike-shape parameters such as amplitude and width, as shown in Fig. 3Ab. In contrast, such spike-shape encoding does not occur in FS and LTS cells (Tateno and Robinson 2006).

The ASTCT is partly determined by how the distance to the spike threshold varies during successive spikes for the excitatory input, which can be characterized by interspike interval (ISI) probability density functions (normalized ISI histograms in Fig. 3Ba) or by hazard functions (Fig. 3Bb) (see METHODS). Because of the AHP, the distance to spike threshold is large immediately following a spike and the hazard rate is zero or very low, as shown in Fig. 3Bb. As the AHP decays, the membrane potential rises toward threshold, leading to a progressive increase in the hazard rate (e.g., after 40 ms in Fig. 3Bb). However, if the mean level of membrane depolarization is below threshold after the AHP has completely decayed, the hazard rate levels off at a constant level and spikes then occur as a result of positive noise-induced deflections (the thin-line curve labeled “Low” in Fig. 3Bb; see Matthews 1996; Powers and Binder 2000). For in-between input levels, the membrane potential and the hazard rate monotonically increase after a spike occurs. Thus the hazard rate function provides a quantitative portrait of the spike-generation dynamics in a complex, fluctuating input regime. Because, as shown in Fig. 1, the extent of AHPs in the three types of neurons is very different, the hazard rate for each cell type should reflect its specific intrinsic integrative properties.

Furthermore, the effects of inhibition are expected to show differences among the three cell types (Tateno and Robinson 1996). Figure 3, Ca and Cb shows effects of inhibitory synaptic conductance input on the ISI probability density and hazard functions, respectively, in an NPRS cell. Raising the level of inhibitory input reduced the peak of the ISI distribution, shifting it to the right, and increased the
In a cell-type-specific way. In LTS cells, the membrane potential just before the action potential peak (Fig. 5A) may have a much sharper, more compact prespike trough, as shown in Fig. 5B. Thus the integrative properties of FS cells, as encapsulated by the ISI PDF/hazard rate functions, are more sensitive to inhibitory input than are those of NPRS and LTS cells, and more sensitive to changes in inhibition than to changes in excitatory conductance.

**Spikes history dependence on the ASTCTs**

The prespike trough in the ASTCT (see Fig. 3Aa) may indicate that spikes are more likely to occur in response to depolarizing fluctuations soon after a preceding hyperpolarization removes some inactivation of sodium channels. However, the trough could also originate from an association between, for example, particularly long interspike intervals and a reduced level of excitatory conductance late in the ISI. As shown in Powers et al. (2005), the latter effect can be resolved by examining whether the form of the ASTCT differs for populations of spikes grouped according to their preceding spike interval. Here, we divided ISIs into six groups with equal proportions as shown in Fig. 5, Aa, Ba, and Ca, for NPRS, LTS, and FS cells, respectively.

Generally, in all cell types, the ASTCTs calculated from the shorter ISIs had a larger peak amplitude and little or no preceding trough, whereas ASTCTs calculated from the longer ISIs had a smaller peak amplitude and a deeper trough. The three types of cells showed some clear differences. FS cells showed a much sharper, more compact prespike trough, as highlighted for the 55- to 70-ms group of spikes (indicated by arrows in Fig. 5, Ab, Bb, Cb), than that of the other two cell types. Moreover, Fig. 5, Ac, Bc, and Cc shows that discharge history, as reflected in the preceding ISI, influences the average shape of action potentials in a cell-type–specific manner. In NPRS cells, membrane potential just before and after the action potential peak varies with discharge history as shown in Fig. 5Ac. In LTS cells, the membrane potential just before the action potential (Fig. 5Bc), whereas in FS cells, the membrane potential immediately after the action potential peak (Fig. 5Cc) was most strongly influenced by discharge history.

These results indicate that in all three cell types, each range of ISIs is intrinsically related to a specific average conductance input trajectory and average evoked action potential shape. The ASTCTs reflect the contribution of all of these trajectories, weighted by the probability of different ISIs occurring. In particular, the AHP is likely to influence the specific shape of the ASTCTs associated with different ISIs. Thus ASTCTs reflect the influence of both stimulus history and discharge history on firing probability, in a cell-type–specific way.

**TABLE 2. Summary of spike-triggered excitatory conductance trajectories for NPRS, LTS, and FS cells**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NPRS</th>
<th>LTS</th>
<th>FS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cells</td>
<td>12</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Average firing rate, Hz</td>
<td>18.10 ± 4.2</td>
<td>18.10 ± 1.9</td>
<td>20.60 ± 2.90</td>
</tr>
<tr>
<td>Excitatory conductance input, nS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>3.71 ± 1.78</td>
<td>2.03 ± 1.08</td>
<td>3.65 ± 0.77</td>
</tr>
<tr>
<td>SD</td>
<td>1.23 ± 0.61</td>
<td>0.675 ± 0.359</td>
<td>1.23 ± 0.33</td>
</tr>
<tr>
<td>Average spike-triggered conductance trajectory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak ratio, %</td>
<td>51.00 ± 12.1</td>
<td>47.50 ± 7.9</td>
<td>59.60 ± 19.7</td>
</tr>
<tr>
<td>Trough duration, ms</td>
<td>43.10 ± 10.9</td>
<td>30.60 ± 18.3</td>
<td>31.60 ± 10.0</td>
</tr>
<tr>
<td>Trough depth ratio, %</td>
<td>15.10 ± 9.0</td>
<td>5.23 ± 13.3</td>
<td>11.40 ± 7.7</td>
</tr>
<tr>
<td>SD</td>
<td>48.90 ± 20.7</td>
<td>39.30 ± 25.2</td>
<td>38.70 ± 15.6</td>
</tr>
</tbody>
</table>

Values are means ± SD. “Peak ratio” and “trough depth ratio” are, respectively, the ratios of peak amplitude and trough depth to the overall average of conductance inputs (baseline) in percentage, as shown in Fig 2Ca. “Depth ratio” is the ratio of depth to the overall SD (baseline) of conductance inputs in percentage (Fig 2Cd).

**TABLE 3. Summary of feedback kernel properties for NPRS, LTS, and FS cells**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NPRS</th>
<th>LTS</th>
<th>FS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cells</td>
<td>10</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Average firing rate, Hz</td>
<td>14.00 ± 2.40</td>
<td>11.40 ± 1.50</td>
<td>15.30 ± 3.60</td>
</tr>
<tr>
<td>Feedback kernel properties</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum firing rate, Hz</td>
<td>−72.70 ± 27.70</td>
<td>−40.30 ± 14.40</td>
<td>−94.70 ± 14.70</td>
</tr>
<tr>
<td>Zero crossing time (ZCT), ms</td>
<td>45.10 ± 10.20</td>
<td>50.50 ± 18.50</td>
<td>25.90 ± 11.30</td>
</tr>
<tr>
<td>Slope at the initial time, Hz/ms</td>
<td>4.60 ± 2.27</td>
<td>1.64 ± 0.73</td>
<td>5.16 ± 1.56</td>
</tr>
<tr>
<td>Slope at the half ZCT, Hz/ms</td>
<td>0.703 ± 0.381</td>
<td>0.64 ± 0.20</td>
<td>1.87 ± 1.13</td>
</tr>
</tbody>
</table>

Values are means ± SD.

**TABLE 4. Summary of feedback kernel properties for 10 FS cells in control and TEA application**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>TEA</th>
<th>Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average firing rate, Hz</td>
<td>15.10 ± 1.50</td>
<td>13.60 ± 1.20</td>
<td>14.50 ± 1.40</td>
</tr>
<tr>
<td>Feedback kernel properties</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum firing rate, Hz</td>
<td>−79.50 ± 16.90</td>
<td>−97.50 ± 23.90</td>
<td>−82.80 ± 16.00</td>
</tr>
<tr>
<td>Zero crossing time (ZCT), ms</td>
<td>41.50 ± 3.90</td>
<td>47.40 ± 6.30</td>
<td>44.00 ± 5.10</td>
</tr>
<tr>
<td>Slope at the initial time, Hz/ms</td>
<td>3.45 ± 0.43</td>
<td>2.62 ± 0.69</td>
<td>3.30 ± 0.44</td>
</tr>
<tr>
<td>Slope at the half ZCT, Hz/ms</td>
<td>1.46 ± 0.31</td>
<td>0.85 ± 0.22</td>
<td>1.30 ± 0.32</td>
</tr>
</tbody>
</table>

Values are means ± SD; number of cells, n = 9.
Two-component linear representation of spike discharge

To understand how cells integrate broadband synaptic-like conductance input, we need a quantitative model that is simple, but meaningful and accurate. We used a two-component linear model (Powers et al. 2005; also see METHODS) to model the response function of neurons, to obtain estimates of the effects of stimulus and discharge history on firing probability. As shown in Fig. 6A, the relationship between stimulus input and output spike probability is predicted by a stimulus kernel and a feedback kernel, which respectively correspond to moving average (MA) and autoregressive (AR) parameters in the ARMA model (Harvey 1993) (see METHODS). Each of the kernels is specified by a series of coefficients predicting the firing probability at particular fixed time lags (at intervals of 0.2 ms). The stimulus kernel in the model predicts the average change in firing probability for input stimuli, whereas the feedback kernel predicts the average change in firing probability following previous spikes. The coefficients of the kernels were, from an initial set of random values, adjusted iteratively until they minimized the error of the model prediction (Fig. 6B; see METHODS for details). Figure 6C shows the stimulus and feedback kernels of the model from the discharge record of an NPRS cell for an excitatory conductance stimulus. Each point in the kernels indicates the expected increase or decrease in the number of spikes during a specific short period (e.g., 0.2-ms duration) compared with the average/background firing prob-

FIG. 3. In NPRS cells, analysis of evoked spike responses at 3 different levels of excitatory conductance input and at 2 different levels of inhibitory conductance input. Aa: average spike-triggered excitatory conductance changes from −100 ms prior to the spike to 50 ms afterward with a higher time resolution view in the inset. Thick black trace: a high level of excitatory input (labeled “High” in plots) with average conductance $\mu_{ex} = 4.0$ nS and the SD $\sigma_{ex} = 1.6$ nS; thick gray trace: “Medium,” $\mu_{ex} = 3.0$ nS and the SD $\sigma_{ex} = 1.2$ nS; thin black trace: “Low,” $\mu_{ex} = 2.0$ nS and the SD $\sigma_{ex} = 0.6$ nS. Ab: in the same cell shown in Aa, the average action potentials and a higher time resolution view in the inset. Ba: in the same cell shown in A, interspersed spike interval (ISI) probability density functions, which are ISI histograms normalized by the total ISI number. The bin size of the histograms was 8 ms. The FRs were, at the high level of the conductance input, 13.4 ± 4.4 spikes/s; medium, 9.5 ± 3.5 spikes/s; low, 7.6 ± 3.8 spikes/s. Bb: the hazard rates in the same cell shown in Ba. Ca: in an NPRS cell, ISI probability density functions. The bin size was 8 ms. In all 3 traces, the average of the excitatory conductance input ($\mu_{ex}$) was 3.6 nS and the SD ($\sigma_{ex}$) was 1.2 nS. Thin black trace: in the control condition, the FR was 12.2 ± 5.6 spikes/s. Thick black trace: a high level of the inhibitory input (labeled “High”) with average inhibitory conductance $\mu_{in} = 3.5$ nS and the SD $\sigma_{in} = 1.2$ nS. FR, 7.4 ± 3.6 spikes/s; thin black trace: “Low,” $\mu_{in} = 2.5$ nS and the SD $\sigma_{in} = 0.80$ nS. FR, 5.8 ± 3.5 spikes/s. Cb: the hazard rates in the same cell shown in Ca.
ability, following a pulse of excitatory conductance stimulus. The kernels represent an impulse response function in the sense that it represents the transient in output spike probability, which would be obtained in response to an impulse input. As shown in Fig. 6Ca and the inset, the stimulus kernel has a sharp peak around 2–3 ms, followed by an exponential-like decay to baseline within 10–20 ms. The first-order Wiener kernel, which corresponds to coefficients of a moving average model without autoregressive terms, is indicated as the dotted trace in Fig. 6Ca. Coefficients of the Wiener kernel during the first 20-ms period are usually smaller than those of the stimulus kernel because the feedback kernel makes a negative contribution to the output firing probability of the two-component model. As shown in Fig. 6Cb, for the same cell, the feedback kernel increases monotonically with time until around 60 ms from a negative firing rate before decaying to a baseline.

Looking at the kernels in the period of the first 20 ms of Fig. 6Cb, we can see that the occurrence of a single spike clearly has a more pronounced effect on the output firing probability than does a brief unit pulse of excitatory stimulus. To characterize the feedback kernel, we used four parameters: the minimum firing rate, the zero-crossing time, and slope values at the initial time and the half-time to zero crossing (see METHODS) as shown by arrows in Fig. 6Cb.

Including the feedback kernel in the model seems to have a relatively small effect on the time course of the stimulus kernel as shown in Fig. 6Ca. Therefore it seems possible that the predictions of the Wiener kernel model and the two-component model could be similar, although this is not the case. Figure 6D shows the difference between the Wiener kernel estimate and

![Diagram](http://jn.physiology.org/)

**Fig. 4.** In FS cells, analysis of evoked spike responses at 3 different levels of excitatory conductance input and at 2 different levels of inhibitory conductance input. Aa: ISI probability density functions. The bin size was 8 ms. The 3 levels of the conductance input with average ($\mu_{ex}$) and the SD ($\sigma_{ex}$) and the FRs are: high, $\mu_{ex} = 4.5$ nS, $\sigma_{ex} = 1.5$ nS, FR = 32.6 ± 8.4 spikes/s; medium, $\mu_{ex} = 2.4$ nS, the SD $\sigma_{ex} = 0.8$ nS, FR = 16.0 ± 10.1 spikes/s; low, $\mu_{ex} = 1.8$ nS, the SD $\sigma_{ex} = 0.6$ nS, FR = 9.0 ± 7.9 spikes/s. b: the hazard rates in the same cell in Aa. B: in an FS cell, ISI probability density functions. The bin size was 8 ms. In all 3 traces, the average of the excitatory conductance input ($\mu_{ex}$) was 2.1 nS and the SD ($\sigma_{ex}$) was 0.7 nS. Thin black trace: control condition, the FR was 29.9 ± 9.5 spikes/s. Thick back trace: a high level of the inhibitory input (labeled “High”) with average inhibitory conductance $\mu_{in} = 2.1$ nS and the SD $\sigma_{in} = 0.7$ nS. FR, 9.5 ± 4.8 spikes/s; thin black trace: “Low,” $\mu_{in} = 0.5$ nS and the SD $\sigma_{in} = 0.17$ nS. FR, 12.1 ± 5.9 spikes/s. Bb: the hazard rates in the same cell shown in Bb.
the stimulus kernel from the two-component model, which has a negative-going peak lasting about 30 ms and with a similar duration to the width of the average action potential (cf., action potential waveform shown in the inset of Fig. 6D). Therefore including spike-discharge history in the estimator is essential for an accurate estimation of output spike probability. As shown in Fig. 6Ec, this scenario can be easily understood if we compare the firing probability output of three models: the two-component model, a stimulus kernel model without the feedback kernel, and the first-order Wiener kernel model. The two-component model estimator shows rapid drops in spike rate immediately after occurrence of spikes because of the effect of the feedback kernel (Fig. 6Ed). As a result, the output firing probability of the two-component model was smaller.

FIG. 5. In NPRS, LTS, FS cells, dependence of ASTCTs and evoked action potentials on the duration of the preceding ISIs. A: NPRS cell. a: ISI histogram. The bin size was 8 ms. The FR was 13.1 ± 4.9 spikes/s. b: ASTCTs. Each of the 6 colors corresponds to that in a. The average of the excitatory conductance input ($\mu_{ex}$) was 3.0 nS and the SD ($\sigma_{ex}$) was 1.1 nS. c: average action potentials. Each of the 6 colors corresponds to that in a. B: LTS cell. a: ISI histogram. The bin size was 8 ms. The FR was 12.3 ± 7.2 spikes/s. b: ASTCTs. $\mu_{ex} = 1.2$ nS and $\sigma_{ex} = 0.4$ nS. c: average action potentials. C: FS cell. a: ISI histogram. The bin size was 8 ms. The FR was 21.2 ± 12.1 spikes/s. b: ASTCTs. $\mu_{ex} = 3.0$ nS and $\sigma_{ex} = 1.0$ nS. c: average action potentials.
after occurrence of spikes than that of the other two models and this led to a decreased estimation error.

Characteristics of stimulus and feedback kernels for three cell types

Figure 7A shows the stimulus and feedback kernels estimated from a discharge record of an NPRS cell at three different levels (labeled “High,” “Medium,” and “Low”) of the excitatory conductance input. As shown in Fig. 7Aa, the stimulus kernels all showed single peaks around 2–3 ms and followed by an exponential decay to baseline within 10–15 ms (cf. Fig. 6Ca). In addition, with increasing stimulus level, the peak amplitude of the stimulus kernels increased, although the normalized plot of the three kernels showed no significant change in the time course (data not shown). Feedback kernels for the same cell are shown in Fig. 7Ab. Note that in calculating the feedback kernels, the average firing rate was subtracted, so that all the feedback kernels eventually decay to the baseline around the zero level. As shown in Fig. 7Ab, for the high excitatory input, at the beginning the firing probability in the feedback kernel for a first 30-ms period was very low, monotonically increased until around 50 ms after crossing the zero level at 30–40 ms, and finally decayed to the baseline. At the medium and low levels of the stimuli, the overall trend was similar, although the slope of the increment and the time at the peak point differed. Thus the characteristics of both stimulus and feedback kernels depended on the mean firing rate. In particular, the time course of the feedback kernels clearly changes with mean firing rate, whereas the stimulus kernels calculated from the records of the different discharge rates are quite similar in shape.

Figure 7B shows inhibitory effects on stimulus and feedback kernels for an NPRS cell. In the presence of the inhibitory input at two different levels (labeled “High inhibition” and “Low inhibition”), the stimulus and feedback kernels were estimated from the relationship between excitatory conduc-
NPRS cells

Figure 8A shows the stimulus and feedback kernels estimated from the discharge record of an FS cell at three different levels (labeled “High,” “Medium,” and “Low”) of the excitatory conductance input. Stimulus kernels (Fig. 8Aa) were similar to those of NPRS cells. Feedback kernels for the same cell are shown in Fig. 8Ab. All feedback kernels eventually decayed to the baseline around the zero level. However, the first 30-ms period of each kernel is different. For the high excitatory input, the firing probability in the feedback kernel is very low in the first 8 ms, then rapidly increases to cross zero at around 15 ms, before finally decaying to the baseline. At the medium level of the stimulus, the overall trend was similar, although the rising slope was reduced and the time of the peak was shifted later.

Figure 8B shows inhibitory effects on stimulus and feedback kernels for an FS cell. In control and in the presence of the inhibitory input with two different levels of inhibition (labeled “High inhibition” and “Low inhibition”), the stimulus and feedback kernels were estimated from the relationship between excitatory conductance input and its discharge history. As the level of inhibition increased, the peak of the stimulus kernels decreased in amplitude and shifted leftward in time, as shown in the inset of Fig. 8Ba. Figure 8Bb shows the effect of inhibition on the feedback kernels. Administering inhibitory input to FS cells drastically changed the time course of the feedback kernels, even though the level of the input was relatively small (in Fig. 8Bb, “Low inhibition”) with average inhibitory conductance $\mu_{\text{in}} = 3.5 \text{ nS}$ and the SD $\sigma_{\text{in}} = 1.2 \text{ nS}$. Inhibitory input to FS cells thus has a much more powerful effect on the feedback kernel, accelerating the recovery from refractoriness, than that in NPRS cells.

The results obtained from LTS cells are similar to those from NPRS cells, as shown in Fig. 9. However, all the feedback kernels in LTS cells increased more slowly to the zero level than those of NPRS cells over the first 60 ms, as shown in Fig. 9Ab. The effect of inhibition on the feedback kernels was to shift them upward as the inhibitory input level increased (Fig. 9Bb).

Effects of changes in the AHP on the stimulus and feedback kernels

The decrease in firing probability measured by the feedback kernel is likely to represent the influence of the postspike AHP, especially in FS cells. Although, in response to the excitatory conductance injection, the mean discharge rate was nearly constant at 13–15 spikes/s, changes in AHP should profoundly influence the feedback kernel. In addition, the precise spike timing evoked by the conductance input signal may be influenced by the change in AHP. It is known that a low tetraethylammonium (TEA) concentration ($\leq 1 \text{ mM}$) in the extracellular solution blocks a small fraction of $K^+$ channels and impairs action potential repolarization (Erisir et al. 1999). We
Erisir et al. (1999) reported that this concentration of TEA in the extracellular solution during conductance stimuli (Fig. 10) feedback kernel and on spike timing by adding 1 mM TEA to the 3 cases, the average of the excitatory conductance input. In all 3 cases, the average of the excitatory conductance input. In the 3 cases, the average of the excitatory conductance input (\(\mu_{ex}\)) was the same and 2.1 nS and the SD \(\sigma_{ex}\) was 0.7 nS. Thick line trace: in control condition, the FR was 29.9 ± 0.5 spikes/s. Dotted line trace: a high level of the inhibitory input (labeled “High inhibition”) with average inhibitory conductance \(\mu_{in}\) was 2.1 nS and the SD \(\sigma_{in}\) was 0.7 nS. FR, 9.5 ± 4.8 spikes/s. Thin line trace: “Low inhibition,” \(\mu_{in} = 0.5 \text{ nS}\) and the SD \(\sigma_{in}\) = 0.17 nS. FR, 12.1 ± 5.9 spikes/s.

FIG. 8. For FS cells, stimulus and feedback kernels. The time lag between the coefficients of the kernels was 0.4 ms. A: in the same FS cell in Fig. 4A, the stimulus kernels in a and feedback kernels in b are shown for the 3 different levels of the excitatory conductance input. Dotted line trace: “High” level of the input with average conductance \(\mu_{ex} = 4.5 \text{ nS}\) and the SD \(\sigma_{ex} = 1.5 \text{ nS}\). Thin line trace: “Medium,” \(\mu_{ex} = 2.4 \text{ nS}\) and the SD \(\sigma_{ex} = 0.8 \text{ nS}\). Thick line trace: “Low,” \(\mu_{ex} = 1.8 \text{ nS}\) and the SD \(\sigma_{ex} = 0.6 \text{ nS}\). The FRs were, at the high level of the conductance input, 32.6 ± 8.4 spikes/s; medium, 16.0 ± 10.1 spikes/s; low, 9.0 ± 7.9 spikes/s. B: for the same FS cell in Fig. 4B, the stimulus kernels in a and feedback kernels in b are shown in control and 2 different levels of the inhibitory conductance input. In the 3 cases, the average of the excitatory conductance input (\(\mu_{ex}\)) was the same and 2.1 nS and the SD \(\sigma_{ex}\) was 0.7 nS. Thick line trace: in control condition, the FR was 29.9 ± 0.5 spikes/s. Dotted line trace: a high level of the inhibitory input (labeled “High inhibition”) with average inhibitory conductance \(\mu_{in}\) was 2.1 nS and the SD \(\sigma_{in}\) was 0.7 nS. FR, 9.5 ± 4.8 spikes/s. Thin line trace: “Low inhibition,” \(\mu_{in} = 0.5 \text{ nS}\) and the SD \(\sigma_{in}\) = 0.17 nS. FR, 12.1 ± 5.9 spikes/s.

FIG. 9. Stimulus and feedback kernels for LTS cells. The time lags between coefficients of the kernels was 0.4 ms. A: stimulus kernels in a and feedback kernels in b are shown for the 3 different levels of the excitatory conductance input. Thick line trace: “High” level of the input with average conductance \(\mu_{ex} = 1.5 \text{ nS}\) and the SD \(\sigma_{ex} = 0.5 \text{ nS}\). Thin line trace: “Medium,” \(\mu_{ex} = 1.0 \text{ nS}\) and the SD \(\sigma_{ex} = 0.35 \text{ nS}\). Dotted line trace: “Low,” \(\mu_{ex} = 0.8 \text{ nS}\) and the SD \(\sigma_{ex} = 0.25 \text{ nS}\). The FRs were, at the high level of the conductance input, 14.1 ± 0.8 spikes/s; medium, 10.2 ± 0.8 spikes/s; low, 6.4 ± 0.9 spikes/s. B: for an LTS cell, the stimulus kernels in a and feedback kernels in b are shown for control and 2 different levels of the inhibitory conductance input. In all 3 cases, the average of the excitatory conductance input (\(\mu_{ex}\)) was the same and the mean was 2.4 nS and the SD \(\sigma_{ex}\) was 0.6 nS. Dotted line trace: in control condition, the FR was 14.9 ± 2.6 spikes/s. Thin line trace: a high level of the inhibitory input (labeled “High inhibitory”) with average inhibitory conductance \(\mu_{in}\) was 2.4 nS and the SD \(\sigma_{in}\) = 0.6 nS. FR, 9.7 ± 2.4 spikes/s. Thick line trace: “Low inhibition,” \(\mu_{in} = 1.2 \text{ nS}\) and the SD \(\sigma_{in}\) = 0.3 nS. FR, 11.1 ± 2.5 spikes/s.
The firing rate in FS cells was decreased shown in Fig. 10A, in 1 mM TEA application (b), and in washout conditions (c) for a current step of amplitude 200 pA. Table 5 summarizes spike properties for 10 FS cells in control, 1 mM TEA application, and washout conditions (“Washout”). Other spike shape properties are summarized in Table 5.

Figure 10, Ca and Cb shows, respectively, an example of an excitatory conductance input waveform and the membrane potential trajectory (with curtailed spikes) in response to the input before and during application of 1 mM TEA. Although the conductance input trajectory was exactly the same (Fig. 10Ca), AHPs are reduced during the TEA application. This reduction of AHPs is seen to be associated with a considerable reduction of AHPs during the TEA application. This was due to a reduction in amplitude (i.e., depolarization) of AHPs are reduced during the TEA application. This was due to a reduction in amplitude (i.e., depolarization) of the conductance input waveform and the membrane potential trajectory (with curtailed spikes) in response to the input before and during application of 1 mM TEA. Although the conductance input trajectory was exactly the same (Fig. 10Ca), AHPs are reduced during the TEA application. This reduction of AHPs is seen to be associated with a considerable

### Table 5. Summary of spike properties for 10 FS cells in control, 1 mM TEA application, and washout conditions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>TEA</th>
<th>Washout</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold, mV</td>
<td>−44.00 ± 4.30</td>
<td>−46.80 ± 10.30</td>
<td>−45.00 ± 8.10</td>
<td>—</td>
</tr>
<tr>
<td>Spike amplitude, mV</td>
<td>78.40 ± 10.10</td>
<td>74.40 ± 10.70</td>
<td>77.90 ± 10.90</td>
<td>—</td>
</tr>
<tr>
<td>Afterhyperpolarization, mV</td>
<td>−15.10 ± 2.60</td>
<td>−7.61 ± 3.67</td>
<td>−11.20 ± 4.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First spike width, ms</td>
<td>0.72 ± 0.13</td>
<td>1.36 ± 0.29</td>
<td>0.92 ± 0.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Second spike width, ms</td>
<td>0.86 ± 0.16</td>
<td>1.66 ± 0.45</td>
<td>1.03 ± 0.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum firing rate, Hz</td>
<td>125.00 ± 23.00</td>
<td>83.20 ± 33.80</td>
<td>111.00 ± 32.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Slope of depolarizing phase of first spike, mV/s</td>
<td>292.00 ± 48.00</td>
<td>172.00 ± 42.00</td>
<td>221.00 ± 63.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Slope of hyperpolarizing phase of first spike, mV/s</td>
<td>−136.00 ± 35.00</td>
<td>−79.00 ± 28.30</td>
<td>−111.00 ± 41.00</td>
<td>&lt;0.002</td>
</tr>
</tbody>
</table>

Values are means ± SD. P values are calculated by data from the control and 1 mM TEA application conditions.
change in spike timing, at intermediate levels of the conduc-
tance input signal such as this.

Figure 10, D and E shows the effect of TEA on discharge sta-
tistics. The ISI histograms before (“Control”) and after TEA
(“Washout”) were distributed more widely than those obtained
during TEA application (“TEA”) although the average ISI is
not significantly different: 89.8 ± 35.4 ms in control, 91.9 ±
35.2 ms in washout condition versus 94.5 ± 35.1 ms in TEA
application (P > 0.01). The effects of TEA on the ISI histo-
gram are reflected in a more rightward rising hazard function
than those in the control and washout conditions, as shown in
Fig. 10E.

Figure 10, Fa and Fb shows, respectively, the stimulus
kernels and feedback kernels estimated from firing evoked by
the broadband conductance input (e.g., Fig. 10Ca) before,
during, and after TEA application. The stimulus kernels are not
significantly changed in the three cases, but the peak during 1
mM TEA application is shifted slightly rightward (<1.5 ms).
However, the firing probability of the feedback kernel in TEA
application decreased more than that in the control and wash-
out conditions. The firing probability in TEA remained de-
pressed well below the control case, for some 50 ms, before
returning to the same zero level. In FS cells, this effect implies
that excitability in TEA was lower than that in the control and
washout conditions. As a result, spike history has a larger
influence on the occurrence of the next spike during TEA
application than in the control and washout conditions.

DICUSION

Recent studies have shown that inhibitory interneurons in
the somatosensory cortex have a variety of molecular, electro-
physiological, and morphological characteristics, which could
underlie distinct roles in the cortical networks (Kawaguchi and
Kubota 1997; Markram et al. 2004; Toledo-Rodriguez et al.
2005). In this study, we have examined membrane excitability
properties and input–output functions, to gain insight into the
influence of naturalistic conductance-input signals and prior
activation history on spike generation in three different types of
interneurons: NPRS, FS, and LTS cells.

Analysis of neural discharges driven by broadband or white-
noise signals has been widely used to investigate the response
functions of neurons or the features of input that are relevant in
the spike-triggering process (Bryant and Segundo 1976;
Mainen and Sejnowski 1995; Powers et al. 2005; Tateno and
Robinson 2006). In the present study, with the aim of using a
more naturalistic stimulus mimicking in vivo–like synaptic
input, we applied fluctuating excitatory and inhibitory conduc-
tance input rather than current input. We used independent
Ornstein–Uhlenbeck processes to determine excitation and
inhibition, to create a wide and complex range of conductance
trajectories with in vivo–like statistics of excitation and inhibi-
tion, but without introducing specific assumptions about correla-
tions between them, or oscillatory dynamics, in the input.
We are interested how, in general, the intrinsic properties
of individual cells can organize coherent output firing from
complex, stochastic input. It has been shown that during
activity in vivo, synaptic input to cortical neurons may con-
tribute 80% of the total conductance of the membrane and
that injecting stochastic excitatory and inhibitory conductances
reproduces in vivo–like membrane potential distributions (Des-
texhe et al. 2001). The synaptic conductance input itself radi-
cally alters the basic electrical parameters of the membrane,
such as time constant, membrane resistance, and spatial attenu-
ation. In studying synaptic integration and spike generation it
is thus extremely important to stimulate with conductance
patterns rather than current patterns, to force the neuron’s
spike-generation mechanisms into a much more in vivo–like
electrical state. This study goes beyond previous work, first, by
systematically comparing the integrative properties of different
classes of inhibitory interneuron when driven by electrically
realistic fluctuating conductance and by applying a two-com-
ponent autoregressive model previously applied to spiking
generated by current fluctuations to describe conductance-
driven spiking, allowing the contributions of input conductance
and spike discharge history to be separated. The use of con-
ductance injection here, although technically more demanding
than current injection, was crucial because it is impossible to
simulate a controlled increase in shunting inhibitory conduc-
tance using a predetermined pattern of current injection.

Dependence of ASTCT properties on cell type and on
spike history

ASTCTs describe the mean conductance input preceding
spike generation and allow the possibility of studying how
membrane properties shape integration of naturalistic conduc-
tance inputs into action potentials (Harsch and Robinson
2000). Overall, ASTCTs for excitatory, AMPA receptor-like
conductance in these cell-types were characterized by a shal-
low trough followed by a sharp peak just prior to spike onset
(Fig. 2Ca) as we reported previously (Tateno and Robinson
2006). In addition, the results of this study demonstrated that
the time course of the ASTCTs reflects a combination of the
effects of the conductance stimulus input and recent discharge
history on firing probability.

We computed ASTCTs for subsets of interspike intervals of
different durations and found that a deep trough (1–2 nS) was
present only for short preceding ISIs in NPRS and LTS cells,
but for all durations of ISIs in FS cells. A previous study using
fluctuating current stimulation (Powers et al. 2005) found that
a prespike dip in excitatory current was associated only with
longer ISIs, in regularly spiking pyramidal neurons. This
discrepancy could reflect a fundamental difference in the dy-
namics of these cells from NPRS and LTS cells, as well as the
difference between broadband current and conductance injec-
tion. It is also reported that the hyperpolarizing trough in
average current trajectories reflects the removal of sodium
inactivation (Fellous et al. 2003; Gutkin et al. 2003; Mainen
and Sejnowski 1995) and/or calcium-activated potassium cur-
cent underlying the postspike AHP (Powers et al. 2005). For FS
cells as well as LTS cells, in particular, the effects of discharge
history are likely to be largely mediated by the specific types
(Kv3.1–3.2) of voltage-dependent potassium channels under-
lying the postspike AHP. This is less likely to be the case for
NPRS cells because they have shallower AHPs than those in
FS and LTS cells.

The ASTCT calculated from all spikes at a given mean
discharge rate reflects the combination of the conductance
trajectories associated with particular ISIs, weighted by the
probability of occurrence of particular intervals (Agüera y
Arcas and Fairhall 2003; Pillow and Simoncelli 2003). The ISI
distribution itself reflects the influence of the AHP on discharge probability (Matthews 1996; Powers and Binder 2000). Thus the ASTCT and the related first-order Wiener kernel reflect the influence of both stimulus and discharge history on firing probability in interneurons. For this reason, a two-component model is useful for dissecting the contribution of the two influences separately.

**Influence of stimulus and discharge history in the two-component model**

In general, one method for specifying the input–output relationship of a system to predict the response of the system to arbitrary inputs is to determine the system function from the output response, by using appropriate excitation input to the system. A nonparametric or “black box” approach to the system identification problem can be used to determine the system transfer characteristic without specifying the internal structure or mechanisms (Türker and Powers 2005). In particular, white noise or Wiener kernel analysis is a well-known nonparametric approach to such system identification (French and Marmarelis 1995; Marmarelis and Marmarelis 1978; Westwick and Kearney 1998) that has been used in the study of neurophysiological systems such as visual (Marmarelis and Naka 1972; Sakai 1992), auditory (Eggermont 1993), and mechanoreceptor (Dickinson 1990; French and Wong 1977; French et al. 2001; Kondoh et al. 1995) motor systems (Gamble and DiCaprio 2003; Powers et al. 2005). The actual mechanisms are replaced with a linear/nonlinear filter or a series of kernels with exactly the same transfer characteristics as those of the system under study. In addition, it is pointed out that such filters are closely related to the ASTCTs of neurophysiological systems (Powers et al. 2005). However, the input–output relationship taking account for only the input stimulus is not enough to fully describe the system whose internal states depend on the previous states themselves. Therefore using a two-component model previously applied to fluctuating current-driven spiking (Joeken et al. 1997; Powers et al. 2005; Truccolo et al. 2005), we separated the effects of conductance stimulus and discharge history in the spike trains. In this model, the effects of discharge history are mainly represented by a feedback kernel, whereas the effects of stimulus history are principally represented by a stimulus kernel.

The stimulus kernels predicted a brief (<8 ms) and rapid increase in firing probability following brief fluctuations in the conductance stimulus. In the absence of the feedback kernel in the model, the stimulus kernel (or standard first-order Wiener kernel) showed a greater decrease in firing probability after the peak than did the stimulus kernels of the two-component model and thus the Wiener kernel encapsulates both stimulus and discharge history. When shunting inhibition is added, the peak amplitude of the stimulus kernels decreased as the intensity of inhibitory input increased, for all the cell types. In this sense, the effect of the inhibitory input on the stimulus kernels is simply to counteract proportionately the effect of the excitatory input.

In contrast to the stimulus kernels, the properties of feedback kernels depended strongly on the cell type. For excitatory input in NPRS and LTS cells, the feedback kernels predicted a prolonged (≥70-ms) decrease in firing probability following a spike, whereas, for FS cells, the feedback kernels showed a relatively short lasting (<40-ms) negative phase. In all three cell types, higher levels of excitatory input caused a shortening of the negative phase, often followed by a positive overshoot (Figs. 7Ab and 8Ab), the overshoot time depended on the cell type. Moreover, the effect of simultaneous inhibition was different, eradicating the positive overshoot in FS cells (Fig. 8Bb), whereas for NPRS and LTS cells, causing a simple upward shift of the kernel with increasing inhibition (Figs. 7Bb and 9Bb). Diminishing the AHP current in FS cells by adding 1 mM TEA to the bath solution led to a profound decrease in the amplitude of the feedback kernel, but had relatively minor effects on the stimulus kernel, consequently changing the spike timing driven by the same conductance stimuli.

Powers et al. (2005) concluded, on the basis of the deficiency of prediction simply by the first-order Wiener kernel, that the linear prediction of firing probability from fluctuating current input should rather be taken as the sum of the predicted changes based on both stimulus and feedback kernels. They also stated that prediction using the first-order Wiener kernel alone underestimated the increase in firing probability produced by a depolarizing input and overestimated the decrease produced by a hyperpolarizing input. In this study, although we used a more naturalistic conductance input, the situation was quite similar. The two-component model yielded more accurate spike timing than did the stimulus kernel alone or the first-order Wiener kernel. We also tested another model consisting of both first-order and second-order Wiener kernels, without a feedback kernel, to the data. However, the results of this second-order Wiener-kernel model were worse than those of the linear two-component model (data not shown here). This is a further indication that the discharge history is necessary to predict precise spike timing in cortical interneurons.

An inhibition-controlled switch between intrinsically timed and input-timed spike firing in FS cells: functional implications

FS cells have several distinctive electrical features that distinguish them from other neurons and other inhibitory interneurons in particular: the ability to fire rapidly with little fatigue, a deep AHP, and narrow spike—properties that in hippocampal FS cells appear to be conferred by a large density of Kv 3.1/3.2 channels (Lien and Jonas 2004). It is thus reasonable to suppose that these adaptations subserve a particular function in the network. There are several clues that point to a leading role for FS neurons in the generation of gamma oscillations. Gamma oscillations, in the frequency range 30 to 80 Hz, are a prominent form of synchronization in the awake cortex and are widely believed to underlie various neurocognitive functions, including feature binding, selective attention, and consciousness (Kastner and Ungerleider 2000; Singer and Gray 1995; Tiitinen et al. 1993). Gamma rhythms most often occur in bursts lasting 100–200 ms and can be generated locally in the cortical network, even in small pieces of in vitro cortical tissue (Cunningham et al. 2003; Shu et al. 2003). FS neurons have a hard, “type 2” threshold (Tateno et al. 2004) for excitatory conductance input, firing periodically at a gamma frequency at the onset of spiking. Intriguingly, this critical-threshold frequency can be modulated within the gamma range by the level of simultaneous shunting inhibitory input (Tateno et al. 2004). Furthermore, FS neurons are interlinked by a
specific, gap-junctional network that promotes a high degree of synchrony in their spike timing (Galarreta and Hestrin 2002; Gibson et al. 2005). The predominant gamma oscillatory component of synaptic input into the principal pyramidal cells appears to be inhibition arising from the FS cell population (Hasenstaub et al. 2005; Morita et al. 2008). Spike timing of principal cells in awake and active states appears to be strongly determined by the dynamics of inhibitory synaptic conductance (Rudolph et al. 2007). Recent studies show that specific information-rich signals generate relatively high frequency, including gamma range, asynchronous synaptic inputs to cortical neurons that dominate during active brain states, whereas neurons show rather synchronous membrane voltage activity in quiet states (Petersen 2007; Poulet and Petersen 2008). Understanding the neural mechanism of such brain state transitions is crucial for understanding neurocognitive functions.

In this study, we have demonstrated that shunting inhibitory conductance input to FS neurons converts their integrative function from one in which timing of spikes is determined by the recent spiking history, i.e., an intrinsically timed rhythm corresponding to the steep control feedback kernel in Fig. 8Bb, to one in which it is driven directly by conductance input fluctuations (the dramatic flattening of the feedback kernel by inhibition in Fig. 8Bb). In the context of the putative role of FS neurons in organizing gamma rhythms, this inhibition-controlled switch could be responsible for initiation and termination of local gamma bursts. With little or no inhibitory input to FS neurons, their firing organizes into locally synchronous gamma rhythms. With even a small asynchronous inhibitory input, though, the integrative dynamics demonstrated here should cause the firing of individual FS neurons to become more driven by excitatory input fluctuations, dispersing the synchrony, and thereby terminating the gamma burst.

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