Response Sensitivity of Barrel Neuron Subpopulations to Simulated Thalamic Input

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Pesavento MJ, Rittenhouse CD, Pinto DJ. Response sensitivity of barrel neuron sub-populations to simulated thalamic input. J Neurophysiol 103: 3001–3016, 2010. First published April 7, 2010; doi:10.1152/jn.01053.2009. Our goal is to examine the relationship between neuron- and network-level processing in the context of a well-studied cortical function, the processing of thalamic input by whisker-barrel circuits in rodent neocortex. Here we focus on neuron-level processing and investigate the responses of excitatory and inhibitory barrel neurons to simulated thalamic inputs applied using the dynamic clamp method in brain slices. Simulated inputs are modeled after real thalamic inputs recorded in vivo in response to brief whisker deflections. Our results suggest that inhibitory neurons require more input to reach firing threshold, but then fire earlier, with less variability, and respond to a broader range of inputs than do excitatory neurons. Differences in the responses of barrel neuron subtypes depend on their intrinsic membrane properties. Neurons with a low input resistance require more input to reach threshold but then fire earlier than neurons with a higher input resistance, regardless of the neuron’s classification. Our results also suggest that the response properties of excitatory versus inhibitory barrel neurons are consistent with the response sensitivities of the ensemble barrel network. The short response latency of inhibitory neurons may serve to suppress responses to asynchronous thalamic input. Correspondingly, whereas neurons acting as part of the barrel circuit in vivo are highly selective for temporally correlated thalamic input, excitatory barrel neurons acting alone in vitro are less so. These data suggest that network-level processing of thalamic input in barrel cortex depends on neuron-level processing of the same input by excitatory and inhibitory barrel neurons.

INTRODUCTION

Signal processing in cortical systems depends both on the response properties of individual neurons and on network interactions between those neurons. Unraveling the reciprocal relationship between these two levels of integration is a fundamental prerequisite for understanding how cortical circuits work. Our ultimate goal is to examine the relationship between neuron- and network-level processing in the context of a specific and well-studied cortical function, the processing of thalamic input by whisker barrel circuits in layer IV of rodent somatosensory cortex. In this manuscript, we focus on neuron-level processing and investigate the response properties of barrel neuron subpopulations and how they contribute to the ensemble barrel response.

The rodent whisker-barrel system is an ideal model for exploring the relationship between neuron- and network-level processing in that the anatomy, neuronal subtypes, and network function of barrel cortex are all relatively well-understood (see Fox 2008 for review). Anatomically, layer IV of rodent primary somatosensory cortex contains discrete neural circuits, called “barrels,” that are in one-to-one correspondence with the whiskers on the rat’s face (Welker 1971; Woolsey and Van der Loos 1970). Further, most barrel neurons can be classified as regular spiking (RS), fast spiking (FS), or low-threshold spiking (LTS) (Gibson et al. 1999; McCormick et al. 1985) based on their responses to injected current pulses (cf. Fig. 1). Spike width and firing rate adaptation distinguish RS neurons from FS neurons, whereas more subtle firing patterns characterize LTS neurons. A more striking distinction is that a neuron’s firing properties usually correlate with its morphology and role in cortical circuits; most cortical RS neurons are excitatory spiny stellate or pyramidal cells, whereas most cortical FS and LTS neurons are inhibitory interneurons (Gibson et al. 1999; McCormick et al. 1985; Staiger et al. 2004). Functionally, barrel neurons in vivo respond preferentially to rapid stimuli in the form of high-velocity deflections of their principal whisker (Arabzadeh et al. 2003; Ito and Kato 2002; Pinto et al. 1996, 2000, 2003a; Wilent and Contreras 2004). More precisely, cortical barrel responses depend strongly on the temporal profile of spike volleys arriving in cortex from thalamus (Pinto et al. 2000, 2003a) in response to brief whisker deflections; high-velocity whisker deflections evoke strongly correlated volleys of thalamic population activity.

Several previous studies, including our own, have suggested that the sensitivity of barrel responses to thalamic input timing depends on synaptic interactions within the barrel network (Arabzadeh et al. 2005; Pinto et al. 2000, 2003a; Wilent and Contreras 2004). Specifically, recurrent excitation enhances responses to rapid and highly correlated thalamic input (Adorjan et al. 1999; Douglas et al. 1995; Miller et al. 2001) while feedforward inhibition suppresses responses to slower and less correlated input (Cruikshank et al. 2007; Lawrence and McBain 2003; Pouille and Scanziani 2001; Swadlow and Gusev 2002). Additional evidence, however, suggests that processing by single neurons may also play a role in barrel response sensitivity. Indeed correlated input arriving from the thalamus results in a rapid depolarization of the membrane potential of single neurons compared with less correlated input. Decades of study have established that the generation of action potentials in single neurons is sensitive to the rate of membrane depolarization (Azouz and Gray 2000; Hodgkin and Huxley 1952; Noble and Stein 1966; Stafstrom et al. 1984).

Clearly, both neuronal and network level integration contribute to response processing in barrel cortex. Unraveling the
relationship between them requires comparing the responses of neurons when they are acting as part of the barrel network versus when they are acting alone. Previously, we characterized the responses of barrel neurons acting within the barrel network in vivo in response to fast versus slow whisker deflections. We showed that their responses correlate strongly with the temporal profile of spiking input from thalamus (Pinto et al. 2000, 2003a). In the present study, we characterize the responses of barrel neurons acting alone in an in vitro cortical slice. We activate the neurons using simulated thalamic inputs modeled after real thalamic input evoked using the same whisker deflections as our in vivo study.

Our results suggest that inhibitory FS barrel neurons require stronger thalamic input to reach firing threshold but then fire earlier, with less variability, and respond to a broader range of inputs than do excitatory RS barrel neurons. These differences depend on basic differences in the intrinsic membrane properties of FS versus RS barrel neurons, such as input resistance, and they are also consistent with the response sensitivities of the ensemble barrel network. Specifically, the short response latency of inhibitory FS neurons may serve to suppress ensemble barrel responses to uncorrelated thalamic population input signals. Correspondingly, whereas neurons acting as part of the barrel circuit in vivo are highly sensitive to and selective for temporally correlated thalamic input, excitatory barrel neurons acting alone in vitro are less so. Taken together, these data suggest that network-level processing of thalamic input by barrel cortex depends on differences in the neuron-level processing of thalamic input by excitatory and inhibitory barrel neurons.

METHODS

Preparation and electrophysiology

Cortical slices 400 μm thick were obtained using a mechanical vibratome (World Precision Instruments, Sarasota, FL) from Sprague-Dawley rats on postnatal day P13–24 using the near-coronal slicing angle described by Land and Kandler (2002). Slices were maintained in a submerged holding chamber at room temperature for ≥1 h and then transferred to a recording chamber as needed. Slices were bathed in artificial cerebrospinal fluid (ACSF) containing (in mM) 126 Na, 3 KCl, 1.25 NaH2PO4, 2 MgSO4, 26 NaHCO3, 10 dextrose, and 2 CaCl2 and saturated with 95% O2-5% CO2. ACSF concentrations were the same as reported in Beierlein et al. (2003). Borosilicate glass micropipettes were pulled with a Flaming-Brown puller (P97, Sutter Instruments) to a resistance of ~5–10 MΩ and had a tip size of 1–2 μm. Electrodes were filled with an internal solution consisting of (in mM) 135 K-glucuronate, 4 KCL, 2 NaCl, 10 HEPES, 0.2 EGTA, 4 ATP-Mg, 0.3 GTP-Tris, and 7 phosphocreatine-Tris (pH 7.25, 290 mosM). Whole cell patch recordings were made in current clamp mode using an Axon Instruments Multiclamp 700B amplifier, and neurons were visualized with infrared differential interference contrast (IR-DIC) optics using a Nikon E600FN Eclipse microscope and a Hammamatsu XC-77CCD camera and C2400 controller. The amplifier was zeroed to correct for the liquid junction potential as soon as the patch electrode entered the bath and then zeroed again (if needed) just prior to patching onto a cell. Access resistance was 18–30 MΩ. Recordings were obtained at 35°C. All protocols were reviewed and approved by the University of Rochester Committee on Animal Resources (UCAR).

Barrels were clearly visible in the living slice. Only layer IV barrel neurons were examined in this study. Each recorded neuron was photographed (Videum Capture; Winnov, Santa Clara, CA.) to verify its location. We measured the initial resting potential immediately after patching onto each cell and the dialyzed resting potential after the recording had stabilized for ~5 min. A small constant holding current (<100 pA) was applied to bring the neuron’s dialyzed resting potential to ~65 mV to facilitate comparisons between cells. Experiments were terminated if >100 pA of current was required to maintain a stable resting potential, threshold potentials were <15 mV above rest, or action potential peaks fell short of 0 mV. We controlled current injection, data collection, and real-time (i.e., dynamic clamp) stimulation using Labview-RT software (National Instruments) written specifically for the task. Our dynamic clamp implementation is similar to that of Kullman et al. (2004). Response waveforms were sampled and digitized at a sample frequency of 10 kHz using an A/D converter (National Instruments).

Stimulus protocol

SQUARE CURRENT PULSES. We injected square current pulses into each neuron to classify the neuron and to quantify several standard response measures. Pulses lasted 500 ms, ranged in amplitude between ±0.4 nA in 0.1 nA increments and were presented at a rate of 0.5 Hz. We quantified several intrinsic membrane properties (Fig. 1B) including 1) stabilized resting potential, measured ~5 min after a stable patch was obtained, 2) input resistance, measured as the slope of the current-voltage relationship using negative injected current values, 3) time constant, measured as the time required for the voltage to return 63% of the distance to rest during the rising phase at the end of a ~0.2 nA current pulse, 4) firing threshold, measured as the voltage level at the inflection point just prior to the first spike, 5) spike width, measured as the duration of the action potential at a voltage level half-way between threshold and the action potential peak, 6) firing rate adaptation, measured as the ratio between the first and last inter-spike interval evoked by a +0.2 nA square pulse lasting 500 ms; a ratio of one indicates no adaptation; a ratio less than one indicates adaptation, and 7) afterhyperpolarization (AHP) shift, measured as the difference in voltage between threshold and the trough of

FIG. 1. Barrel neuron subtypes and measures of membrane properties. A: voltage traces from typical regular spiking (RS), fast spiking (FS), and low-threshold spiking (LTS) barrel neurons recorded in response to a 0.2 nA square pulse current. B: our measures for several standard membrane properties including 1) baseline, 2) input resistance, 3) membrane time constant, 4) firing threshold, 5) spike half-width, 6) firing rate adaptation, and 7) AHP shift (see text for details).
Cells were classified as RS, FS, or LTS according to previously established criteria (Gibson et al. 1999) (Fig. 1A). Briefly, FS neurons were distinguished from RS neurons by their narrow action potentials (∼0.5 ms width) and little or no firing rate adaptation. LTS neurons were distinguished by a positive shift in the AHP with ongoing activity and weak firing rate adaptation.

SIMULATED SYNAPTIC INPUT VOLLEYS. We used the dynamic clamp to generate conductance waveforms that simulate thalamic synaptic input volleys evoked by fast, medium, and slow whisker deflections. The dynamic clamp is a technique by which a neuron’s membrane potential is measured in real time and used to determine a current to be injected back into the same neuron. By changing the injected current in a voltage-dependent manner, one can effectively simulate the effects of voltage-dependent conductances in individual neurons (Sharp et al. 1993). Here we use the technique to mimic changes in synaptic conductance evoked by the arrival of thalamic input spikes based on previously reported synaptic measures (Beierlein et al. 2003). Simulating changes in synaptic conductance rather than injecting fixed synaptic currents captures some of the effects of sublinear summation due to dendritic integration (Suter and Jaeger 2004).

We simulated thalamic input spike times by modeling real thalamic spike time distributions evoked by fast, medium, and slow whisker deflections as reported previously (Pinto et al. 2000). Simulated spike times were constructed using a family of logistic functions known as Fisk distributions (Fisk 1961). Commonly used for data fitting analyses, Fisk functions are a convenient family of skewed distributions that provide a good approximation of real thalamic input distributions as reported previously (Pinto et al. 2000). Importantly, Fisk distributions can be varied parametrically, allowing us to examine systematically the effect on cortical responses of the temporal distribution of thalamic input. The Fisk probability density function (PDF) is

\[
f(t, B, C) = \frac{C}{B} \left( \frac{t/2}{B} \right)^{C-1} \left[ 1 + \left( \frac{t/2}{B} \right)^C \right]^{-1} - 1
\]

and the corresponding cumulative distribution function (CDF) is

\[
F(t; B, C) = \frac{1}{1 + \left( \frac{t/2}{B} \right)^C}
\]

where \(B\) and \(C\) are shape parameters. The distribution functions and their corresponding cumulative functions for the fast \([F; (B, C) = (1, 2)]\), medium \([M; (B, C) = (2.5, 3)]\), and slow \([S; (B, C) = (4, 3)]\) input volleys used here are shown in Fig. 2A.

**Fig. 2.** Simulating whisker-evoked volleys of thalamic input in vitro. A: skewed probability distribution functions (PDF) used to construct simulated volleys of fast (F), medium (M), and slow (S) thalamic input. Distributions were quantified as the time required to generate 50% of the input as indicated on the corresponding cumulative distribution functions (CDF) shown in the lower subpanel. B, top: the same probability functions laid over an example input histogram containing 18 spikes with times drawn from the fast distribution. Inset: voltage data from an RS neuron in response to current induced by the simulated arrival of a single spike. B, bottom: overlaid voltage data from an RS neuron, generated across 25 trials, in response to the current induced by the 18 spikes shown in top but with times drawn from the fast, medium, and slow distributions, respectively. The dashed line aligns the start times of the input and response data. C: population histograms of real and simulated thalamic responses to fast, medium, and slow whisker deflections. The top subpanels show histograms gathered from the responses of 63 thalamic neurons to caudal whisker deflections at three different velocities (210, 145, and 80 mm/s). Each stimulus was repeated 10 times for a total of 630 responses per histogram. The bottom subpanels show histograms gathered from 600 spike times drawn randomly from three different skewed distributions (fast, medium, and slow; see text). Top panel adapted from Pinto et al. (2000).
To generate an input volley, a fixed number of spike times were drawn randomly from a given Fisk distribution. Each spike time represents the arrival of a thalamic spike in cortex. The shape of the resulting distribution is determined by the cumulative distribution function (Fig. 2A, bottom). That is, 50% of the spikes in the fast, medium, and slow input volley arrive (on average) within the first 2, 5, and 8 ms after the onset of thalamic input, respectively. These correspond to the timing of real thalamic responses as previously reported (Pinto et al. 2000). Figure 2B, top, presents an example histogram of 18 spike times drawn from the fast distribution. Shape parameters were chosen so that the simulated spike distributions closely approximate real distributions obtained previously from thalamic recordings in vivo. Figure 2C compares our simulated thalamic input volleys with actual thalamic spiking responses to fast, medium, and slow whisker deflections.

Each spike in a volley elicits a simulated synaptic conductance, \( \alpha(t) \). The resulting injected current is calculated as the sum of these conductances multiplied by the driving force of the synapse

\[
I_{\text{syn}}(t) = \sum \alpha(t - t_i)(E_{\text{syn}} - V(t))
\]

\[
\alpha(t) = \begin{cases} 
0 & t < 0 \\
\gamma(e^{-r_2t} - e^{-r_1t}) & t \geq 0
\end{cases}
\]

where \( I_{\text{syn}}(t) \) is the injected current, \( t_i \) is the arrival times of the \( n \) individual spikes, \( E_{\text{syn}} = 0 \text{ mV} \) is the reversal potential of an excitatory thalamocortical synapse, \( V(t) \) is the neuron’s membrane potential updated in real-time using the dynamic clamp, \( \gamma \) is the maximal synaptic conductance discussed in the following text, and \( r_1 = 0.0935 \text{ ms}, r_2 = 1.4286 \text{ ms} \) are related to the rise and fall times of a unitary excitatory postsynaptic potential (EPSP), respectively (Ermentrout 1998; Hausser and Roth 1997; Kleppe and Robinson 1999).

Values for \( r_1, r_2, \gamma \) were chosen to provide a good fit to experimental data examining unitary thalamocortical EPSPs onto barrel neurons (Beierlein et al. 2003). Importantly, Beierlein et al.’s recordings were made at or near the soma after thalamocortical EPSPs had been shaped by dendritic spatial integration and/or active dendritic processing. Thus our simulations partially capture the effects of dendritic processing on unitary responses.

The maximal synaptic conductance, \( \gamma \), was adjusted at the start of recording for each neuron so that a single input spike evoked a unitary EPSP having a magnitude of 2 mV measured from rest. Experimentally, unitary thalamic EPSPs evoked onto FS cells are generally larger than those evoked onto RS cells (Beierlein et al. 2003; Bruno and Simons 2002; Cruikshank 2007), and the synaptic kinetics are somewhat faster (Cruikshank et al. 2007). However, to facilitate direct comparisons between cell types, we set the kinetics and magnitude of simulated EPSPs to be the same for all neurons. The value of 2 mV was chosen because it is in the upper range of observed values for unitary thalamocortical EPSPs onto RS cells and in the lower range for EPSPs onto FS cells (Beierlein et al. 2003). LTS cells do not typically receive direct thalamic input (Gibson et al. 1999). The inset in the upper subpanel of Fig. 2B presents an example voltage trace obtained from an RS neuron generated in response to the current “evoked” by a single input spike.

We assessed the responses of each neuron to input volleys across three distributions [fast (F), medium (M), and slow (S)], each having five different magnitudes, for a total of 15 volleys. Input timing was quantified as the time required to generate 50% of the total spike count, i.e., 2, 5, and 8 ms for fast, medium, and slow volleys, respectively. Input magnitude was quantified as the number of spikes in the input volley. Spike counts were varied in increments of three spikes and were centered on a value that evoked a single output spike on ~50% of all trials using the medium distribution (~20 spikes). This is consistent with experimental data suggesting that barrel neurons fire sparsely in response to whisker deflections (Brecht and Sakmann 2002). Incrementing the count by three spikes roughly corresponds to a 15% change in thalamic input magnitude that we observed in vivo using whisker deflections of different magnitudes (Pinto et al. 2000). Each input volley was presented 25 times at a rate of 2 Hz with both the distribution timing and spike count randomized between trials. A new set of specific spike times were drawn randomly from the distributions each time a stimulus was presented.

The three lower subpanels in Fig. 2B show overlaid voltage traces from an RS neuron, generated from 25 trials, in response to the summed current elicited by an input volley containing 18 spikes with spike times drawn randomly from the fast, medium, and slow distributions, respectively. The same neuron was tested using volleys containing 12, 15, 18, 21, and 24 input spikes (data not shown).

To facilitate comparisons with previous in vivo studies, we also quantified simulated input volleys in terms of temporal contrast (TC) (Pinto et al. 2000, 2003a). Temporal contrast quantifies the initial rate of change of a population histogram measured over different time windows. TC\text{50}, for instance, is defined as 50% of the total number of spikes in the histogram divided by the time required to generate 50% of the total spike count. For instance, an input volley containing 18 spikes with times drawn from the medium distribution has a TC\text{50} = 1.8 spike/ms (9 spike/5 ms). Values for TC\text{10–90} are defined similarly. TC measures can be understood visually as the slopes of the nonnormalized cumulative response histogram measured at different percentage points along the y-axis (cf. Fig. 2A) (see Pinto et al. 2000 for additional details).

Response measures

We measured each neuron’s response to the input volleys by quantifying its response threshold, latency, and variability. Response threshold was defined as the minimum number of input spikes required to evoke an output spike within 50 ms of stimulus onset on 50% of the trials. Response latency was defined as the time to first spike after stimulus onset, measured as the first zero crossing of the membrane potential during the Upstroke of the first action potential. Response variability was defined as the SD of latency measured over 25 trials using the same input volley parameters. We also quantified population responses by collecting the responses of RS, FS, and LTS cells into separate population histograms and measuring the average number of spikes per stimulus per neuron.

We quantified the sensitivity of each response measure (threshold, latency, variability) to each input parameter (timing, magnitude) using multivariate linear regression analysis on a cell by cell basis (Origin Lab 7.5). The sensitivity of response threshold to input timing is quantified as the slope of the regression line relating the two (cf. Fig. 3A, left). The sensitivity of response latency to input timing is quantified as the slope of the regression plane measured along the input timing axis (cf. Fig. 3A, middle). The sensitivity of latency to input magnitude is quantified as the slope of the same plane but measured along the input magnitude axis. The sensitivity of response variability to input timing and magnitude is measured in the same way (cf. Fig. 3A, right).

Conductance clamp experiments

For some cells, we used the dynamic clamp to add or subtract the effects of specific membrane conductances. This allowed us to probe the causal relationship between intrinsic membrane properties and response measures. We altered the input resistance of neurons by simulating a passive leak conductance

\[
I_{\text{leak}}(t) = g_{\text{leak}}[E_{\text{leak}} - V(t)]
\]

where \( g_{\text{leak}} \) is the maximum leak conductance (in nS), \( E_{\text{leak}} = -67 \text{ mV} \) is the leak reversal potential, and \( V(t) \) is the neuron’s membrane potential updated in real time using the dynamic clamp.
We altered the firing rate adaptation of neurons by simulating a slow potassium (K) conductance $I_{\text{ahp}}(t) = g_{\text{ahp}} w(V) - w$ where $g_{\text{ahp}}$ is the maximum AHP conductance, $w$ is a dynamic gating variable, described in the next section, $E_{K} = -90 \text{ mV}$ is the potassium reversal potential, and $V(t)$ is the neuron’s membrane potential updated in real time using the dynamic clamp. The dynamic gating variable, $w$, incorporates a voltage dependent time constant $\tau_w(V)$ and steady state level $w_\infty(V)$. The dynamic equations for the slow K conductance are derived from previously published equations characterizing firing rate adaptation in cortical neurons (Kopell et al. 2000).

**Simulations**

Computer simulations were used to further explore the relationship between intrinsic membrane properties and response measures in individual neurons. We modeled an RS and an FS neuron using current-balance equations that describe membrane voltage...
where $C_m$ is the specific membrane capacitance, $V_m$ is the membrane potential for an RS or FS neuron, $I_{ion}$ are ionic currents detailed in the appendix, $I_{app}$ is the applied current such as a square pulse, and $I_{syn}$ is the simulated synaptic input from thalamus as described in the preceding text. For each ionic current, $g_{ion}$ is the maximal conductance, $a$ and $b$ are the proportion of channels that are activated and deinactivated, respectively, $p$ and $q$ are integers, and $E_{ion}$ is the reversal potential for the given ion. Currents in the model RS neuron included fast sodium (Na) and potassium currents ($K_a$), an afterhyperpolarization current (AHP), and a passive leak current (leak). Currents in the model FS neuron included fast sodium (Na) and potassium currents ($K_a$), a slowly inactivating potassium current ($D$), and a passive leak current (leak). We varied the values of each maximal conductance $g_{ion}$ so that the intrinsic properties of the model neurons match those of real barrel neurons measured using square current pulses, as reported previously by Beierlein et al. (2003) and in accord with our own data (Table 1).

The kinetic equations, parameter values, and implementation specifics for both the RS and FS model neurons are provided in the appendix. All simulations were conducted using Matlab 8.2 (Mathworks) and incorporated C” code written specifically for the task. The dynamic clamp was implemented with LabView-RT (National Instruments).

**RESULTS**

**Responses of barrel neuron subpopulations to simulated thalamic input**

We measured and compared the spiking activity of 65 RS, 17 FS, and 8 LTS neurons in response to 15 simulated thalamic spike input volleys varied in timing (temporal distribution) and magnitude (spike count). The results are presented in Fig. 3. In general, most response measures were sensitive to both input timing and input magnitude for all neuron subtypes. However, several interesting differences between neuronal subpopulations were also apparent.

The first column of Fig. 3 presents data examining response latency defined as the time to the first output spike following the onset of the input volley. The response latency of all three subpopulations was sensitive to changes in both input timing and input magnitude (Fig. 3A, middle). FS neurons responded significantly earlier than RS or LTS neurons to input volleys that were at threshold (T) or larger (Fig. 3B, middle, top; $P < 0.001$ for both). Moreover, the response latency of FS neurons was less sensitive to input timing than RS neurons (Fig. 3B, middle, middle panel; $P < 0.001$), and was less sensitive to input magnitude than either RS or LTS neurons (Fig. 3B, middle, bottom; $P < 0.001$ for both). Mean latency was measured across all input volleys at or above threshold.

In summary, most response measures for all neurons were sensitive to both input timing and input magnitude. Inhibitory (FS) neurons require more input to reach threshold than excitatory (RS) neurons but then respond earlier, with less variability, and are less sensitive to changes in input parameters, i.e., they respond to a broader range of inputs.

**Correlation between response sensitivity and intrinsic membrane properties**

We explored which intrinsic membrane properties might best account for the different response properties of barrel neuron subtypes, independent of their subjective classification (i.e., RS, FS, or LTS). Table 1 quantifies the seven intrinsic membrane properties we examined in detail (cf. Fig. 1). Values are consistent with previous studies by others using whole cell patch recordings in slices from barrel cortex (e.g., Beierlein et al. 2003).

We examined correlations between each membrane property and each response measure independent of neuron subtype. Our results are presented in Fig. 4. Figure 4A presents representative correlation data showing scatter plots relating two membrane properties (input resistance and firing rate adaptation) and three response measures (mean threshold, latency, and variability). Mean values were measured across all input volleys presented to each neuron.

Recall that $R^2$ values in correlation analyses are interpreted as coefficients of determination (Zar 1999); they describe the percentage of variance in the dependent measure (y axis) that is due to the independent measure (x axis) and vice versa. In particular, $R^2$ values are cumulative. For instance, examining Fig. 4A, mid-

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**Table 1. Intrinsic membrane properties of barrel neuron subtypes**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RS (N = 65)</th>
<th>FS (N = 17)</th>
<th>LTS (N = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, mV</td>
<td>$-67.5 \pm 0.3$</td>
<td>$-65.6 \pm 0.6^*$</td>
<td>$-65.5 \pm 0.5$</td>
</tr>
<tr>
<td>Input resistance, $\Omega$</td>
<td>$153.7 \pm 7.0$</td>
<td>$95.3 \pm 8.3^*$</td>
<td>$154.7 \pm 23.1^*$</td>
</tr>
<tr>
<td>Time Constant, ms</td>
<td>$19.0 \pm 0.7$</td>
<td>$10.0 \pm 0.5^*$</td>
<td>$13.1 \pm 1.1^**$</td>
</tr>
<tr>
<td>Threshold, mV</td>
<td>$-45.6 \pm 0.5$</td>
<td>$-42.6 \pm 1.3^*$</td>
<td>$-45.5 \pm 1.2$</td>
</tr>
<tr>
<td>Spike width, ms</td>
<td>$1.11 \pm 0.03$</td>
<td>$0.52 \pm 0.03^*$</td>
<td>$0.84 \pm 0.08^**$</td>
</tr>
<tr>
<td>Adaptation</td>
<td>$0.73 \pm 0.01$</td>
<td>$0.11 \pm 0.04^*$</td>
<td>$0.60 \pm 0.07^*$</td>
</tr>
<tr>
<td>AHP, mV</td>
<td>$-3.1 \pm 0.5$</td>
<td>$3.6 \pm 0.4^*$</td>
<td>$4.3 \pm 1.0^*$</td>
</tr>
</tbody>
</table>

Values shown are means ± SE. Asterisks (*) indicate values significantly different from regular spiking (RS) cells ($P < 0.01$). Pluses (+) indicate values significantly different from fast-spiking (FS) cells ($P < 0.01$). Baseline voltage is measured after applying a holding current. LTS, low-threshold spiking.
dle, we note that input resistance and firing rate adaptation together account for 43% of the variance in mean latency.

Figure 4B presents \( R^2 \) values obtained by correlating each response measure with each membrane property. Values are presented in the form of a cumulative bar graph. Importantly, it should be noted that the correlations likely include interactions between many of the response measures and/or intrinsic properties, for instance the membrane time constant depends on the membrane input resistance. This might account for the result that cumulative values exceed 100% in some cases. Moreover, it is likely that factors other than the properties we measured also contribute to the variance (e.g., membrane noise). This might explain the fact that the variance cannot be 100% accounted for in most cases.

Our data suggest that much of the variance in the response measures can be explained by four membrane properties—input resistance, time constant, firing rate adaptation, and spike width. Interestingly, the same membrane properties also distinguish the different barrel neuron subtypes. FS cells, for instance, have a lower input resistance and are nonadapting compared with RS neurons (Table 1). Correspondingly, FS neurons require more input to reach threshold but respond earlier and with less variability than RS cells (cf. Fig. 3).

Of these four membrane properties, the correlation of our response measures with spike width is likely to be coincidental rather than causal due to the transient nature of the simulated thalamic input. That is, spike width is governed by currents that...
are mostly active after the neuron has spiked and so their contributions to firing time are likely to occur too late to influence our response measures. The relationships between response measures and the other three membrane properties (input resistance, time constant, and firing rate adaptation) are investigated in the next section.

Response properties of simulated barrel neurons

We hypothesized that differences in the response properties of excitatory (RS) versus inhibitory (FS) barrel neurons to simulated thalamic input can be understood in terms of their basic intrinsic membrane properties. To explore this, we examined the responses of model RS and FS neurons to the same simulated thalamic inputs. As described in METHODS, our model barrel neurons were designed to match the membrane properties of real barrel neurons recorded in vitro and measured using square pulses of injected current (cf. Fig. 1). Figure 5A presents voltage trace data from real and simulated RS and FS neurons generated in response to a square current pulse of 0.2 nA.

Model parameters were established and fixed such that our simulated neurons both quantitatively matched the membrane properties as recorded in real barrel neurons (Table 2) and qualitatively resembled experimental response characteristics that were not quantified (e.g., spike shape; see appendix for details). Using the same parameter values, we then examined the responses of our model neurons to the same volleys of simulated thalamic input as in Fig. 3. Our results are presented in Fig. 5B. We found that differences in the response properties of simulated FS versus RS neurons match those of real FS versus RS neurons. Specifically, FS neurons require more input to reach threshold than RS neurons but then responded earlier, with less variability, and are less sensitive to changes in input

![Response properties of simulated barrel neurons](http://jneurophysiology.org/)

**FIG. 5.** Response properties of conductance-based models of RS and FS barrel neurons. **A**: presents voltage trace data of real and simulated RS and FS barrel neurons in response to a 0.2 nA square pulse of applied current. **B**: bar graphs comparing the responses of real (■) and simulated (○) neurons, both RS (□) and FS (▲), to simulated thalamic input volleys varied in timing and magnitude. Data are presented as in Fig. 3B.
parameters. These results support the hypothesis that the differences in the response properties of barrel neuron subpopulations can be understood in terms of their basic intrinsic membrane properties.

Causal versus coincidental effects on simulated response measures

Based on correlation data alone, it cannot be determined whether the relationship between membrane properties and response measures is causal versus coincidental. To address this question, we varied the membrane properties of our model neurons and examined the effect on simulated response measures.

Figure 6 (left and right) examines the effects of input resistance and firing rate adaptation on simulated response measures, respectively. The effects of the membrane time constant are similar to input resistance (data not shown). We varied the model neuron’s input resistance by changing the leak conductance ($g_{\text{leak}}$) and we varied firing rate adaptation by changing the slow AHP conductance ($g_{\text{AHP}}$). Figure 6A quantifies the relationship between $g_{\text{leak}}$ and input resistance; a higher conductance yields a lower input resistance as expected. Figure 6B quantifies the relationship between $g_{\text{AHP}}$ and firing rate adaptation; a higher conductance yields more adaptation.

We then assessed the model neuron’s responses to simulated thalamic spike input volleys as described in the preceding text. Figure 6, C and E quantify the effects of input resistance on two response measures, mean latency and mean threshold. Our results suggest that changing the input resistance has two effects. First, neurons with a high-input resistance have longer response latency than neurons with a low input resistance (Fig. 6C). Second, neurons with a high-input resistance have a lower input threshold than neurons with a low input resistance (Fig. 6E).

Figure 6, D and F, quantifies the effect of firing rate adaptation on the same two response measures, mean latency and mean threshold. In contrast to input resistance, our simulations suggest that changes in firing rate adaptation have little effect on response properties; firing rate adaptation has a negligible effect on either response latency (Fig. 6D) or on input threshold (Fig. 6F).

### TABLE 2. Intrinsic membrane properties of conductance-based model neurons and barrel neurons in vitro

<table>
<thead>
<tr>
<th></th>
<th>Model RS</th>
<th>In vitro RS</th>
<th>Model FS</th>
<th>In vitro FS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, mV</td>
<td>−67.4</td>
<td>−67.5</td>
<td>−69.96</td>
<td>−65.6</td>
</tr>
<tr>
<td>Input Resistance, MΩ</td>
<td>143.15</td>
<td>153.7</td>
<td>88.2</td>
<td>95.3</td>
</tr>
<tr>
<td>Time Constant, ms</td>
<td>17.29</td>
<td>19.0</td>
<td>4.01</td>
<td>10.0</td>
</tr>
<tr>
<td>Threshold, mV</td>
<td>−44.6</td>
<td>−45.6</td>
<td>−38.19</td>
<td>−42.6</td>
</tr>
<tr>
<td>Spike Width, ms</td>
<td>0.88</td>
<td>1.11</td>
<td>0.37</td>
<td>0.52</td>
</tr>
<tr>
<td>Adaptation</td>
<td>0.755</td>
<td>0.73</td>
<td>−0.008</td>
<td>0.11</td>
</tr>
<tr>
<td>AHP, mV</td>
<td>−1.45</td>
<td>−3.1</td>
<td>3.3</td>
<td>3.6</td>
</tr>
</tbody>
</table>

---

**FIG. 6.** Effect of membrane properties on response measures of conductance-based model neurons. A and B: scatter plots quantifying how changes in the maximal leak conductance ($g_{\text{leak}}$) or AHP conductance ($g_{\text{AHP}}$) effect the input resistance and firing rate adaptation, respectively, in a model RS neuron. C and D: scatter plots quantifying how those same changes effect the latency of responses to simulated thalamic input. E and F: present scatter plots quantifying their effects on response threshold.
Causal versus coincidental effects on real response measures

Our simulation results suggest that the effect of input resistance on response measures is causal while the effect of firing rate adaptation is coincidental. We tested these model predictions experimentally by inserting virtual conductances into real barrel neurons using the dynamic clamp. To vary input resistance, we added or subtracted a virtual leak conductance ($g_{\text{leak}}$). To vary firing rate adaptation, we added or subtracted a virtual slow AHP conductance ($g_{\text{AHP}}$). The results are presented in Fig. 7.

Figure 7A presents example voltage trace data from an RS neuron in response to a hyperpolarizing square current pulse both with (gray trace) and without (black trace) the addition of a virtual leak conductance of 5 nS; adding the leak conductance decreases the neuron’s input resistance as expected. Figure 7B presents similar data using a virtual AHP conductance of 5 nS; subtracting the AHP conductance decreases the level of firing rate adaptation.

Figure 7, C and D, presents summary data from 20 and 19 RS neurons, respectively. Lines connect data obtained from the same neuron but with different levels of applied conductance. Data were analyzed using linear regression analysis and the significance of slopes examined using a Student’s $t$-test. Changes in the virtual leak conductance result in a significant and consistent change in input resistance (Fig. 7C) (slope = $-4.15, P < 0.001$). Similarly, changes in the virtual AHP conductance result in a significant and consistent change in firing rate adaptation (Fig. 7D; slope = 0.0068, $P < 0.001$). These data confirm that the addition or subtraction of the virtual conductances alter the neuron’s membrane properties as expected.

While applying the virtual conductances, we then measured the neuron’s responses to simulated thalamic spike input volleys as before. Figure 7, E and F, for instance, shows the effect of the virtual conductances on mean response latency. Increasing the virtual leak conductance results in faster response times (Fig. 7E; slope = 0.038, $P < 0.001$), consistent with the correlation data presented in Fig. 4A and with the simulation data presented in Fig. 6C. By contrast, changing the virtual AHP conductance has no consistent effect on response latency (Fig. 5F; $P = 0.11$), consistent with the simulation data presented in Fig. 6F. Similar results were obtained for all of the response measures (data not shown).

Taken together, both simulated and real data suggest that the correlation of response measures with input resistance is causal, whereas the correlation of response measures with firing rate adaptation is coincidental. The coincidental effect of firing rate adaptation on response measures will be explored in depth in a separate manuscript. Briefly, our analysis suggests that standard measures for adaptation are in fact not independent of other membrane properties, including input resistance.
Comparing response measures in vitro versus in vivo

Finally, we compare the responses of excitatory RS neurons acting alone in vitro to the responses of excitatory RSU neurons acting as part of the barrel network in vivo. Figure 8A presents population histograms gathered from 65 RS neurons recorded in vitro generated in response to simulated thalamic volleys having three different distributions (fast, medium, and slow) and three different spike counts (strong, moderate, weak). Moderate histograms were compiled from responses with inputs just at response threshold (T). Weak and strong histograms are compiled from responses having T–3 and T+3 input spikes, respectively. Figure 8B presents analogous population histograms gathered from 40 RSUs recorded in vivo generated in response to whisker deflections having three different velocities and three different amplitudes as reported previously (Pinto et al. 2000). Importantly, the simulated thalamic inputs used to generate the in vitro responses shown in Fig. 8A were modeled after real thalamic response data recorded in vivo using the same whisker deflections that evoked the responses shown in Fig. 8B.

Examining the in vivo data (Fig. 8B), there is a clear increase in population response magnitude for faster inputs. Changes in input magnitude, however, have little effect on population response magnitude. Examining the in vitro data (Fig. 8A), population response magnitude is seen to depend more on input magnitude than on input timing.

The in vitro and in vivo population response histograms are quantified in Fig. 8, C–F. As detailed in METHODS, population responses were quantified as spikes per stimulus per neuron.

Input timing was quantified as the time required to generate 50% of the thalamic input (2, 5, and 8 ms for fast, medium, and slow inputs, respectively). Changes in input magnitude were quantified as the percent change of input spike count (i.e., a 15% increase from weak to moderate to strong; see METHODS).

Figure 8, C and D, presents plots of the population response as a function of input timing for in vitro and in vivo responses, respectively; lines connect responses evoked using the same input magnitude. Consistent with the histograms, the scatter plots suggest that in vitro responses are more sensitive to input magnitude than to input timing (Fig. 8C), whereas in vivo responses are almost exclusively sensitive to input timing (D).

Figure 8, E and F, presents bar graphs quantifying the sensitivity of the two populations to thalamic input timing (E) and thalamic input magnitude (F). Sensitivity to input timing was quantified as the change in population response (spikes per stimulus per neuron) divided by the change in input timing (time to 50%). Sensitivity to input magnitude was quantified as the change in population response divided by the percent change in input magnitude. Again, the data suggest that in vitro responses are more sensitive to input magnitude while in vivo responses are more sensitive to input timing.

Taken together, these data suggest that the population responses of RS neurons recorded in vitro have fewer spikes per stimulus, are less sensitive to input timing, and are more sensitive to input magnitude than RSUs recorded in vivo using similar thalamic input volleys.

We also quantified and compared the population response data in terms of the TC of real or simulated thalamic input.
Previous studies have shown the temporal contrast of thalamic input is a strong predictor of barrel population responses (see METHODS) (see also Pinto et al. 2003). The results are presented in Fig. 9.

Figure 9, A and B, presents scatter plots showing the relationship between thalamic TC at 40% and the population response of RS neurons acting alone in vitro (A) and RSUs acting within the barrel circuit in vivo (B). Data shown in Fig. 9A are gathered from responses in vitro to simulated thalamic volleys having five magnitudes and three distributions. Data shown in Fig. 9B are gathered from responses in vivo to whiskers deflections having three amplitudes, five velocities, and in both the caudal and preferred direction. Note that the TC scale is different for in vitro versus in vivo thalamic inputs. This is because input magnitude in vitro is measured as the total spike count in each simulated input volley, as described in METHODS. Input magnitude in vivo, on the other hand, is measured as the total spikes per neuron per stimulus, as described in Pinto et al. (2000).

In strong contrast to the in vivo response, TC correlates poorly with the population response of RS neurons acting alone in vitro. We also examined the correlation of population responses with TC measures in 10% increments along the thalamic response (Fig. 9C, see METHODS). As reported previously, the best correlation of in vivo RSU responses to thalamic input is obtained using temporal contrast measured at 40% along the total response (Pinto et al. 2000). By contrast, for RS neurons acting alone in vitro, no measure of temporal contrast correlates as well with response measures as does the total input magnitude (mag).

Taken together, these data suggest that the responses of excitatory RS neurons acting alone in vitro are both less sensitive to and less selective for temporally correlated thalamic input than the responses of excitatory RSUs acting as part of the barrel circuit in vivo.

**DISCUSSION**

We examined and compared the responses of barrel neuron subpopulations in vitro to simulated thalamic synaptic inputs applied using the dynamic clamp method. Simulated inputs were modeled after real thalamic inputs recorded in vivo in response to brief whisker deflections as reported previously. Barrel neurons were classified as RS, FS, or LTS based on their responses to injected square current pulses. Our results suggest that FS barrel neurons require stronger thalamic input to reach firing threshold, but then fire earlier, with less variability, and respond to a broader range of inputs compared with RS neurons. Moreover, differences in the response properties of barrel neurons correlate with differences in their basic membrane properties, such as input resistance and firing rate adaptation, independent of the neuron’s subjective classification.

We also used the dynamic clamp to modify the membrane properties of individual barrel neurons. This revealed that the correlation of response properties with input resistance is causal, whereas the correlation with firing rate adaptation is coincidental. Results using conductance based models of barrel neurons suggested that the effect of input resistance on response properties is twofold. First, lowering the input resistance weakens the effect of synaptic inputs. Thus leaky neurons require more input to reach threshold than less-leaky neurons. Second, lowering the input resistance decreases the membrane time constant so that the neuron depolarizes faster. Thus leaky neurons respond earlier to above-threshold stimuli than less-leaky neurons. Interestingly, differences in input resistance alone can account for most of the differences in response properties between FS versus RS barrel neurons.

Finally, we compared the population responses of RS neurons acting alone in vitro to the responses of RSU neurons acting as part of the barrel network in vivo. Simulated thalamic inputs used to evoke barrel neuron responses in vitro were modeled after real thalamic response data recorded using the same whisker deflections used to evoke barrel neuron responses in vivo. Whereas previous studies have shown that barrel responses in vivo are highly sensitive to the temporal pattern of thalamic input spikes, our data suggests that responses of RS neurons acting alone in vitro are both less...
sensitive to and less selective for temporally correlated thalamic input.

Barrel neurons in vitro versus in vivo

Our results require several caveats. First, it is well understood that neurons recorded in vitro are functioning in a vastly different environment than are neurons in vivo. The extent of network interactions in the slice is severely reduced, axonal and dendritic processes may be partially or wholly severed, neurons are bathed in artificial cerebral spinal fluid, and the tissue has endured the trauma of the slicing procedure. Among other effects, these factors contribute to changes in the neurons’ intrinsic properties, including a higher input resistance and lower firing threshold compared with neuron’s recorded in vivo (Destexhe et al. 2001; Feldmeyer et al. 2006; Sarid et al. 2007; Zhu and Connors 1999).

Despite these limitations, however, most intrinsic and synaptic properties recorded in vitro are surprisingly similar to the same properties recorded in vivo. Strong thalamocortical inhibition, for instance, was first described in the slice (Agmon and Connors 1991) before it was confirmed in the whole animal (Swadlow 2003). In both environments, FS neurons have faster spikes, are nonadapting, and have a lower input resistance compared with RS neurons (Table 1; Nowak et al. 2003; Zhu and Connors 1999). Whether the specific differences between RS, FS, and LTS neurons reported here are the same in vitro versus in vivo remains to be determined.

Second, it can be argued that neurons in vitro are not acting alone but rather are still functioning within an intact, albeit reduced, barrel circuit. Indeed several studies have used the slice model to study the dynamics of synaptic interactions both within the cortical barrel circuit and between thalamus and cortex (Agmon and Connors 1991; Beierlein et al. 2003; Petersen and Sakmann 2000). To account for the possibility of network interactions, our initial experiments used kynurenic acid, a glutamate receptor antagonist, and picrotoxin, a GABA receptor antagonist, in the bathing solution to block all synaptic activity in the slice. The results suggested that there was no significant effect. This was not surprising, however, because while many structural aspects of the barrel network survive the slice procedure, network activity is greatly reduced and the level of spontaneous network activity in the slice is much lower than in vivo. More importantly, the simulated thalamic input used here is applied to a single barrel neuron and evokes a single spike that is not likely to result in network-based feedback. By contrast, real thalamic input acts on many barrel neurons simultaneously in which case the resulting network feedback is likely to be substantial.

Third, the neurons in vitro were recorded from slices taken from juvenile rats (P13-24), whereas the in vivo recordings were obtained from adult rats. This suggests that some of the differences in response sensitivity may be due to developmental changes in the cells or circuit of barrel cortex. Indeed Shoykhet and Simons (2008) recently reported that the tuning properties of barrel cortex develop within a similar time frame (P14–P28), consistent with the maturation of excitatory and inhibitory synaptic connections (Blue and Parnavelas 1983; White et al. 1997). On the other hand, the membrane and response properties of individual cortical neurons are fully mature by P14 (Maravall 2004) and change very little in adult (Hickmott 2005) or senescent rats (Burke and Barnes 2006).

Fourth, the simulated thalamic input we use to activate neurons in vitro differs significantly from natural thalamic inputs evoked by whisker deflections. Many of these differences are due to unavoidable effects of the dynamic clamp method. For instance, real thalamic inputs are distributed spatially along the dendrites of barrel neurons. Simulated thalamic inputs, while matched in amplitude and timing to real PSPs, are applied at or near the soma via the patch electrode. This difference may explain our finding that population responses of RS neurons recorded in vitro have fewer spikes per stimulus and are less temporally distributed than the responses of RSUs recorded in vivo. Specifically, rather than depolarizing the soma all at once, dendritic processing would result in thalamic input arriving at the soma in a form that is more temporally distributed, allowing time for a multiple spike response and spreading the output over a longer response window.

Despite these caveats, we feel that our method for simulating thalamic input provides a realistic probe for comparing the responses of neurons when acting alone versus when they are functioning as part of the barrel circuit. Using the dynamic clamp allows us to simulate changes in synaptic conductance rather than directly applying synaptic currents. The relative size and distributions of the simulated input volleys are designed to match those of real thalamic responses recorded in vivo. While some differences between in vivo and in vitro responses may indeed be due to the slicing method, we feel that a better explanation is that neurons in vivo are subject to synaptic interactions with other neurons within the local barrel circuit, whereas neurons in vitro are processing input signals in isolation.

Implications of synaptic scaling

To compare directly the response properties of barrel neuron subtypes, we normalized unitary synaptic conductances so that a single spike evoked a postsynaptic response having the same kinetics and magnitudes for all cell types. It is well known, however, that FS neurons receive stronger synaptic inputs from the thalamus than do RS neurons (Beierlein et al. 2003; Bruno and Simons 2002; Cruikshank et al. 2007). Indeed this finding has been interpreted by others and by us as evidence for strong feedforward inhibition in barrel cortex. Our present results, however, suggest an additional explanation.

FS neurons have higher input thresholds and fire earlier and more reliably than RS neurons (Fig. 3). These results follow from the fact that FS neurons also have a lower input resistance (Table 1; Fig. 5). Stated differently, the cost of firing early and reliably is that the membrane must be leaky and, therefore, that strong thalamic input is required to bring the neuron to threshold. In terms of system design, one might conclude that the tight control of inhibitory response timing warrants the added metabolic expense of both strong synapses and leaky membranes. Moreover, results from recent studies suggest that the kinetics of excitatory synapses onto inhibitory neurons provide additional machinery that contributes to their fast responses (Cruikshank et al. 2007).
Implications for network processing

Our results suggest that RS neurons acting alone in vitro are neither as sensitive to nor as selective for temporally correlated thalamic input as are RSUs acting within the barrel circuit in vivo. We hypothesize that the enhanced sensitivity to timing of neurons acting within the barrel circuit is due to synaptic interactions between barrel neuron subtypes. Our results also suggest that the differences in the response sensitivity of barrel neuron subpopulations can serve to enhance the response sensitivity of the ensemble barrel network. Specifically, we found that inhibitory neurons respond earlier and with less variability than excitatory neurons. When the two populations are synaptically connected, inhibition is likely to selectively suppress responses to slow inputs by inhibiting long latency excitatory responses. Thus the tuning properties of feed-forward inhibition in barrel cortex may depend on the intrinsic membrane properties of individual barrel neurons.

APPENDIX

We created single compartment conductance-based models of RS and FS neurons using current balance equations. The maximum conductances of each model were adjusted so that simulated responses to injected square current pulses matched those of real neurons recorded in vitro (cf. Table 1). Membrane parameters are given in terms of specific conductance and channel density. Simulated thalamic input volleys were applied to each model neuron as described in METHODS.

RS neuron

Equations describing our model RS neuron dynamics are modified from those given by Golomb and Amitai (1997) and Pinto et al. (2003b). Other than maximal conductance values, the only significant changes include a shift in some of the gating kinetics as indicated to raise the firing threshold to more biologically realistic values.

CURRENT BALANCE EQUATION

\[ C_m \frac{dV_m}{dt} = I_{\text{leak}} + I_{\text{Na}}(V, h) + I_{\text{K}}(V, n) + I_{\text{AHP}}(V, w) + I_{\text{app}} + I_{\text{syn}} \]  

The spherical radius of the RS neuron is \( r = 0.0031 \) cm, giving a surface area of \( 1.2076 \cdot 10^{-4} \) cm\(^2\). The membrane capacitance is \( C_m = 120.76 \) pF (1 \( \mu \)F/cm\(^2\)).

LEAK CURRENT, \( I_{\text{leak}} \)

\[ I_{\text{leak}}(V) = g_{\text{leak}}(E_{\text{leak}} - V) \]  

The leak conductance is \( g_{\text{leak}} = 6.883 \) nS (0.057 mS/cm\(^2\)), with a reversal potential of \( E_{\text{leak}} = -67 \) mV.

SODIUM CURRENT, \( I_{\text{Na}} \)

The fast Na\(^+\) current is calculated with a fast activation m-gate and an inactivating h-gate. The m-gate is assumed to be instantaneous.

\[ I_{\text{Na}}(V, h) = g_{\text{Na}} m_a^3(V) h(V) (E_{\text{Na}} - V) \]  

\[ \frac{dh}{dt} = \frac{1}{\tau_h(V)} \]  

\[ m_a(V) = \frac{1}{1 + \exp\left(\frac{V - \theta_m}{\sigma_m}\right)} \]  

\[ h_a(V) = \frac{1}{1 + \exp\left(\frac{V - \theta_h}{\sigma_h}\right)} \]

where \( g_{\text{Na}} = 5.072 \) nS (42 mS/cm\(^2\)), \( E_{\text{Na}} = 55 \) mV, and the kinetic equation parameters are \( \theta_m = -20 \) mV, \( \sigma_m = 9.5 \) mV, \( \theta_h = -40 \) mV, \( \sigma_h = -7 \) mV, \( \theta_{r} = -40.5 \) mV, \( \sigma_{r} = -6 \) mV. \( \theta_m \) was shifted 10 mV to the right along the voltage axis to match the observed in vitro spike threshold.

DELAYED RECTIFIER POTASSIUM CURRENT, \( I_{\text{Kdr}} \)

\[ I_{\text{Kdr}}(V, n) = g_{\text{Kdr}} n^4(E_{\text{K}} - V) \]  

\[ \frac{dn}{dt} = \frac{n_a(V) - n}{\tau_n(V)} \]  

\[ n_a(V) = \frac{1}{1 + \exp\left(\frac{V - \theta_n}{\sigma_n}\right)} \]  

\[ \tau_n(V) = 0.37 + 2.78 \frac{1}{1 + \exp\left(\frac{V - \theta_{r}}{\sigma_{r}}\right)} \]

where \( g_{\text{Kdr}} = 0.266 \) nS (2.2 mS/cm\(^2\)), \( E_{\text{K}} = -90 \) mV, \( \theta_n = -20 \) mV, \( \sigma_n = 9.5 \) mV, \( \theta_{r} = -40.5 \) mV, \( \sigma_{r} = -6 \) mV. \( \theta_n \) is shifted 12 mV to the right along the voltage axis to match the observed in vitro spike threshold.

AHP CURRENT, \( I_{\text{AHP}} \)

The AHP current is a slow K\(^+\) current that is responsible for firing rate adaptation in RS neurons, similar to other slow K\(^+\) currents used in other models (cf. Prescott and Sejnowski 2008). The form of the equation that we use is based on Pinto et al. (2003b) and Kopell et al. (2000)

\[ I_{\text{AHP}}(V, n) = g_{\text{AHP}} w(E_{\text{K}} - V) \]  

\[ \frac{dw}{dt} = \frac{w(V) - w}{\tau_w(V)} \]

\[ w_a(V) = \frac{1}{1 + \exp\left(\frac{V - \theta_w}{\sigma_w}\right)} \]

\[ \tau_w(V) = \frac{800}{3.3 \exp\left(\frac{V - \theta_w}{\sigma_{wr}}\right) + \exp\left(\frac{V - \theta_w}{\sigma_{wr}}\right)} \]

where \( g_{\text{AHP}} = 0.00966 \) nS (0.08 mS/cm\(^2\)), \( E_{\text{K}} = -90 \) mV, \( \theta_w = -25 \) mV, \( \sigma_w = 10 \) mV, \( \sigma_{wr} = 20 \) mV. \( \theta_w \) is shifted 10 mV to the right along the voltage axis to match the observed in vitro spike threshold. The scaling parameter in the numerator of \( \tau_{w}(V) \) has also been changed to give a peak time constant of 22 ms at -37 mV, matching the observed time constant of in vitro RS neurons (data not shown).

FS neuron

Equations describing our FS neuron are based on Golomb et al. (2007); Mancilla et al. (2007) and Erisir et al. (1999). The model contains two K\(^+\) currents: a fast K\(^+\) current based on Kv3.1/2 channels (Erisir et al. 1999), and a slowly inactivating n-current, based on Kv1.1/2/6 channels (Golomb et al. 2007).
CURRENT BALANCE EQUATION

\[
C_m \frac{dV_{FS}}{dt} = I_{kdr}(V) + I_{Na}(V,h) + I_{ka}(V,n) + I_D(V,w) + I_{app} + I_{syn}
\]

(21)

The spherical radius of the FS neuron is \( r = 0.0019 \) cm, giving a surface area of \( 4.5365 \times 10^{-3} \) cm\(^2\). The membrane capacitance is \( C_m = 45.365 \) pF (1 \( \mu F/cm^2\)).

LEAK CURRENT, \( I_{LEAK} \)

\[
I_{LEAK} = g_{leak}(E_{leak} - V)
\]

(22)

The leak conductance is \( g_{leak} = 11.3 \) nS (0.25 mS/cm\(^2\)), with a reversal potential of \( E_{leak} = -67 \) mV.

SODIUM CURRENT, \( I_{Na} \)

The fast Na\(^+\) current is calculated with a fast activation m-gate and an inactivating h-gate. The m-gate is assumed to be instantaneous,

\[
I_{Na}(V,h) = g_{Na} m^3(V) h (E_{Na} - V)
\]

(23)

\[
dh = \frac{h_{d}(V) - h}{\tau_h(V)}
\]

(24)

\[
m_{d}(V) = \frac{1}{1 + \exp(-\frac{V - \theta_m}{\sigma_m})}
\]

(25)

\[
h_{d}(V) = \frac{1}{1 + \exp(-\frac{V - \theta_h}{\sigma_h})}
\]

(26)

\[
\tau_h(V) = 0.5 + 14.0 \frac{1}{1 + \exp(-\frac{V - \theta_h}{\sigma_h})}
\]

where \( g_{Na} = 2268.2 \) nS (50 mS/cm\(^2\)), \( E_{Na} = 55 \) mV, \( \theta_m = -24 \) mV, \( \sigma_m = 11.5 \) mV, \( \theta_h = -58.3 \) mV, \( \sigma_h = -6.7 \) mV, \( \sigma_{hr} = -60 \) mV. Our value of \( \theta_m \) gives simulation results that are in agreement with Golomb et al. (2007) and that closely approximate observed in vitro responses of real FS neurons to simulated thalamic input.

DELAYED RECTIFIER POTASSIUM CURRENT, \( I_{kdr} \)

The delayed rectifier K\(^+\) current \( I_{kdr} \) is based on Kv3.1/2 channels found in FS neurons and is responsible for both their narrow action potential width (Beierlein et al. 2003; Chow et al. 1999) and for their high firing frequency (Erisir et al. 1999; Lien and Jonas 2003). All parameters are identical to those used in Erisir et al. (1999)

\[
I_{kdr}(V,n) = g_{kdr} n^3(E_K - V)
\]

(27)

\[
\frac{dn}{dt} = \frac{n_{d}(V) - n}{\tau_n(V)}
\]

(28)

\[
n_{d}(V) = \frac{1}{1 + \exp(-\frac{V - \theta_n}{\sigma_n})}
\]

(29)

\[
\tau_n(V) = [0.087 + \frac{11.4}{1 + \exp(-\frac{V + 14.6}{8.6})}] \times [0.087 + \frac{11.4}{1 + \exp(-\frac{V - 1.3}{18.7})}]
\]

(30)

where \( g_{kdr} = 6804.7 \) nS (150 mS/cm\(^2\)), \( E_K = -90 \) mV, \( \theta_n = -12.4 \) mV, \( \sigma_n = 6.8 \) mV.

D-TYPE INACTIVATING K\(^+\) CURRENT, \( I_{D} \)

The \( I_{D} \) current is a voltage-dependent K\(^+\) current with fast activation and slow inactivation (Coetzee et al. 1999; Storm 1988; Toledo-Rodriguez et al. 2004), and is dendrotoxin-sensitive. Slowly inactivating Kv1.1 channels have been found in FS cells (Goldberg et al. 2008) and serve to regulate the firing rate of FS neurons in response to near-threshold depolarizations. This channel is distinct from the Kv1.3 channel used by Erisir et al. (1999), which was based on human T-lymphocytes. Parameters were chosen so that our simulated FS neuron responded to square current pulses similar to real FS neurons recorded in vitro

\[
I_D(V,a,b) = g_D a b (E_K - V)
\]

\[
\frac{da}{dt} = \frac{a_{d}(V) - a}{\tau_a}
\]

(31)

\[
\frac{db}{dt} = \frac{b_{d}(V) - b}{\tau_b}
\]

(32)

\[
a_{d}(V) = \frac{1}{1 + \exp(-\frac{V - \theta_a}{\sigma_a})}
\]

(33)

\[
b_{d}(V) = \frac{1}{1 + \exp(-\frac{V - \theta_b}{\sigma_b})}
\]

where \( g_D = 6.085 \) nS (0.15 mS/cm\(^2\)), \( E_K = -90 \) mV, \( \theta_a = -50 \) mV, \( \sigma_a = 20 \) mV, \( \tau_a = 2 \) ms, \( \theta_b = -70 \) mV, \( \sigma_b = 60 \) mV, \( \tau_b = 150 \) ms. The maximum conductance \( g_D \) was selected such that the model FS neuron displays classic type-2 dynamics, as we and others have observed in vitro (Golomb et al. 2007).

Numerical methods

Model equations were solved using a fourth-order Runge-Kutta method with time step \( \Delta t = 0.01 \) ms. For the dynamic clamp, AHP current dynamics were calculated using Euler’s method with a time step of \( \Delta t = 0.1 \) ms.

GRANTS

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DISCLOSURES

No conflicts of interest are declared by the authors.

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