van Rossum, M.C.W., B. J. O'Brien, and R. G. Smith. Effects of noise on the spike timing precision of retinal ganglion cells. J Neurophysiol 89: 2406–2419, 2003. First published January 22, 2003; 10.1152/jn.01106.2002. Information in a spike train is limited by variability in the spike timing. This variability is caused by noise from several sources including synapses and membrane channels; but how deleterious each noise source is and how they affect spike train coding is unknown. Combining physiology and a multicompartment model, we studied the effect of synaptic input noise and voltage-gated channel noise on spike train reliability for a mammalian ganglion cell. For tonic stimuli, the SD of the interspike intervals increased supralinearly with increasing interspike interval. When the cell was driven by current injection, voltage-gated channel noise and background synaptic noise caused fluctuations in the interspike interval of comparable amplitude. Spikes initiated on the dendrites could cause additional spike timing fluctuations. For transient stimuli, synaptic noise was dominant and spontaneous background activity strongly increased fluctuations in spike timing but decreased the latency of the first spike.

We studied quantitatively the contribution of various noise sources to the ganglion cell’s spike variability. A major source of noise is thought to be synaptic input from bipolar cells, which release synaptic vesicles at a rate modulated by their graded (nonspiking) membrane potential. These synaptic inputs are noisy because vesicles are thought to be released in a random, Poisson-like fashion (Barrett and Stevens 1972; Freed 2000b, Stevens 1993). In addition, the amplitude of synaptic current varies from event to event due to stochastic opening of postsynaptic channels. Another possible noise source stems from the voltage-gated ion channels. From patch-clamp studies it is known that ion channels open and close stochastically, leading to a noisy current (Hamill et al. 1981). However, empirical studies of the effect of channel noise on spike train variability are difficult. One might attempt to study the channel noise while selectively blocking spiking, but the magnitude (and to a lesser extent the power spectrum) of the channel noise depends on the voltage. For example, close to spike threshold the noise from voltage-gated channels is much larger than at rest (Schneidman et al. 1998). Therefore in experiments, the effect of this noise source on variability in the spike train is inseparable from spike generation. However, a model’s noise sources can be turned on and off at will, so their effect on variability can be studied directly (Chow and White 1996; Skaguen and Walloe 1979; Steinmetz et al. 2001; Tiesinga et al. 2000). Previous modeling studies on voltage-gated channel noise have been limited to reduced models with one or few compartments, classically modeled at 6°C (Hodgkin and Huxley 1952), Skaguen and Walloe observed that noise tends to smear the steep firing threshold of a Hodgkin-Huxley model and so linearizes the input current versus spike frequency ($F-I$) relation (Skaguen 1980a,b; Skaguen and Walloe 1979). Chow and White studied a single compartment Hodgkin-Huxley model of small membrane patches and found that channel noise induces spontaneous spikes at a rate decreasing exponentially with membrane area (Chow and White 1996; Schneidman et al. 1998). However, for real neurons or more realistic models, the effect of channel noise on spike generation is unknown (but see White et al. 1998).

We studied spike train variability using a multicompartment model of a ganglion cell in cat retina, explicitly including the synaptic and voltage-gated channel noise sources. The model was based on a previous multicompartment model in which release synaptic vesicles at a rate modulated by their graded (nonspiking) membrane potential. These synaptic inputs are noisy because vesicles are thought to be released in a random, Poisson-like fashion (Barrett and Stevens 1972; Freed 2000b, Stevens 1993). In addition, the amplitude of synaptic current varies from event to event due to stochastic opening of postsynaptic channels. Another possible noise source stems from the voltage-gated ion channels. From patch-clamp studies it is known that ion channels open and close stochastically, leading to a noisy current (Hamill et al. 1981). However, empirical studies of the effect of channel noise on spike train variability are difficult. One might attempt to study the channel noise while selectively blocking spiking, but the magnitude (and to a lesser extent the power spectrum) of the channel noise depends on the voltage. For example, close to spike threshold the noise from voltage-gated channels is much larger than at rest (Schneidman et al. 1998). Therefore in experiments, the effect of this noise source on variability in the spike train is inseparable from spike generation. However, a model’s noise sources can be turned on and off at will, so their effect on variability can be studied directly (Chow and White 1996; Skaguen and Walloe 1979; Steinmetz et al. 2001; Tiesinga et al. 2000). Previous modeling studies on voltage-gated channel noise have been limited to reduced models with one or few compartments, classically modeled at 6°C (Hodgkin and Huxley 1952), Skaguen and Walloe observed that noise tends to smear the steep firing threshold of a Hodgkin-Huxley model and so linearizes the input current versus spike frequency ($F-I$) relation (Skaguen 1980a,b; Skaguen and Walloe 1979). Chow and White studied a single compartment Hodgkin-Huxley model of small membrane patches and found that channel noise induces spontaneous spikes at a rate decreasing exponentially with membrane area (Chow and White 1996; Schneidman et al. 1998). However, for real neurons or more realistic models, the effect of channel noise on spike generation is unknown (but see White et al. 1998).

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salamander (Fohlmeister and Miller 1997b; Sheasby and Fohlmeister 1999) and single-compartment model in cat (Benson et al. 2001) but was matched to our own physiological data. With the model thus calibrated, we determined the effect of synaptic and channel noise on spike timing during sustained spiking. When the model cell was driven with current injection, the contributions of background synaptic noise and channel noise were of comparable magnitude. When the cell was driven synaptically, we found that synaptic noise was dominant but channel noise had a surprisingly large contribution. For transient stimuli, we found differential effects of synaptic noise and channel noise on the timing precision. The results compare favorably with known spike train statistics and suggest a mechanistic basis for the limits of coding precision of ganglion cells.

**METHODS**

**Physiology**

The current-clamp data in this study came from female pigmented cats ranging in age from 4 mo to adult (O’Brien et al. 2002). Animals were sedated with a mixture of acepromazine (10 mg/kg im) and atropine (0.06 mg/kg im) and deeply anesthetized with pentobarbital sodium (Nembutal, 20 mg/kg iv). After enucleation, the globe was hemisected behind the ora serrata, the vitreous body was removed, and the remaining eye cup was sectioned into quadrants. In most cases, the retinal pigs were isolated from the remaining layers of the eye and mounted photoreceptor side down on a poly-l-lysine coated (1 mg/ml, 185 K D Sigma) coverslip. In all cases, the coverslip served as the floor of a perfusion chamber (Warner Instruments) through which oxygenated (95% O₂, 5% CO₂) Ames medium was perfused at 3–5 ml/min. The chamber was mounted on the stage of an upright Olympus microscope equipped with a ×40 water-immersion lens (Nikon). The fluorescent vital dye acridine orange was added transiently to the bath to assist in localization of ganglion cell somata.

To obtain whole cell recordings of good quality from retinal ganglion cells, we cleared a path for the pipette through the inner limiting membrane and optic fiber layers of the retina by inserting an unfilled patch pipette through the tissue overlying the ganglion cells, then tearing a small hole through which a recording pipette could be maneuvered (Taylor and Wässe 1995). Recording pipettes (4–7 MΩ) were filled with a solution containing (in mM) 215 K gluconate, 5 NaCl, 4 KCl, 10 EGTA, 10 HEPES, 7 phosphocreatine, and 0.3 GTP-Tris; 266 mosM, pH = 7.3. In some cases, the concentration of the calcium buffer EGTA in the internal solution was lowered to 0 or 0.5 mM to examine its effect on the regularity of the firing behavior. In other cases, apamin or Cd²⁺ was added to the Ames solution to test for the presence of KCa channels. Lucifer yellow (0.2%, dipotassium salt) and biocytin (0.5%) were added to this solution to enable later morphological analysis of cell type. Whole cell current-clamp recordings from retinal ganglion cells were obtained using standard procedures (Hamill et al. 1981). After rupturing the cellular membrane, the pipette series resistance was measured and compensated for with the bridge balance circuit of the amplifier. In all cells recorded, the series resistance was <20 MΩ. The input resistance of the cells was 110 ± 17 (SD) MΩ (n = 4, no synaptic block applied). Physiological data were digitized at 5–10 kHz using the Labview 5.0 hardware and software system (National Instruments) and stored on disk. All experiments were performed at room temperature.

When the recording was complete, the retinal tissue was isolated, mounted onto filter paper (MSI) and fixed for 2–3 h in buffered 4% paraformaldehyde. After fixation, the tissue was processed immuno-}

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**FIG. 1.** Geometry of the beta ganglion cell used in the simulation. The cell was digitized in 2 dimensions from a photograph, and each branch point was assigned a depth to approximate the original 3-dimensional location.

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**EFFECTS OF NOISE**

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cytochemically using previously established protocols (Pu and Berson 1992). Labeled cells were classified morphologically on the basis of many different parameters including: soma size, dendritic field size and structure, laminar stratification, eccentricity, and distance from visual streak (for details, see Berson et al. 1998). Laminar stratification was estimated via through focus analysis by relating the dendritic depths to the outer and inner boundaries of the inner plexiform layer.

**Model of the cell**

The model was based on a cat β ganglion cell from 36° retinal eccentricity that was injected with a tracer, photographed in a light microscope, and digitized (Freed and Nelson 1994) (Fig. 1). The soma diameter was 21 μm, the dendritic arbor diameter was 240 μm, and the membrane surface area of soma and dendrites together was 14 × 10⁷ μm². The model consisted of a soma and 909 traced cable segments, which were spatially discretized into compartments with electrotonic lengths <0.05 λ (Perkel and Mulloney 1978), where λ is the electrotonic decay distance of the passive cable (Rall 1958). For the simulations with voltage-gated channel noise, we found that a time step of 1 μs was necessary, but without channel noise, we chose a time step of 20 μs. The model was constructed using standard numerical integration methods (Cooley and Dodge 1966; Joyner et al. 1978; Hines 1989) with the simulation language Neuron-C (Smith 1992; Smith 2003). Simulations were run at 35°C to compare with in vivo data of Troy and Robson (1992) and at 22°C to compare with our physiological data. The temperature of the model was reflected in several parameters that were varied with temperature according to Q₁₀ values: kinetics of the voltage-gated channels (Q₁₀ = 3), their unitary conductances (Q₁₀ = 1.4), the Ca pump (Q₁₀ = 2), and Ca diffusion (Q₁₀ = 1.3) (Hille 2001).
**Model**

VOLTE-GATED CHANNELS. In an effort to reach a high level of realism in the model, seven voltage-activated currents were included in the model: Na, A type K (K_A), delayed rectifier K (K_DR), L-type Ca, and three Ca-activated K conductances (K_Ca) (Ishida 1995; Lipton and Tauck 1987). This set of channel types was similar but more extensive than previous ganglion cell spike-generators models (Benison et al. 2001; Fohlmeister and Miller 1997a). Kinetics for Na, K_A, and K_DR channels were based on values from the literature (Table 1). The Na current observed in mammalian retinal ganglion cells (Kaneda and Kaneko 1991; Skaliora et al. 1993) is similar to classical Na kinetics (Hodgkin and Huxley 1952), but because classical Na kinetics give inappropriate recovery from inactivation, we implemented a more recent Markov description (Vandenbarg and Bezanilla 1991). The K_DR current measured in retinal ganglion cells is similar to the classical one but has a more depolarized activation function (Skaliora et al. 1995).

In mammalian ganglion cells, evidence for both BK and SK types of Ca-activated K currents has been found (Wang et al. 1998). Two of the K_Ca currents were modeled after the SK type, which is slowly activating with small unitary conductance and little voltage dependence (Hirschberg et al. 1998; Sah and Clements 1999). Therefore these SK currents did not affect spike shape. The addition of a voltage-dependent BK-type K_BK current with fast kinetics (Cox et al. 1997) activated both during spike termination (similar to the K_A current) and also during the interspike interval, consistent with experimental data where blockade of BK type currents leads to an increase of the spiking frequency (Wang et al. 1998). Not included were the K current I_K, which is generally activated only at voltages more negative than -70 mV (Tabata and Ishida 1996) and the slowly inactivating K currents I_H and I_L (Lukasiewicz and Werblin 1988; Sucher and Lipton 1992).

All channel kinetics were implemented with Markov descriptions (Table 1). Because the Markov descriptions in the literature were derived from a variety of systems, we modified them to more closely match the spiking properties of ganglion cells. For this purpose, an offset voltage could be added to a channel’s rate functions, and additional rate factors could multiply the rate functions for activation and/or inactivation. These two features simplified testing channels and matching wave shapes to the real data. For example, to achieve the correct depolarized activation function of the KDR channel (Skaliora et al. 1995), we added a voltage offset to the classical kinetics. The kinetic equations reported in Table 1 include these voltage offsets and rate multipliers.

**Table 1. Kinetic rate functions used**

<table>
<thead>
<tr>
<th>Channel</th>
<th>Markov Diagram</th>
<th>Forward Rate, s⁻¹</th>
<th>Reverse Rate, s⁻¹</th>
<th>Conductances, pS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>closed open</td>
<td>y = 53963 exp(0.0183V)</td>
<td>z = 3155 exp(-0.065V)</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a = 18682 exp(0.0173V)</td>
<td>b = 14501 exp(-175 × 10⁻⁶V)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>c = 50909 exp(0.0597V)</td>
<td>d = 4422 exp(-0.0199V)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>f = 2796 exp(37.9 × 10⁻⁶V)</td>
<td>i = 25.98 exp(-0.0378V)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>g = 4984 exp(37.9 × 10⁻⁶V)</td>
<td>j = 46.15 exp(-0.0378V)</td>
<td></td>
</tr>
<tr>
<td>K_DR</td>
<td>closed open</td>
<td>a = -621(V + 33)</td>
<td>b = 629 exp(V + 43)</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>exp(-0.1(V + 33))</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>K_A</td>
<td>closed open</td>
<td>a = -60(V + 80)</td>
<td>b = 100 exp(-0.1(V + 20))</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>exp(-0.1(V + 80))</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>c = 40 exp(-0.05(V + 70))</td>
<td>d = 600 exp(-0.1(V + 40)) + 1</td>
<td></td>
</tr>
<tr>
<td>Ca</td>
<td>closed open</td>
<td>a = 3367(V + 15)</td>
<td>b = 11223 exp(V + 38)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>exp(-0.1(V + 15))</td>
<td>-18</td>
<td></td>
</tr>
<tr>
<td>bK_CA</td>
<td>closed open</td>
<td>a = 10²[Ca²⁺]</td>
<td>b = 11 × 10¹</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>u = 0.05</td>
<td>z = 1100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>w = exp(-0.05(V + 45))</td>
<td>d = 3936w</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>e = 2.39w</td>
<td>f = 1152w</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>g = 40u</td>
<td>h = 659w</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>i = 295u</td>
<td>j = 486w</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>k = 557u</td>
<td>l = 92w</td>
<td></td>
</tr>
<tr>
<td>sK_CA1</td>
<td>closed open</td>
<td>a = 200 × 10²[Ca²⁺]</td>
<td>b = 80</td>
<td>14.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c = 160 × 10²[Ca²⁺]</td>
<td>d = 80</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>e = 80 × 10²[Ca²⁺]</td>
<td>f = 200</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>g = 160[Ca²⁺]</td>
<td>h = 1000</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>i = 1200[Ca²⁺]</td>
<td>j = 100</td>
<td></td>
</tr>
<tr>
<td>sK_CA2</td>
<td>closed open</td>
<td>a = 10 × 10²[Ca²⁺]</td>
<td>b = 0.5</td>
<td>14.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c = 600[Ca²⁺]</td>
<td>d = 400</td>
<td></td>
</tr>
</tbody>
</table>

Kinetic rate functions used in the model at 22°C; for 35°C, multiply by a factor of 4.17. V is membrane voltage in mV, [Ca²⁺] is the Ca concentration in M for the shell just inside the cell membrane. For right column, single-channel conductance in pS at 22°C. Other parameters of the model were: R_m = 20 kΩcm², R_C = 200 Ωm, C_m = 1 μF/cm², V_Na = 40 mV, V_K = -80 mV, and V_leak = -60 mV. References: Na, Vandenberg and Bezanilla (1991); K_A, Hille (2001); K_Ca, Fohlmeister and Miller (1997a); Ca, Kaneda and Kaneko (1991); bK_CA, Cox et al. (1997); sK_CA, Hirschberg et al. (1998), Sah and Clements (1999).
SETTING THE CHANNEL DENSITIES. To simplify the assignment of
channel densities and parameters, we distinguished four morpholog-
ical regions: dendrites, soma, axon hillock/thin segment of the axon,
and remainder of the axon (Fohlmeister and Miller 1997b). The
dendritic region contained the largest membrane surface area (12
× 10^3 μm^2), so even with a relatively low channel density, it con-
tained the most channels. The soma region was the next largest (2
× 10^4 μm^2) and was a major influence on spiking properties. The axon
hillock/thin segment region was the smallest (250 μm^2).

We found that voltage-gated channels in the dendrites were neces-
sary to reproduce a realistic F-I curve (Fohlmeister and Miller 1997b).
The reason is that a passive dendritic tree represents a heavy capac-
itive load, which causes a high-threshold current for spiking. When
spikes are initiated in the soma, they charge up the dendritic mem-
brane capacitance, which discharges into the soma during the inter-
spike interval, causing inappropriately high spike rates. Therefore to
allow low spike rates requires active spike propagation by dendritic
voltage-gated channels to discharge the dendritic membrane capaci-
tance. Evidence for dendritic voltage-gated channels in ganglion cells
has been observed (Velte and Masland 1999). The standard model had
nearly a constant channel density in the soma and axon hillock with a
lower density (35%) on the dendrites. The channel densities in the
axon did not greatly affect the spiking properties so they were fixed at
a constant value.

IMPLEMENTATION OF CHANNEL NOISE. The kinetics and the noise
of the channel conductances were based on Markov state diagrams,
which provide an accurate description of the kinetics and noise
properties (Chow and White 1996; Strassberg and DeFelice 1993).
Before the simulation was started, the number of channels in each
compartment was computed from the local conductance density and
the unitary conductance (adjusted for temperature; see Table 1).
Channels could be run in macroscopic mode or in microscopic mode.
In macroscopic mode, the channels in a compartment were charac-
terized by the fraction residing in each state of the Markov diagram,
and the transitions between different states were noiseless and matched
classical kinetics.

In microscopic mode, the channels in a compartment were charac-
terized by the number residing in the each state of the Markov
diagram. The transitions between states were proportional to the
macroscopic rates but were probabilistic. At every time step, the
number of transitions from a given state A to a given state B was
drawn from a binomial distribution \( P_{AB} (\sum_k p) \), where \( \sum_k \)
the number of transitions from state A to state B, the transition probability \( p \) was taken
as \( \Delta t \cdot r_{AB} \), where \( \Delta t \) is the time step, and \( r_{AB} \) is the voltage-
dependent transition rate. This was repeated for all transitions of all
channels and for all compartments. As a result, individual channels
opened and closed randomly. An example of the resulting channel
noise for a membrane patch containing \( K_{\text{dr}} \) channels is shown in Fig.
24. This simulation shows that the conductance fluctuates around the
classical noiseless kinetics and its variance is voltage dependent.

Because most states have two to four transitions to other states, it
can occur that after all random transitions have been subtracted from
a certain state, its occupation would become less than zero, which is
incorrect and physically impossible. This problem was prevented by
automatically reducing the simulation time step (Smith 2003).

CALCIUM SYSTEM. The concentration of internal calcium in the
model was space and time dependent. The concentration depended on
flux through open Ca channels, buffering, a Ca pump, and internal
cytoplasmic diffusion. The external calcium concentration \( \left[ \text{Ca}_{\text{out}} \right] \)
was set to 5 mM and the initial internal concentration \( \left[ \text{Ca}_{\text{in}} \right] \) was set to 50
nM. Calcium currents varied according to the GHK current equation
based on the Ca channel’s conductance, \( \left[ \text{Ca}_{\text{out}} \right] \), \( \left[ \text{Ca}_{\text{in}} \right] \), \( [\text{K}_{\text{in}}] \),
and the relative permeability of K⁺ ions through Ca channels (Hille 2001).
At each compartment where Ca channels were located, calcium diffusion
was modeled with 2–10 (0.1 μm) radial cytoplasmic shells and an
internal core that represented a large homogeneous Ca store (de
Schutter and Smolen 1998; Yamada et al. 1989). Lateral diffusion was
not included. The shells allowed Ca transients during spikes that
decayed during the interspike interval. Calcium in the shells and core
was buffered with second-order kinetics (de Schutter and Smolen
1998). The calcium was actively pumped out of the cell with a current density of

\[
I_{\text{pump}} = 0.07 g_{\text{Ca}} \left[ \text{Ca}_{\text{in}} \right] \left[ \text{Ca}_{\text{out}} \right] \left[ \text{Ca}_{\text{in}} \right] + k_i
\]

where \( k_i \) was 5 μM, and \( \left[ \text{Ca}_{\text{in}} \right] \) represented the minimum effective
concentration at which the pump is active (set to 50 nM).

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**Fig. 2.** Main noise sources in the model cell. A: noise due to stochastic opening and closing of the channels. Illustrated with
a 10 μm² membrane patch containing 100 \( K_{\text{dr}} \) channels. The conductance of the stochastic channel model (——) and the continuum
limit (—). Voltage clamp was stepped from −70 to 0 mV. Note the voltage dependence of the fluctuations. The other voltage-gated
channels showed similar fluctuations. B: noise sources in the synaptic input. Vesicles are released according to a Poisson process,
yielding a fluctuating glutamate concentration; this is the 1st noise source (bottom). The transmitter causes a stochastic opening of
the postsynaptic AMPA channels, constitutes the second noise source (middle bottom). The corresponding membrane voltage in the
postsynaptic compartment (middle top) and in the somatic compartment (top, note different scale).
The Ca pump currents were set high enough for \([\mathrm{Ca}^+]_{\text{in}}\) to remain within physiological bounds during a fast burst of spikes but low enough to allow \(K_{\text{ca}}\) channels to be activated during sustained activity. Because the Ca pump current was hyperpolarizing, it tended to reduce activation of the voltage-gated Na and Ca channels; this further reduced \([\mathrm{Ca}^+]_{\text{in}}\). The calcium level also depended on the density of Ca and \(K_{\text{ca}}\) channels and was set to some extent by a negative feedback loop. An increase in \([\mathrm{Ca}^+]_{\text{in}}\) tended to activate \(K_{\text{ca}}\) channels and hyperpolarize the membrane, which reduced Ca channel currents and therefore limited the original \([\mathrm{Ca}^+]_{\text{in}}\) increase, causing spike frequency adaptation. The time constant of this spike frequency adaptation was related to the time constant of the Ca decay (Wang 1998). The parameters were adjusted to give spike frequency adaptation time constant of 40 ms to match our physiological data (see also Lankheet et al. 1989b).

**EFFECT OF TEMPERATURE.** We calibrated the model to give reasonable spike shape and frequency at both 22 and 35°C. Changing the simulated temperature had several profound effects on the spiking. With a Q10 of 3, the channel kinetics at 35°C are a factor \(q = 4.17\) times faster than at 22°C. To understand the effect of this, consider the space-dependent Hodgkin-Huxley equation

\[
\frac{\mathrm{d}V(t)}{\mathrm{d}t} = -\frac{1}{r_i} \frac{\mathrm{d}V(t)}{\mathrm{d}x} + \sum_i g_i(V, t) \left( V(t) - V_{\text{rev}}^i \right) + g_{\text{calc}}(V(t) - V_{\text{calc}}^i) + I_{\text{inj}} = 0
\]

where \(r_i\) is the axial resistivity and \(g_i\) are the ionic conductances densities. At 35°C, the channel conductances speed up to \(g_i(V, t) = g_i(V, qt)\), that is, spikes are faster. But in terms of this scaled time \(qt\), the capacitance term becomes larger, \(C \mathrm{d}V/\mathrm{d}t \rightarrow qC \mathrm{d}V/\mathrm{d}qt\), and as a result, the spikes are damped more (Huxley 1952). This means that higher channel densities are required for a model to work both at 22 and at 35°C than a model adjusted to work just at 22°C. Consistent with this reasoning, the firing rate increased from 22 to 35°C, and the spike amplitude decreased (~80 vs. 60 mV), matching what is observed in recordings. Also the spike timing variability increased by ~50% from 22 to 35°C for the same interspike interval (see RESULTS).

**SYNAPSES AND SYNAPTIC NOISE.** The β ganglion cell receives synaptic input from bipolar cells and amacrine cells ( McGuire et al. 1996). In the model, synaptic inputs of AMPA type were connected from presynaptic terminals to 880 of the ganglion cell dendritic compartments ( Kier et al. 1995). These 880 synapses were homogeneously distributed over the dendritic tree. Each synapse contained 5 postsynaptic channels of 22 pS conductance each, so that, assuming a high open probability the synaptic conductance was ~100 pS. In our model, all the presynaptic bipolar terminals were clamped to the same voltage, so average release rates were identical. The maximal light response of a bipolar cell has been measured in the ganglion cell to be an increase of ~20 vesicles/s/synapse, and noise analysis of the light response is consistent with a Poisson release process; the dark release rate has been estimated at 1.7 vesicles•s•s−1•synapse−1 ( Freed 2000a,b).

Two noise sources were included in the synaptic model ( Smith 1992, 2003). First, equally sized vesicles were released from the presynaptic terminal by a Poisson process (Barrett and Stevens 1972; Freed 2000b). The temporal waveform of vesicle events was defined by a low-pass function with a time constant of 2 ms and Michaelis-Menten binding to the postsynaptic receptor. The second noise source was the stochastic opening of postsynaptic channels, defined by a 2-state Markov diagram with an open and a closed state. The forward transition rate (closed → open) was proportional to the neurotransmitter concentration. The time constant of the closing transition was 5 ms. The two noise sources could be included separately so that simulations contained vesicle release noise, postsynaptic channel noise, or both. Figure 28 shows the effects of both noise sources on the membrane potential. In the noiseless mode, the synaptic conductances were continuous and were derived from the presynaptic voltage.

Inhibitory inputs, presumed to be from amacrine cells, have been measured in ganglion cells at rates 50–100% of excitatory inputs ( Tian et al. 1998). To explore the effect of inhibitory synaptic inputs on spike timing variability, we included GABA A channels, with a reversal potential of ~80 mV and a single channel conductance of 22 pS, modeled with a five-state Markov diagram (Busch and Sakmann 1990). The Markov model gave a biexponential decay time course, with time constants of 18 and 300 ms, in reasonable correspondence with previous data ( Tian et al. 1998). Note that in comparison to the excitatory input the inhibitory input is much slower. The model contained 440 inhibitory synapses with 50 channels each, yielding a 100-pS peak conductance per synapse ( Tian et al. 1998).

**RESULTS**

Effect of noise in simplified models

To gain intuition about the effect of noise on a spike generator, we developed some initial simulations to quantify spike variability. We first considered a nonleaky integrate-and-fire neuron, injected with a constant stimulus and a noise current (Gaussian white noise). We characterized the amount of noise in the spike train with the relation between the mean \((t_{\text{ ISI}})\), and SD \(\Delta t_{\text{ ISI}}\) of the interspike intervals. For the nonleaky integrate and fire neuron, the SD depends on the mean interval as \(\Delta t_{\text{ ISI}} = a(t_{\text{ ISI}})^b\), where the power \(b = 1.5\), and \(a\) is proportional to the amount of noise injected. This exponential relation could not be expected a priori to be valid in general, but despite its simplicity, it also reasonably fit the value of \(b\) determined from the data. From in vivo recordings, Troy and Robson (1992) found that the SD of the interspike interval in steady illumination has an exponent \(b \sim 1.5\) for X-cells and 1.2 for Y cells. In more realistic integrate-and-fire models, which included leak and adaptation, we found the preceding relation to be approximately valid for \((t_{\text{ ISI}})\) ranging from 2 to 100 ms. For Poisson models, the exponent \(b = 1\), thus high-frequency spike trains in integrate-and-fire models are less variable than in Poisson models. The reason is that in integrate-and-fire models for short intervals there is less time for the noise to accumulate, whereas in Poisson models there is no such accumulation process.

Next, we studied a single-compartment Hodgkin-Huxley model with noise originating from the stochastic opening and closing of the voltage-gated channels (Chow and White 1996; Schneidman et al. 1998). Note that because the single-channel conductance and the channel kinetics are known, the only free parameters were the area of the compartment and the stimulus current. First we varied the area of the compartment. For small compartments, we observed spontaneous spikes in the absence of a stimulus current. Because the effect of a single-channel opening on the membrane voltage is proportionally smaller for a larger membrane area, the frequency of spontaneous spikes fell exponentially with area (Chow and White 1996). When enough DC current was injected to push the cell well above spike threshold, the average spike frequency was independent of the amount of noise and membrane area, but the noise caused fluctuations in the interspike interval that diminished as the area was increased. As observed by Schneidman et al. (1998), we found that the noise in the interspike interval was mainly caused by the noise in the \(K_{\text{ca}}\) channel. The SD of the interspike interval depended on the membrane area as
EFFECTS OF NOISE

\[ \langle \delta v \rangle = \frac{1}{\sqrt{A}} = \frac{1}{\sqrt{N_{\text{chan}}}} \]  

This is consistent with a system in which \( N_{\text{chan}} \)-independent noise currents are summed, because the CV of the total noise decreases as \( 1/\sqrt{N_{\text{chan}}} \). However, it is important to note that the spike timing noise is proportional to the current noise only if there is a (locally) linear relation between current and spike frequency, such that \( f(I + \delta I) \approx f(I) + \delta f \cdot f'(I) \).

Next, we varied the stimulus current while the area of the cell was kept constant. As in the preceding text, the SD in this case also depended strongly on the mean interval. A power-law fit gave an exponent \( b \approx 2.06 \). As discussed in the following text, this larger exponent is due to the steep firing threshold in the Hodgkin-Huxley model, which causes small fluctuations in the currents near thresholds to give large fluctuations in interspike interval.

For a multicompartment model, the effect of noise is far more complex. In the subthreshold regime, homogeneous, white noise in an infinite cable is averaged temporally over one membrane time constant and spatially over an element of one electrotonic length (Tuckwell and Walsh 1983). However, above threshold, the interaction of noise, spike generation, and spike propagation is unknown. This is further complicated by the fact that the noise from the channels is voltage dependent. For a better understanding of the noise in a realistic cell, simulations were required.

Physiology

We performed whole cell patch recordings on five beta cells with dendritic arbor diameter of 150 ± 30 \( \mu \)m (\( n = 4 \)). The cells were stimulated with steps of DC current injected at the soma. The resulting spike times were used to determine both the \( F-I \) curve and also the fluctuations in the interspike intervals (Fig. 3). In both model and real cells, the steady-state \( F-I \) curve was linear and had a threshold of \( \approx 20 \) pA. Although both showed spike frequency adaptation, the real cells often responded with a fast spike doublet at stimulus onset, which can be interpreted as a very fast form of adaptation.

To further explore spike frequency adaptation, in one experiment, we removed EGTA from the patch pipette, and added 20 \( \mu \)M CdCl\( _2 \) to the bath to block Ca channel activity. The presence of Cd\( ^{2+} \) lowered the maintained spike rate due to synaptic block but raised the driven spike rate (i.e., the \( F-I \) curve) by 25–50\%, suggesting an increase in \( R_{\text{in}} \) and also block of \( K_{\text{Ca}} \) channel gating (Fig. 4D). However, spike frequency adaptation remained almost unchanged.

The removal of EGTA increased the degree of spike frequency adaptation, but the presence of EGTA did not eliminate adaptation. This is consistent with a system where Ca\( ^{2+} \) entry is tightly coupled to fast local binding on \( K_{\text{Ca}} \) channels (Sah and Davies 2000). In another experiment where we added 1 \( \mu \)M apamin to block \( sK_{\text{Ca}} \) currents, spike frequency adaptation in response to current injection was also reduced but not eliminated, consistent with reports showing the existence of SK and BK currents in mammalian ganglion cells (Lipton and Tauck 1987; Wang et al.1998). Because not all slowly activating \( K_{\text{Ca}} \) currents are affected by this standard blocker (Sah and Clements 1999), spike frequency adaptation could be accomplished mostly or entirely by \( K_{\text{Ca}} \) channels as previously proposed. Another possibility is that a slowly activating Ca-insensitive K conductance (Tabata and Kano 2002) and/or a slowly inactivating Na conductance contribute to adaptation. During the calibration of the model, we found the slowly modulated conductance involved in adaptation is constrained to be a minor fraction (<1–2\%) of the Na conductance. Therefore assuming similar unitary conductances and noise properties, these alternatives would likely affect noise generated in the spike generator in a similar way to the \( K_{\text{Ca}} \) conductances in the model.

**FIG. 3.** Comparison of the physiological data with the model. A: the instantaneous spike frequency for current injection in the soma. Left: experimental data (stimulus currents: 0, 40, 0, 80, . . ., 0, and 200 pA, each lasting 200 ms) shown for 4 repetitions. Right: noiseless model stimulated with the same currents. Thick falling lines, standard model; horizontal lines, model without \( K_{\text{Ca}} \) and Ca channels, which increases the spike frequency and removes adaptation. B: comparison of spike shapes and noise in somatic potential during current injection. Left: experimental data. Right: model with both vesicle release noise and voltage-gated channel noise at 22°. Bottom: enlargement of the membrane potential.
Calibrating the model

In an initial set of simulations, we selected parameters for a single-compartment model to approximately match the spikes of the real neurons based on spike frequency and shape. First, we matched spike properties by varying the kinetic rate functions and membrane density of the voltage-gated channels (Tables 1 and 2). Action potentials occurred when a subthreshold potential activated enough Na channels to cause local regenerative action, which rapidly opened the remaining Na channels. K_A and K_dr channel activation followed, which terminated the spike. K_A channels rapidly inactivated, leaving the K_dr channels to complete termination. Next, we matched the spike rate and the adaptation to the experimental data. In our measurements, ganglion cells typically had a rate of 0.5–1 Hz/pA and 10–50% spike rate adaptation (O’Brien et al. 2002). Adaptation in the model was due to Ca influx through the Ca channels during spikes, which in turn activated the K_Ca currents and hyperpolarized the cell to reduce action potential frequency. We included K_Ca channels in the proper proportion to match the amount and time constant of adaptation observed.

In a second stage of calibration, we checked the multi-compartment model with the parameters of the single-compartment model, applying the same tests for spike shape and rate (Fig. 3). At this stage, there were too many parameters to explore the effect of varying both rate functions and densities, so we generally fixed the rate functions and varied densities to achieve good matches. As Fohlmeister and Miller (1997b) observed, we found that the dendritic morphology and dendritic channel densities were an important factor in the overall spike rate. Without dendritic channels, the F-I curves had a strong threshold and low firing rates were difficult to obtain.

### Table 2. Densities of the voltage-gated channels in the standard model in mS/cm² at 22°C

<table>
<thead>
<tr>
<th></th>
<th>g_{Na}</th>
<th>g_{K_A}</th>
<th>g_{K}</th>
<th>g_{K_{Ca1}}</th>
<th>g_{K_{Ca2}}</th>
<th>g_{Ca}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dendrites</td>
<td>25</td>
<td>10</td>
<td>2</td>
<td>0.05</td>
<td>0.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Soma</td>
<td>70</td>
<td>10</td>
<td>2</td>
<td>0.05</td>
<td>0.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Hillock/Thin segment</td>
<td>80</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Axon</td>
<td>80</td>
<td>10</td>
<td>70</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

FIG. 4. Noise-induced spike timing fluctuations during somatic DC current injection in the model. A: short sample spike train, showing the interspike interval as a function of time at 35°C (solid line: model; dashed line: data). For the static analysis, the initial adapting portion of the spike train was discarded. The steady-state portion shows random fluctuations due to the presence of noise. In the actual data analysis, much longer spike trains were used. B: SD of noise sources in the model plotted against the mean interspike interval at 35°C from (in decreasing order of strength from upper to lower curves): all noise sources active (thick upper curve), noise from voltage gated channels (long dashed line), vesicle release noise from the background release (dotted line), noise from postsynaptic channel fluctuations (dashed line), and Johnson noise (thin line). Error bars indicate SE. C: the contributions of the different voltage-gated channel types to the voltage-gated channel noise in the model at 35°C. The major noise source is from the delayed rectifier K_A channels (black long dashed curve) and Na channels (short dashed black curve). The contribution of Ca-activated K conductances is shown with circle symbols: bK_{Ca} (solid line), sK_{Ca1} (dashed gray), sK_{Ca2} (dotted gray). The thick solid curve labeled “all” gives the noise when all voltage-gated channels are stochastic (i.e., identical to the curve labeled “Volt. Channels” in B). D: comparison of the physiological data obtained with somatic current injection to the model run at 22°C. Symbols represent physiological data, different symbols correspond to different cells. Open symbols, control condition; filled squares, Cd condition; gray squares, Cd washout. Lines represent the model. Dotted line, model with only channel noise; dashed line, model with only vesicle noise; solid line, model with all noise sources.

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Spike timing variability: somatic current injection in model

After tuning the model, we determined the effect of the noise sources on the spiking. To measure the effect of noise during maintained firing, we injected a step current into the soma of the modeled cell. A background level of excitatory synaptic vesicle release rate of 1.5 Hz/synapse was included (Freed 2000a), causing a low spontaneous firing rate (7 Hz). To study the steady-state fluctuations, we applied a long-lasting stimulus current that evoked ~200 spikes. After removing the onset transient during which the spike frequency adapts, we calculated the mean interspike interval and its SD and repeated this for a range of stimulus currents (Fig. 4A).

When all noise sources in the model were included, the SD of the interspike interval was an exponential function of the mean interspike interval (Fig. 4B, upmost curve). On a log-log plot, this corresponds to a straight line. A fit to (eqn) yielded an exponent b = 1.5 ± 0.1. Next, we determined the contribution of the individual noise sources by switching on the noise sources separately. For most parameter sets, channel noise and background synaptic vesicle release noise had comparable effects on the variability of spike timing, but synaptic noise had a smaller effect at short interspike intervals (Fig. 4). The reason may be that when driven primarily by current injection at short interspike intervals (high firing rates), the overall current is dominated by the voltage-gated channels and their fluctuations. The effect of the noise from the postsynaptic ligand-gated channels on the spike time fluctuations was small because the influence of a quantal miniature postsynaptic current (mPSC) on postsynaptic potential is greater than the fluctuations of individual PSC currents (Fig. 2B). In some simulations, we included thermal Johnson noise (Manwani and Koch 1999), present in every conductance, but found it had a negligible effect on the spike-timing. We therefore omit further mention of these two noise sources.

To distinguish the contribution of the different voltage-gated channels to the variability of the spike train, we ran simulations in which only one of the channel types was noisy while the other channel types were noiseless (Fig. 4C). The K_{Ca} channel had the largest contribution to the interspike interval fluctuations, ~50% (at 100 Hz), due to its high probability of being open at the mean membrane potential. The Na channel contributed 25%, in accordance with the single-compartment model of Schneidman et al. (1998). The K_{Ca} channels also contributed substantially to variability. There was a distinct difference between the bK_{Ca} channel, which due to its higher Ca threshold was important mainly at high firing rates, whereas the sK_{Ca} channels dominated for longer interspike intervals (ISIs). The K_{Ca} channel had a much smaller contribution.

The SD measured with all noise sources present was only slightly larger than that of the individual components (Fig. 4B). In the model, the sum of the variances from the different channel types was approximately equal to the variance when all channel noises were present. This was consistent with additivity because the variance of noise from independent sources sums linearly. As a result, the SDs summed as root-mean-square, and the effect of multiple sources appeared especially small on log-log plots. As a separate check for additivity, we ran simulations in which all noise sources except for one were present. The result was that the lack of any one of the noise sources made only a small difference in the overall variability of the spike train, further confirming that the noise sources were additive.

Next, we studied the effect of the calcium system on the fluctuations in the model, the calcium feedback, consisting of the Ca and K_{Ca} channels, causes spike frequency adaptation and lowers the steady-state spike frequency (Fig. 3). In principle, this negative feedback could reduce the fluctuations in the spike timing, and indeed when a noiseless Ca/K_{Ca} system was included, the fluctuations fell by ~35%. But when a noisy Ca/K_{Ca} system was included, this noise reduction was counteracted by the noise from the K_{Ca} channels. Taken together, we found that the net effect of the Ca feedback on the fluctuations was small.

Comparison to empirical data: noise and adaptation

To compare the model to empirical data, we recorded responses from the model and from real ganglion cells using similar experimental paradigms. We injected a DC current into a ganglion cell soma, causing it to spike regularly, and recorded the spike train. After discarding the spikes from the initial adaptation phase (~200 ms), we measured the mean and SD of the interspike interval (5 cells). The exponent was 1.33 ± 0.05 (Fig. 4D). This variability measured in the real cell’s spike train was compared with the model simulated at 22°C. Reducing the temperature from 35 to 22°C lead to a 50% reduction of the fluctuations, and the relative contribution of the voltage-gated channels to the noise became slightly larger. Comparing the model and the data, the dependence of the SD on the mean spike interval (i.e., the slope) was similar (Fig. 4D). In the experiments where we removed EGTA in the pipette or added Cd^{2+} to the bath, we found the maintained and driven spike rates were affected, but these manipulations did not change the relation between mean and SD significantly (Fig. 4D). This is consistent with the observation that neither the Ca system or the individual K_{Ca} channels dominated the noise.

The level of noise in the model was consistently lower than in the real data. Because the model contained only the known synaptic and intrinsic noise sources (see DISCUSSION), any additional noise source or nonstationarity (Teich et al. 1997) would lead to additional variability. Although the identity of other noise sources is unknown, one possibility we explored was inhibitory input (see following text).

Effect of geometry on channel noise

At first glance, the voltage-gated channel noise seems surprisingly large in the model. One might expect that the noise should be much less if the noise from all channels in the cell were averaged. However, it is important to realize that at threshold only a small fraction of the channels are open, and this relatively small number determines the noise (Schneidman et al. 1998). Furthermore, in a spatially extended model, the total noise is not simply the average over all the channels but depends on the cell’s geometry.

To research the influence of the geometry on the amount of fluctuations in the spike train (Fig. 5), we first replaced the original spatially extended cell by a single big sphere that had a surface area equal to the soma plus dendrites of the full model. This led to a somewhat steeper F-I curve and a reduc-
Spike timing fluctuations: synaptic stimulation

In the intact retina, the beta ganglion cell normally receives its input mainly from bipolar synapses (Freed 2000a; McGuire et al. 1986). To model the spike fluctuations during synaptically driven activity, we drove the model cell with excitatory synaptic input. The vesicle release rates ranged between 2 and 60 vesicles · s⁻¹ · synapse⁻¹, which caused firing between 12 and 200 Hz. As in the preceding text, we measured the noise during maintained activity and measured the interspike interval and its SD. Under these conditions, vesicle release noise was dominant (Fig. 6A), but the contribution of the channel noise was still substantial. The exponent of the SD versus mean relation in the upper, linear part of the curve (10–100 ms ISI) was 1.4 ± 0.1, which is somewhat less than for somatic current injection. Nevertheless, the fluctuations in spike timing were similar to those found with somatic current injection, both in amplitude and in exponent (thin line, shown for comparison).

Comparison to visual stimulation

We compared the spike timing fluctuations in the model during synaptic stimulation to maintained discharge experiments from Troy and Robson (1992). In those experiments, a constant light stimulus was given while spike trains were recorded extracellularly in vivo. The fluctuations in the model driven by synaptic stimulation showed a similar slope to fluctuations in the maintained discharge (Fig. 6), but as in the preceding text, the model’s fluctuations had lower amplitude. One possible reason for this discrepancy was the lack of inhibitory drive. The ganglion cell likely receives some inhibitory input during visual stimulation that would increase the relative strength of fluctuations by decreasing the net stimulus current as well as increasing the current noise. We included a constant inhibitory drive in the model with a vesicle release rate of 5 Hz/synapse. This led to a 20-Hz reduction in spike rate across a wide range of frequencies (subtractive inhibition). The input resistance of the cell was reduced by 10.2 ± 0.3%. The variability in the spike times was substantially higher, approaching the level of noise seen in the empirical data (Fig. 6). The exponent was steeper in this case because for shorter interspike intervals the effect of the tonic inhibition was relatively less, approaching the level of noise in the absence of inhibition.
Effect of channel distribution

Because the distribution of voltage-gated channels could potentially be an important determinant for channel noise, we tested several variants of the model with different channel density distributions. These alternate models were not developed to be correct descriptions of the ganglion cell but rather to test the robustness of our results under extreme conditions. The first variant, model 2, had fully passive dendrites and doubled somatic densities. Model 3 had equal densities on soma and dendrites, and model 4 had a very high channel density in the axon hillock but lower density in the soma and dendrites. Models 1 and 4 had approximately the same number of channels, model 2 had the fewest total channels, and model 3 had the most. The F-I curves for original model, the model with homogeneous densities (3) were very similar (Fig. 7A) and were similar to the model with high axon hillock density (4; not illustrated). The F-I curve for the passive dendrite model (2) had a strong threshold, and low firing rates were difficult to obtain. Spike height in the dendrites was largest for the homogeneous model and smallest for the passive dendrite model (not illustrated).

To determine the effect of the different density distributions, we measured the spike timing fluctuations during synaptic driven activity. The noise in the standard model and the homogeneous model (3) were very similar (Fig. 7B) as was noise in the model with high axon hillock density (4; not illustrated). However, in the model with passive dendrites (2), spike timing fluctuations were greater than for the original model and the exponent was much larger (2.4 ± 0.1). This enhancement might have been caused by the strong threshold in the F-I curve. With a strong threshold, small changes in current can cause large changes in spike frequency. Consistent with this, the noise was strongest close to the threshold, i.e., for large intervals. These results demonstrated that the noise properties of model were fairly robust: as long as the F-I curves were similar, large changes in channel distribution did not cause large changes in the noise. Further, although one might expect that concentrating the voltage-gated conductances in the soma would reduce variability, in the model with passive dendrites we found that the variability increased. Therefore the results from our standard model are unlikely to overestimate the spike train variability.

Remarkably, in the model with homogeneous densities (3), irregular firing patterns were observed when the cell was driven synaptically, even when no noise sources were present. The reason was that spikes were initiated at various locations in the dendritic tree (Fig. 8). Interference between spikes and their refractory periods due to the different time delays for spike propagation caused a complicated pattern of spikes, leading to irregularities in the spike timing even though there was no noise in the system (Fig. 7B). The spike train was insensitive to small changes in initial conditions, such as relaxation time before stimulus and small changes in the rate, indicating that the spike train was not chaotic (but see Fohlmeister and Miller 1997b). At the largest interspike intervals (the weakest input), the fluctuations disappeared, and spikes were generated exclusively in the soma. With somatic current injection, such irregularities in the absence of noise
never occurred. Also in the standard model and the model with passive dendrites, spikes were always generated at the soma/hillock region, and therefore no spike timing fluctuations occurred in the absence of noise. In other words, this effect occurred only with reasonably strong synaptic stimulation and high dendritic excitability.

**Response to transient stimuli**

Ganglion cells are known to respond quite reliably to transient stimuli (Berry and Meister 1998). To determine what factors affect reliability of coding such stimuli, we measured the effect of the different noise sources on transient precision. We applied a square wave of synaptic input (0.1 s on, 0.5 s off) to the cell and measured the timing of the first several spikes after the onset of the pulse. The simulations included four conditions (Fig. 9): both channel noise and vesicle noise, along with background vesicle release that caused irregular conditions (Fig. 9): both channel noise and vesicle noise, along after the onset of the pulse. The simulations included four factors to the cell and measured the timing of the first several spikes after the onset of the pulse. The simulations included four conditions (Fig. 9): both channel noise and vesicle noise, along with background vesicle release that caused irregular firing (20 Hz) during the off-phase of the stimulus; vesicle release noise without background release; channel noise without background release; and both vesicle release and channel noise without background release.

The mean time to spike was roughly proportionate to the spike number (Fig. 9B), which reflected a constant firing rate. Background spiking reduced the average latency (compare Fig. 9B, far left with other graphs in B). The reason is that the background activity sets the neuron closer to its spiking threshold. This effect was most pronounced for weak stimuli (low contrasts). Further, with background activity fluctuations in spike timing were large and consistent from one spike to the next (Fig. 9C, left), because the first spike’s latency depended on the time of the previous background spike as well as the stimulus. The background spiking increased the variability of time to spike more strongly than the direct influence of the noise sources on the response, as observed before in more simplified neuron models (Lansky and Musila 1991; van Rossum 2001). Without spontaneous spiking, the latency of the first spike was greater and the SD was substantially lower (Fig. 9, B and C), confirming that background activity was responsible for both effects.

With transient stimuli, vesicle release noise and channel noise had different effects (Fig. 9C). When only vesicle noise was present, the first spike was fairly precise and subsequent spikes were less so because the jitter accumulated from one to the next (increasing as the square root of the spike number). However, when only channel noise was present, the timing of the first spike was very precise but for subsequent spikes the fluctuation in spike timing increased supralinearly. After a few spikes, the fluctuations became similar to the effect of vesicle noise, which is expected as the system approaches the steady state. A likely reason for the high precision of the first spike is the strong voltage dependence of the channel noise (e.g., Fig. 2). Only after the first spike is all the membrane charged, opening the channels more and thus increasing the noise. When both noise sources were present, the fluctuation in the timing was roughly given by the sum of the individual contributions.

**DISCUSSION**

In this study, we constructed a detailed multicompartmental model of a mammalian retinal ganglion cell and determined the contribution of various noise sources to the variability in spike timing. Fluctuation in synaptic vesicle release was an important factor in spike time variability at all firing rates, especially when excitatory synaptic input was summed with uncorrelated inhibitory input (Fig. 6B). When the ganglion cell was driven by synaptic input to spike at low rates, the effect of synaptic noise was greater than voltage-gated channel noise by a factor of 3–5 (Figs. 6 and 9). However, when driven by injected current with a low background rate of synaptic stimulation, the effect of synaptic noise was comparable to voltage-gated channel noise, especially at high firing rates (Fig. 4B).

The contribution of noise from voltage-gated channels was largest for tonic stimuli. The reason is that the number of channels actively fluctuating open and closed near spike threshold is the most important factor determining spike time variability (Schneidman et al. 1998), and in a prolonged response, channels are more active than in periods without spiking. In single-compartment models, channel noise is reduced by averaging over large areas (Chow and White 1996), but in the multicompartment model such averaging does not occur (Fig. 5). This suggests that the contribution of channel noise in larger ganglion cells might be independent of its size. Finally, our results also show that the channel noise is relatively independent of the precise channel distribution (Fig. 7).

For transient stimuli, the contribution of synaptic noise to spike time fluctuations was dominant. Background spiking activity increased the variability of the time to first spike but also reduced the latency, especially for low contrast inputs. Channel noise had little effect on the variability of the time to first spike. Because many ganglion cells have a transient component to their light response (Enroth-Cugell and Robson 1966; Lankheet et al. 1989a,b) and substantial background activity (Robson and Troy 1987; Troy and Robson 1992), this suggests that a quick response has priority for sensory processing. In addition, transient vesicle release rates are normally greater than steady-state release, decreasing latency even further (von Gersdorff et al. 1996). A higher-order neuron could reduce timing fluctuation by averaging over inputs from many
ganglion cells, but even in that case, precisely synchronized synaptic inputs would be most salient. This suggests that for transient input the spike train maintains temporal precision in a trade-off between a fast, jittery response and a slower but more precise response.

Validity of model

Important questions are how reliable are our approximations and how do our results depend on them? For most parameters, we took values from the literature, either for ganglion cells or from biophysical properties of similar neurons. Unlike more abstract models of noise in neurons, this fixed many of the noise parameters in the model. The synaptic noise depended on the vesicle parameters, the number of synapses and their conductance, and the kinetics of the response. There is little uncertainty about the synaptic conductance because both the single-channel conductance of the AMPA receptor and its kinetics are well known. Synaptic release is thought to be random and has been characterized as a rate modulated Poisson process (Barrett and Stevens 1972; Freed 2000b; Smith 2003), but both spatial and slow temporal correlations could exist in the release, tending to increase the noise in a predictable manner. For example, if the retina is in a state similar to dark-adaptation, its responses might be bursty and hence noisier. A study of such effects was beyond the scope of the present manuscript, but we did consider the effect of stochastic inhibitory inputs. With different release rates of inhibitory synaptic conductances included in the model (Freed 2000b; McGuire et al. 1986; Tian et al. 1998), the noise increased correspondingly, because inhibition reduced the mean drive to the cell but increased the synaptic noise. Note that the inhibition we included in the model is not a direct analog of the surround antagonism found in many ganglion cells. The reason is that the surround is thought to originate in several sources including horizontal cells (Dacey et al. 2000) and amacrine cell feedback to bipolar cells (Shields et al. 2000) in addition to the direct inhibitory inputs from amacrine cells (Demb et al. 2001).

The magnitude of voltage-gated channel noise was constrained by several factors. The noise depended linearly on the unitary conductance, which is accurately known for most channel types in the model. The power spectrum of the fluctuations is set by the channel kinetics, which are also known for most common channel types, so here we are also confident in our results.

Less well known is the precise spatial distribution of the channels on the membrane. Previous modeling studies have found that a certain minimal density of channels on the dendrites is necessary to account for realistic F-I curves (Fohlenmeister and Miller 1997b). Voltage-gated Na channels and active spike propagation in dendrites of retinal ganglion cells have recently been observed (Velt et al. Masland 1999). With low dendritic channel densities, we found that spikes always initiated near the soma and propagated with progressively lower amplitudes into the dendrites. With dendritic channel densities up to ~50% of the soma density, action potentials initiated in the soma and back-propagated into the dendritic tips. At this density, current injected into the dendritic tree often evoked a spike that propagated in subthreshold mode to cause full-blown spikes at the soma. Important for the validity of our results, we found that variations in the distribution of the channels did not change the noise much. Interestingly, when the dendritic channel densities were high and the cell was driven by synaptic inputs, we observed additional variability in spike timing due to spike initiation at different dendritic sites. In this case, an action potential that initiated in a dendrite and propagated to the soma often back-propagated into other dendrites. This implies that somatic current injection does not always reveal the full spiking properties of the ganglion cell.

Comparison with data

For both in vitro physiological data and the model, the spike time variability for sustained activity depended strongly on the mean interval. This behavior has previously been described as $<\delta t_{\text{isi}}^2> = a(t_{\text{isi}})^b$, with $b = 1.2-1.5$ (Troy and Robson 1992). Interestingly, this behavior is consistent with a leakless integrate-and-fire neuron with additive noise (Lankheet et al. 1989a). The exponent derived from our model approximated the physiologically measured exponent for both somatic current injection and visual stimuli. Because the exponent was affected by the stimulation method and the channel distribution, this result is an additional validation of the model.

Nevertheless, the model gave a lower estimate for the spike train fluctuations than given by the physiological data. This result is not surprising, because by its very nature, except for the explicitly included noise sources, the simulated cell was ideal. This discrepancy might be narrowed by adding further noise from inhibitory inputs, and this should be empirically testable by measuring the effect of blocking inhibitory synaptic inputs. However, other features of the retinal circuit that we did not include could also be responsible: noise and correlation in the synaptic inputs due to noise sources in the presynaptic circuitry, fluctuation in other constitutive membrane channels such as voltage-independent $K^+$ and $Cl^-$ channel types or persistent $Na^+$ channels (White et al. 1998), and, finally, slow adaptive mechanisms and modulator effects (Teich et al. 1997) that were not present in our model would lead to additional fluctuations.

Although the model did not account for all the observed noise, it generated a significant fraction of the variability we measured in the real cells without relying on presynaptic noise sources (e.g., photon noise, noise in the bipolar cells). Thus the vesicle release and voltage-gated channels together are responsible for a significant part of the fluctuations. It has been argued that presynaptic noise sources might contribute only a part of noise seen in the spike train (Croner et al. 1993; Freed 2000a,b; Schellart and Spekreise 1973; Troy and Robson 1992). The question remains how much the presynaptic noise sources precisely contribute. A precise quantitative answer using an extension of this model would require a detailed of all presynaptic circuitry and is currently computationally unfeasible. However, this question might be addressed physiologically by comparing the noise during light stimulation and current stimulation.

Implications for neural processing

The question of noise and reliability of spike timing has received a lot attention, not only in the retina (Berry and Meister 1998), but also for cortical networks. It has been
observed that cortical spiking is often very irregular (e.g., Softky and Koch 1993), but when driven by a fluctuating current, spike times can be very precise (Mainen and Sejnowski 1995; Tiesinga et al. 2002; but also see Steinmetz et al. 2001). It has therefore been concluded that either the inputs it receives are noisy and correlated and/or that the cell receives inhibition that balances the excitation.

The present model has been developed to closely approximate the mammalian ganglion cell. This has the advantage that many parameters are precisely known and few free parameters are left. However, there is no straightforward generalization of our results to other neurons because, for example, the beta cell is small compared with cortical cells, and the synaptic input to the ganglion cell is provided by nonspiking cells. Nevertheless, some phenomena observed here might carry over to other systems: 1) when stimulated with a DC current, SD of the interspike interval relates to the mean with an exponent of \( \sim 1.5 \) (Troy and Robson 1992). 2) When the dendrites are soexcitable that spikes initiate on the dendrites, additional irregularities in the spiking can result. 3) Noise from voltage-gated channels is larger than expected from averaging all channels in the cell. 4) Transient responses can have extra precision because voltage-gated channel noise affects transients less than sustained responses.

Noise in a sensory pathway limits the amount of information in spike trains and therefore how well an organism can sense fine details with limited energy and with a limited number of neurons (Barlow 1981). Interestingly, the channel noise cannot be reduced simply by taking more channels with lower conductances. The gating charge associated to each channel would be reduced simply by taking more channels with lower conductances. The gating charge associated to each channel would be reduced simply by taking more channels with lower conductances.

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