

**Roberto F. Galán, G. Bard Ermentrout and Nathaniel N. Urban**  
*J Neurophysiol* 99:277-283, 2008. First published Oct 10, 2007; doi:10.1152/jn.00563.2007

**You might find this additional information useful...**

---

This article cites 20 articles, 11 of which you can access free at:

<http://jn.physiology.org/cgi/content/full/99/1/277#BIBL>

Updated information and services including high-resolution figures, can be found at:

<http://jn.physiology.org/cgi/content/full/99/1/277>

Additional material and information about *Journal of Neurophysiology* can be found at:

<http://www.the-aps.org/publications/jn>

---

This information is current as of January 22, 2008 .

# Optimal Time Scale for Spike-Time Reliability: Theory, Simulations, and Experiments

Roberto F. Galán,<sup>1,2</sup> G. Bard Ermentrout,<sup>2,3</sup> and Nathaniel N. Urban<sup>1,2</sup>

<sup>1</sup>Department of Biological Sciences, Carnegie Mellon University, Pittsburgh; <sup>2</sup>Center for the Neural Basis of Cognition, Mellon Institute, Pittsburgh; and <sup>3</sup>Department of Mathematics, University of Pittsburgh, Pittsburgh, Pennsylvania

Submitted 21 May 2007; accepted in final form 6 October 2007

**Galán RF, Ermentrout GB, Urban NN.** Optimal time scale for spike-time reliability: theory, simulations, and experiments. *J Neurophysiol* 99: 277–283, 2008. First published October 10, 2007; doi:10.1152/jn.00563.2007. Use of spike timing to encode information requires that neurons respond with high temporal precision and with high reliability. Fast fluctuating stimuli are known to result in highly reproducible spike times across trials, whereas constant stimuli result in variable spike times. Here, we first studied mathematically how spike-time reliability depends on the rapidness of aperiodic stimuli. Then, we tested our theoretical predictions in computer simulations of neuron models (Hodgkin-Huxley and modified quadratic integrate-and-fire), as well as in patch-clamp experiments with real neurons (mitral cells in the olfactory bulb and pyramidal cells in the neocortex). As predicted by our theory, we found that for firing frequencies in the beta/gamma range, spike-time reliability is maximal when the time scale of the input fluctuations (autocorrelation time) is in the range of a few milliseconds (2–5 ms), coinciding with the time scale of fast synapses, and decreases substantially for faster and slower inputs. Finally, we comment how these findings relate to mechanisms causing neuronal synchronization.

## INTRODUCTION

Currents from thousands of synaptic inputs arrive at the neuronal soma, where these inputs result in the generation of trains of action potentials. To understand how the brain processes information, we must understand which features of these inputs that arrive at the soma are encoded, processed, and transmitted by neurons. Thus determining what kinds of somatic currents reliably generate or alter the timing of action potentials is critical to understanding how neurons function. That is, we must determine how to maximize the reliability of a neuron's output (firing patterns) given fixed amplitudes of the input signal and the background noise (fixed signal-to-noise ratio). One feature of the input signal that is critical to neuronal reliability is the rapidness of the stimulus fluctuations. In fact, fast fluctuating currents are known to result in highly reproducible spike times across repetitions, whereas constant (i.e., infinitely slowly fluctuating) currents result in nonreproducible spike times (Bryant and Segundo 1976; Mainen and Sejnowski 1995; Movshon 2000). Here we address the question whether, "faster is always better" and, in particular, whether there is an optimal time scale for input fluctuations to induce reliable firing. The existence of such an optimal time scale is likely to indicate adaptation of the neuron's natural design to a preferred type of input. This in turn would represent the time scale in which neural processing occurs most efficiently.

Address for reprint requests and other correspondence: R. F. Galán, Carnegie Mellon University, Department of Biological Sciences, Mellon Institute, 4400 Fifth Ave., Pittsburgh, PA 15213 (E-mail: galan@cnbc.cmu.edu).

## METHODS

### Experimental

All experiments were conducted under a protocol approved by the Carnegie Mellon University Institutional Animal Care and Use Committee using procedures described previously (Urban and Sakmann 2002). Sagittal slices of the olfactory bulb and coronal slices from somatosensory, motor, and prefrontal cortex were prepared from mice aged 14–24 days. Whole cell current-clamp recordings were performed at 33°C in the presence of blockers of fast synaptic transmission (APV 25 μM, CNQX 10 μM, bicuculline 10 μM). Cells were injected with currents (duration: 2.5 s) consisting of a bias current (200–300 pA in mitral cells; 400–500 pA in pyramidal cells) plus current fluctuations of variable amplitude (from 0 to 90 pA). Aperiodic fluctuations were generated by convolving frozen white noise with an alpha function,  $t/\tau \cdot \exp(-t/\tau)$  with time-to-peak  $\tau$  and rescaling to the desired variance, so that the amplitude of the fluctuations was the same for all  $\tau$ . Each stimulus was presented five times to study the reliability of the response. The mean firing rate of the neurons was between 10 and 80 Hz. Experimental estimation of the background noise level was performed by measuring the SD of the random currents recorded in voltage clamp at –65 mV. This was ~7 pA.

### Signal processing

The reliability of the neuronal response was calculated as the mean pairwise correlation of the spike trains obtained in different trials. Specifically, we first converted the spike trains into binary strings, where 1 represents a zero-crossing of the membrane potential and 0 represents any other value. These strings were convolved with a square function of width  $2\delta$  ( $\delta = 4$  ms, in Fig. 3) and unitary amplitude. The pairwise correlation was calculated as the dot product of these signals—without subtracting the mean—normalized by the product of their norms. This roughly corresponds to the number of reliable spikes divided by the total number of spikes fired. This measure of reliability is equivalent to other measures of reliability and synchrony previously used by several authors (Galán et al. 2006a,b; Hunter et al. 1998; Schreiber et al. 2004).

### Simulations

We used the single-compartment simple neuron model proposed in Izhikevich (2004), which has two dynamical variables, the membrane potential,  $v$ , and the recovery variable,  $u$ , that obey the equations

$$\begin{cases} dv/dt = 0.08v^2 + 10v + 280 - 2u + I(t) + \eta(t) \\ du/dt = a(bv - u) \end{cases}$$

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

with  $a = 0.04$  and  $b = 0.2$ . In addition, when  $v > 30$ , the membrane potential is reset to  $v = -65$  mV, and the recovery variable is reset to  $u = u + 2$ . The input,  $I(t)$  consisted of a bias current ( $8-13 \times 10$  pA) plus the fluctuating stimulus ( $6 \times 10$  pA), which was 1.4 times larger than the background noise,  $\eta(t)$ . We also used the conductance-based single-compartment model by Hodgkin and Huxley (1952)

$$\begin{cases} C \cdot dV/dt = g_{Na} m^3 h (E_{Na} - V) \\ \quad + g_K n^4 (E_K - V) + g_L (E_L - V) + I_0 + I(t) + \eta(t) \\ dm/dt = \alpha_m (1 - m) - \beta_m m \\ dn/dt = \alpha_n (1 - n) - \beta_n n \\ dh/dt = \alpha_h (1 - h) - \beta_h h \end{cases}$$

where  $V$  is the membrane potential and  $m$ ,  $n$ , and  $h$  are the gating variables of the channels, which depend on the functions

$$\begin{aligned} \alpha_m &= \frac{0.1 \cdot (V + 40)}{1 - \exp[-0.1 \times (V + 40)]} & \beta_m &= 4 \cdot \exp[-0.0556 \times (V + 65)] \\ \alpha_h &= 0.07 \cdot \exp[-0.05 \times (V + 65)] & \beta_h &= 1/[1 + \exp[-0.1 \times (V + 35)]] \\ \alpha_n &= \frac{0.1 \cdot (V + 55)}{1 - \exp[-0.1 \times (V + 55)]} & \beta_n &= 0.125 \cdot \exp[-0.0125 \times (V + 65)] \end{aligned}$$

In these equations, the following parameters were used: bias current,  $I_0 = 6-9 \mu\text{A}/\text{cm}^2$ ; the mean amplitude of the input fluctuations,  $I$ , was  $5 \mu\text{A}/\text{cm}^2$ ; the mean amplitude of the background noise,  $\eta(t)$ , was  $2 \mu\text{A}/\text{cm}^2$ ;  $g_{Na} = 120 \text{ mS}/\text{cm}^2$ ,  $g_K = 36 \text{ mS}/\text{cm}^2$ ,  $g_L = 0.3 \text{ mS}/\text{cm}^2$ ,  $E_{Na} = 50$  mV,  $E_K = -77$  mV,  $E_L = -54.387$  mV,  $C = 1 \mu\text{F}/\text{cm}^2$ . The data from simulations were analyzed in the same fashion as the experimental data (see *Signal processing*).

Several studies have emphasized the importance of fast fluctuating inputs in generating spike times that are reliable from trial to trial (Bryant and Segundo 1976; Mainen and Sejnowski 1995). Here we ask whether faster is always better and in particular whether there is an optimal time scale for aperiodic fluctuating stimuli to induce reliable firing. To this end, we have combined theoretical, computational, and experimental studies.

### Mathematical theory

From a conceptual perspective, spike-time reliability is equivalent to a limit case of noise-induced synchronization (Galán et al. 2006b; Teramae and Tanaka 2004): In the former, the timing of spikes is preserved across repeated trials in which the same fluctuating stimulus is delivered to a single neuron. In the latter, a pattern of synchronous spikes is generated across different neurons receiving similar (correlated) fluctuating inputs. Thus the study of reliability can be reduced to the study of two identical neurons receiving identical (perfectly correlated) fluctuating inputs in the presence of background noise. Let  $y_i(t)$  be the voltage traces of these two neurons (outputs) and  $x_i(t)$  be the respective inputs received ( $i = 1, 2$ ). The relationship between the inputs and the outputs is given to a first order approximation by (Rieke et al. 1997)

$$\begin{cases} y_1(t) = \int_0^\infty K(s)x_1(t-s)ds \\ y_2(t) = \int_0^\infty K(s)x_2(t-s)ds \end{cases}, \quad (1)$$

where the convolution kernel,  $K(s)$  is the spike-triggered average (STA) of the neurons reversed in time. The inputs  $x_i(t)$  consist of two components: a fluctuating signal (colored noise) common to both

neurons  $I(t)$  with autocorrelation time,  $\tau$ , (the shorter  $\tau$ , the faster the fluctuations) plus uncorrelated white noise,  $\eta_i(t)$

$$x_i(t) = I(t) + \eta_i(t) \quad (2)$$

with

$$\langle \eta_1(t)\eta_2(t-s) \rangle = 0, \quad \langle \eta_i(t)\eta_i(t-s) \rangle = \sigma_\eta^2 \delta(t-s),$$

$$\langle I(t)I(t-s) \rangle = \sigma_I^2 \exp(-|s|/\tau) \quad (3)$$

We define reliability (or synchronization across neurons),  $R$ , as the correlation coefficient of the voltage traces

$$R \equiv \frac{\int_{-\infty}^{\infty} y_1(t)y_2(t)dt}{\sqrt{\int_{-\infty}^{\infty} y_1(t)y_1(t)dt \int_{-\infty}^{\infty} y_2(t)y_2(t)dt}} = \frac{\int_{-\infty}^{\infty} y_1(t)y_2(t)dt}{\int_{-\infty}^{\infty} y_1^2(t)dt} \quad (4)$$

where we have used the fact that the integral of the square of  $y_1(t)$  and the integral of the square of  $y_2(t)$  are equal. Substituting Eq. 1 into Eq. 4, followed by the application of Eqs. 2 and 3, we first calculate

$$\begin{aligned} \int_{-\infty}^{\infty} y_1(t)y_2(t)dt &= \int_0^\infty \int_0^\infty K(s)K(s') \int_{-\infty}^{\infty} x_1(t-s)x_2(t-s')dtdsds' \\ &= \int_0^\infty \int_0^\infty K(s)K(s') \langle x_1(t-s)x_2(t-s') \rangle dsds' \\ &= \sigma_I^2 \int_0^\infty \int_0^\infty K(s)K(s+u) \exp(-u/\tau) dsdu \\ &= \sigma_I^2 \int_0^\infty \exp(-u/\tau) \int_0^\infty K(s)K(s+u) dsdu \\ &= \sigma_I^2 \int_0^\infty \exp(-u/\tau) Q(u) du \end{aligned}$$

where we have defined  $Q(u) = \int_0^\infty K(s)K(s+u)ds$ . Analogously, we calculate

$$\begin{aligned} \int_{-\infty}^{\infty} y_1(t)y_1(t)dt &= \int_0^\infty \int_0^\infty K(s)K(s') \int_{-\infty}^{\infty} x_1(t-s)x_1(t-s')dtdsds' \\ &= \int_0^\infty \int_0^\infty K(s)K(s') \langle x_1(t-s)x_1(t-s') \rangle dsds' \\ &= \sigma_I^2 \int_0^\infty \int_0^\infty K(s)K(s+u) \exp(-u/\tau) dsdu \\ &\quad + \sigma_\eta^2 \int_0^\infty \int_0^\infty K(s)K(s+u) \delta(u) dsdu \\ &= \sigma_I^2 \int_0^\infty \exp(-u/\tau) \int_0^\infty K(s)K(s+u) dsdu + \sigma_\eta^2 Q(0) \\ &= \sigma_I^2 \int_0^\infty \exp(-u/\tau) Q(u) du + \sigma_\eta^2 Q(0) \end{aligned}$$

Thus  $R(\tau) = R$  becomes

$$R(\tau) = \frac{\sigma_1^2 \int_0^\infty \exp(-u/\tau) Q(u) du}{\sigma_1^2 \int_0^\infty \exp(-u/\tau) Q(u) du + \sigma_\eta^2 Q(0)} \quad (5)$$

Note that in the absence of background noise, i.e., if  $\sigma_\eta = 0$ ,  $R = 1$  for any  $\tau$ , whereas in the absence of a fluctuating signal, i.e., if  $\sigma_1 = 0$ ,  $R = 0$  for any  $\tau$ . Figure 1A shows the curves  $R$  versus  $\tau$  for two neuron models [Hodgkin-Huxley's (HH) from Hodgkin and Huxley 1952 and a simple neuron model (SM) from Izhikevich 2004] at different firing rates as predicted from their kernels,  $K(t)$ , shown in Fig. 1B. Clearly, in all cases,  $R(\tau)$  has a maximum in the few millisecond range. Note that the HH model can fire only above  $\sim 50$  Hz, whereas the SM model can fire in the beta/low gamma range as well. This is important for the explanation below. In addition, whereas the HH model contains a detailed dynamical description of realistic conductances, the SM is basically a modified quadratic integrate-and-fire model, i.e., a nonlinear device with a resetting threshold, whose kernel,  $K(t)$  resembles those of real neurons and that according to Eq. 5 leads to nonmonotonic curves,  $R(\tau)$ .

How does the optimal time-scale for spike-time reliability,  $\tau_{\text{opt}}$ , depend on the average interspike interval,  $T$ ? As neurons fire faster,  $T$  decreases and the spike-triggered average is, in a first approximation, "compressed" accordingly (Fig. 1B). Thus  $\tau_{\text{opt}}$  will decrease with  $T$ ; typically, in simulations and experiments,  $\tau_{\text{opt}} \approx 10\%T$ . This result can also be obtained by applying dynamical system theory as follows. Consider two identical neurons in the form of phase oscillators (Kuramoto 2003) and driven by (Eq. 2)

$$\begin{cases} d\theta_1/dt = 2\pi/T + Z(\theta_1) [I(t) + \eta_1(t)] \\ d\theta_2/dt = 2\pi/T + Z(\theta_2) [I(t) + \eta_2(t)] \end{cases} \quad (6)$$

where  $T$  is the average natural period (mean interspike interval) of the neurons and  $Z(\theta)$  is the phase-dependent sensitivity of the oscillator [phase resetting or phase response curve (PRC)], which can be determined experimentally in real neurons (Galán et al. 2005; Mancilla et al. 2007; Tateno and Robinson 2007). We now consider the relative phase of the oscillators  $\phi = \theta_2 - \theta_1$ . From Eq. 6, we get

$$d\phi/dt = [Z(\theta_1 + \phi) - Z(\theta_1)] I(t) + [Z(\theta_2)\eta_2(t) - Z(\theta_1)\eta_1(t)] \quad (7)$$

Using the approximation

$$[Z(\theta_1 + \phi) - Z(\theta_1)] \approx Z'(\theta_1)\phi$$

and averaging on time we obtain

$$d\phi/dt = -\lambda\phi + \sigma_A\eta(t)$$

where  $-\lambda$  is by definition the Liapunov exponent for system Eq. 6

$$\lambda = \lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T Z'[\theta(t)] I(t) dt$$

and  $\sigma_A$  is the SD of the stochastic term in Eq. 7

$$\sigma_A^2 = \frac{\sigma^2}{\pi} \int_0^{2\pi} Z^2(\theta) d\theta$$

The Liapunov exponent of a dynamical system quantifies its robustness to the effect of noise: the larger its absolute value, the more robust the dynamics. Because we are assuming that the effect of the fluctuating input is small relative to the natural frequency, we can use the approximation

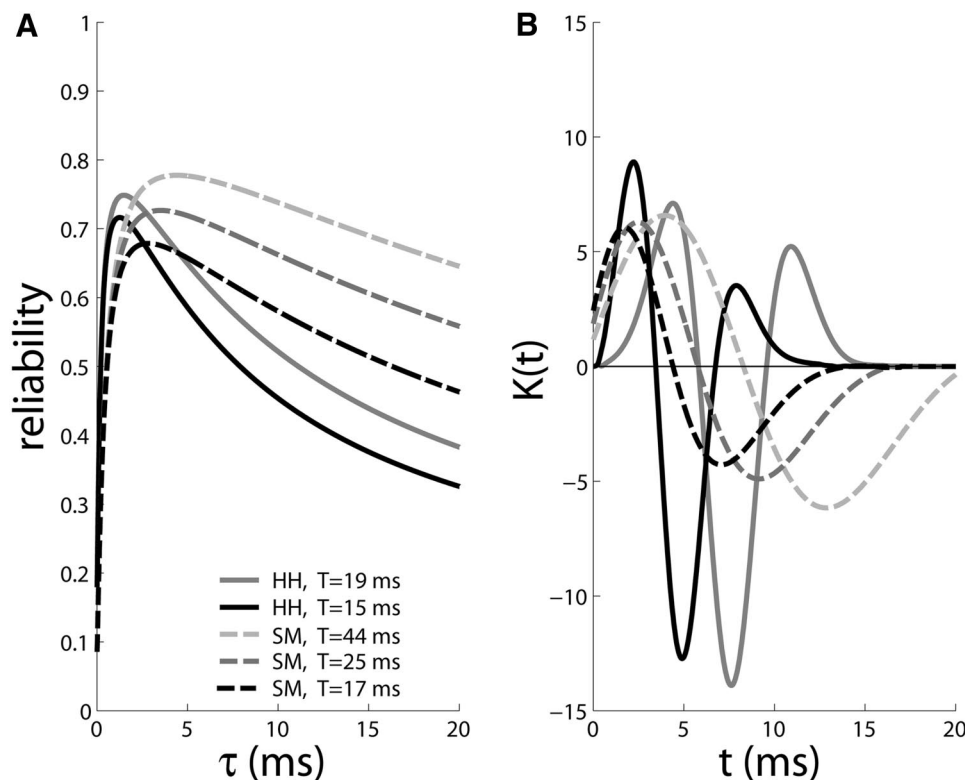


FIG. 1. Prediction of the mathematical theory. A: spike-time reliability,  $R$ , as a function of the time scale,  $\tau$  of the stimulus fluctuations for the Hodgkin-Huxley model (HH) from Hodgkin and Huxley (1952) and for the modified simple neuron model (SM) from Izhikevich (2004). For firing rates in the beta/gamma band, the theory predicts maximal values of reliability between  $\tau = 2$  and 5 ms. B: spike-triggered average reversed in time,  $K(s)$  of the neuron models from which the curves in A are predicted.

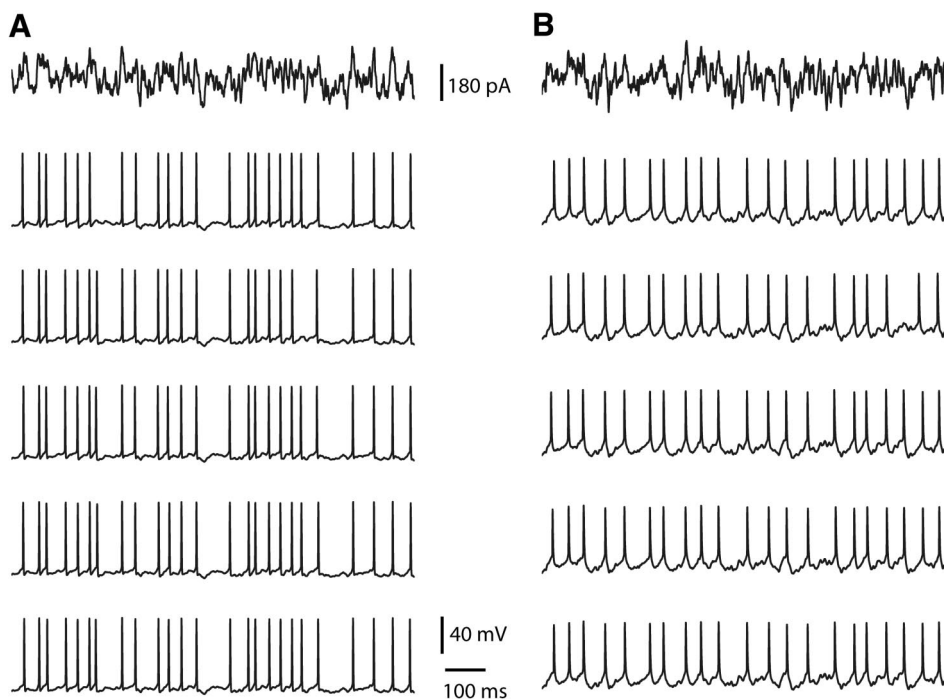


FIG. 2. Maximal reliability in real cells. Aperiodic frozen currents (top traces;  $\tau = 3$  ms) are injected 5 times into a mitral cell (A) and into a neocortical pyramidal cell (B). In both neurons, virtually all spikes are preserved across all trials.

$$\theta(t) \approx t + \int_0^t Z(s)I(s)ds$$

to calculate the Liapunov exponent explicitly

$$\begin{aligned} \lambda &= \lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T [Z'(t)I(t) + Z''(t) \int_0^t Z(s)I(t)I(s)ds]dt \\ &\approx 0 + \lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T Z''(t) \int_0^t Z(s)C(t-s)dsdt \quad (8) \end{aligned}$$

where  $C(t-s)$  is the autocorrelation function of the input. For a typical phase response,  $Z(t)$  of a real neuron, the absolute value of the Liapunov exponent is maximal for a finite  $\tau = \tau_{\text{opt}}$  of the autocorrelation function,  $C(s) = \sigma_I^2 \exp(-|s|/\tau)$ . Furthermore, since  $Z(t)$  can, in a first approximation, be described by a sinusoidal, from Eq. 8, one obtains  $\tau_{\text{opt}} \approx T/(2\pi) \approx 16\%T$ . Despite the simplicity of the approximation, this value is in the same order of magnitude as the actual  $\tau_{\text{opt}}$  observed in simulations and experiments, which is  $10\%T$  (see below).

## RESULTS

### Simulations and experiments

To test the predictions of our theory, we have designed the following experiments with simulated and real neurons. We repetitively presented “frozen colored noise” stimuli (see METHODS) that consisted of a constant current (such that the neurons fired regularly in the beta/gamma band, 10–80 Hz) plus aperiodic fluctuations,  $I(t)$ , generated by passing white noise through different low-pass filters (see *Signal processing*)

to generate signals with different autocorrelation times,  $\tau$  (the shorter  $\tau$  is, the faster are the fluctuations). We performed the experiments (Fig. 2) on mitral cells ( $n = 18$ ) of the olfactory bulb and on neocortical pyramidal cells ( $n = 20$ ) of mice, obtaining similar results: on average, spike-time reliability is maximal for  $\tau = 2$ –5 ms (Fig. 3A). For this time scale, reliability monotonically increased with increasing amplitude of the fluctuations (Fig. 3B). Interestingly, already one half of the spikes were reliable as soon as the input fluctuations doubled the background input noise ( $<10$  pA). Similar curves of reliability are followed by the HH conductance model (Hodgkin and Huxley 1952) and even by a SM model (Izhikevich 2004) lacking any conductances (Fig. 3). In the computer simulations background, uncorrelated noise,  $\eta(t)$  was also added (see METHODS).

Our measure of spike-time reliability for simulations and experiments (see METHODS) differs slightly from Eq. 4: it detects spikes that are preserved across trials within a time bin of  $2\delta$  ms, i.e., the tolerance to “spike jitter” is  $\pm\delta$  ms. In Fig. 3, we chose  $\delta = 4$  ms. Obviously, the optimal time scale for neural reliability should not depend on this choice, and it does not, as shown in Fig. 4A. However, the values of reliability should increase overall as we tolerate larger spike jitter across repetitions. This can also be observed in Fig. 4A.

Next we studied the dependence of the optimal time scale for spike-time reliability on the average interspike interval. This analysis was performed across the population of neurons studied to cancel out the variability observed in single cell recordings. In effect, although the shape of the curve  $R(\tau)$  is highly consistent across different experiments in the same and different cells (Fig. 3A), the exact position of the peak varies from experiment to experiment, even in the same cell, within a range that is comparable to the change predicted by the firing-rate dependence. Thus we pooled all the data recorded for each neural type and calculated a linear regression for each type. As predicted by our theory,  $\tau_{\text{opt}}$  increases with the mean interspike

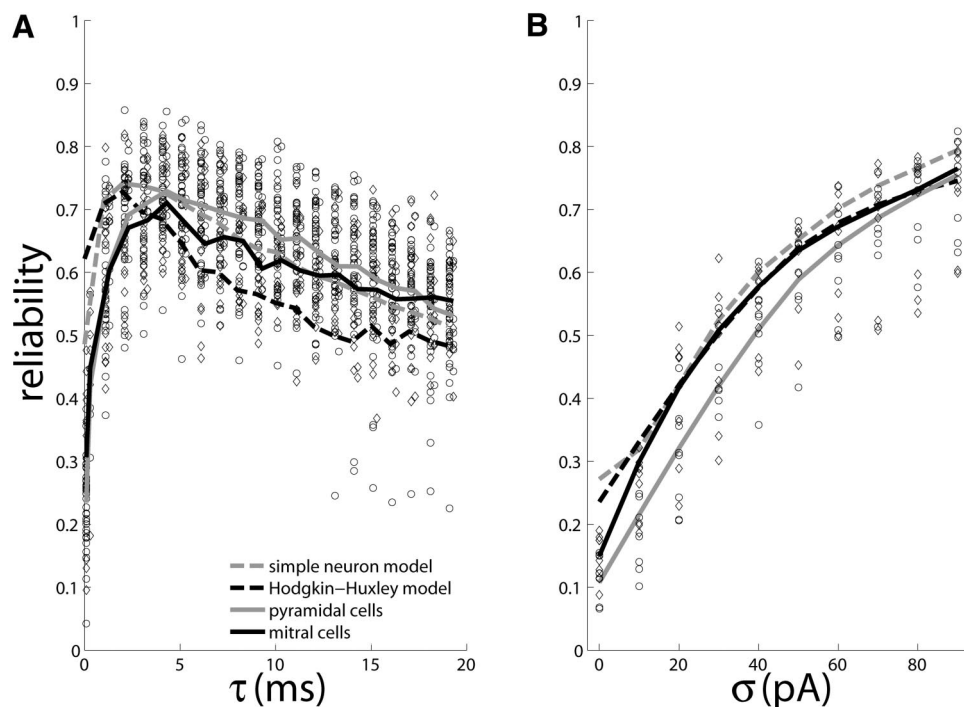


FIG. 3. Optimal time scale for reliability in real and simulated neurons. *A*: on average, reliability is maximal between 2 and 5 ms. The trend of reliability with  $\tau$  is reproducible across experiments (mitral cells:  $\diamond$ ; pyramidal cells:  $\circ$ ). Continuous lines connect average values from all experiments or simulations with each neural type at each  $\tau$  for a tolerance to jitter,  $\delta = 4$  ms. *B*: dependence of reliability on the amplitude of the stimulus fluctuations for  $\tau \approx 3$  ms. Reliability monotonically increases with the fluctuations amplitude,  $\sigma_T$ .

interval,  $T$ , in simulations and experimental data (Fig. 4*B*). In all cases, however, the increase is between 8.4 and 11% $T$ , which is lower than  $T/(2\pi) \approx 16\%T$ . This is not surprising, because the relationship  $\tau_{\text{opt}} \approx T/(2\pi)$  was obtained from Eq. 8 by approximating the phase-response of the neurons with a pure sinusoidal, which is a rather crude approximation for both, mitral cells (Galán et al. 2005) and pyramidal cells (Tsabo et al. 2007) and also for the simulated neurons. We expect that a nonsinusoidal phase-response curve should shift the ratio  $\tau_{\text{opt}}/T$ . Nevertheless, this simple approximation permits us to obtain the correct order of magnitude for  $\tau_{\text{opt}}$  as a function of the mean interspike interval.

#### DISCUSSION

We presented a mathematical theory that predicts a maximum of spike-time reliability for a finite value of the autocorrelation time of aperiodic stimuli and provided experimental evidence of this phenomenon in real neurons. In particular, we showed that the optimal time scale for neural reliability is in the range of 2–5 ms for neurons firing in the beta/gamma frequency band.

Previous studies showed that spike-time reliability in response to fast fluctuations can be enhanced by specific interactions between the membrane potential and the ionic currents

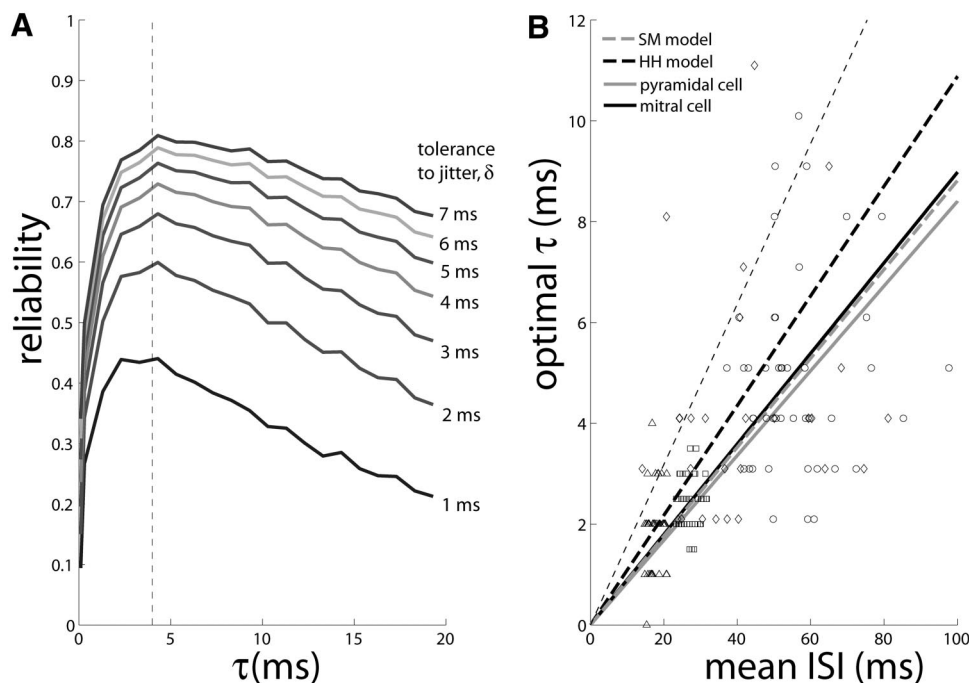


FIG. 4. *A*: optimal time scale for spike-time reliability is independent of our choice of tolerance to jitter,  $\delta$ . Spike-time reliability of pyramidal cells in Fig. 3 has been recalculated for several values of  $\delta$ . As expected, reliability increases overall with increasing tolerance to jitter without affecting the position of peak. Curve for  $\delta = 4$  ms is the one plotted in Fig. 3. *B*: effect of mean interspike interval (ISI or mean period,  $T$ ) on optimal time scale,  $\tau$  for spike-time reliability. As predicted by our theory,  $\tau_{\text{opt}}$  increases with increasing  $T$  (mitral cells:  $\diamond$ , pyramidal cells:  $\circ$ , Hodgkin-Huxley model:  $\triangle$ ; simple neuron model:  $\square$ ). From our data,  $\tau_{\text{opt}} = 8.4\text{--}11\%T$ , which is lower than the value expected if the neurons were perfect oscillators with a pure sinusoidal phase-response curve (thin dashed line).

(Schreiber et al. 2004). This is consistent with our finding that the spike-triggered average of the neuron, which relies on the activation/inactivation of intrinsic currents, determines the function  $R(\tau)$ , for a fixed signal-to-noise ratio in Eq. 5. However, we showed here that even simple models lacking any conductances, like the modified quadratic integrate-and-fire, support high levels of spike-time reliability that is maximal at a finite time scale. In fact, it has been suggested that reliability is a rather general property of neurons that is facilitated by stimuli driving the membrane potential with a large slope at the firing threshold (Hunter et al. 1998; Rodriguez-Molina et al. 2007). In agreement with this argument, here we showed mathematically that the trajectory of the membrane potential not only at threshold, but also in the preceding moments, i.e., the spike-triggered average, determines spike-time reliability as a function of the autocorrelation time of the inputs. Our theory can be intuitively interpreted in the following way: whereas the average number of spikes within a given time window is determined by the steady-state input–output relationship ( $F$ - $I$  curve), the exact times at which the spikes occur rather depend on the input fluctuations that modulate the firing rate. Thus if the stimulus is constant or very slow, the precise timing will be dominated by the major source of fluctuations: nonreproducible background noise. On the other hand, if the stimulus fluctuations are too fast, threshold crossings will occur when stimulus and noise add to pass threshold, so that the neuron will sometimes fire even when at the preceding moment it was far from threshold. As a result, the precise timing of the spikes will be nonreproducible across trials. In the intermediate case, when the stimulus fluctuations are neither too fast nor too slow, the neuron will most likely fire when it is close to threshold only. This results in an optimal time scale for spike-time reliability.

Other authors have studied the effect of intrinsic time constants on spike-time reliability to periodic, multiperiodic, and notch-filtered inputs (Hunter and Milton 2003; Schreiber et al. 2004; Thomas et al. 2003). Here, in contrast, we focused on reliability to aperiodic inputs. The use of these inputs has the following biological motivation: During highly active states, when the neurons are receiving large barrages of mixed synaptic excitation and inhibition, the synaptic currents approach a random process. Some authors refer to these stochastic inputs as “synaptic noise” (Destexhe and Rudolph 2004; Rudolph and Destexhe 2004). In addition, the kinetics of the synapses, the specific details of the morphology, and the electrotonic properties are going to low-pass filter those inputs, introducing a finite autocorrelation time,  $\tau$ . Interestingly, the autocorrelation time that maximizes spike-time reliability,  $\tau_{\text{opt}}$  is within the range expected for integration times of fast synapses plus conduction delays.

In our theory, the only time scale that is directly related to  $\tau_{\text{opt}}$  is the average interspike interval,  $T$ . In agreement with this, the optimal time scale of 2–5 ms reported here is inconsistent with other time scales of the neurons: membrane time constants are typically one order of magnitude slower; subthreshold resonance, when present, is also much slower typically occurring between 5 and 15 Hz (65–200 ms), i.e., one to two orders of magnitude slower than  $\tau_{\text{opt}}$ . In fact, our theory is applicable for neural resonators (like mitral cells) or integrators (like pyramidal cells). Moreover, intrinsic currents in mitral cells and pyramidal cells have

different characteristics resulting in clearly distinguishable voltage traces (Fig. 2). In fact, whereas mitral cells possess type II excitability (Galán et al. 2005) (neural resonators), there is increasing evidence that at least a large fraction of pyramidal cells possess type I excitability (Tateno and Robinson 2006; Tsubo et al. 2007) (neural integrators). Despite these differences the curves of reliability are very similar and closely resemble those of neuron models (Fig. 3).

Although fairly general, our theoretical predictions may not be applicable for all neural types. In particular, our theory may be inaccurate for neurons whose dynamics covers several time scales, because the Volterra expansion used in Eq. 1 would require additional, higher-order terms. For example, our theory may fail in predicting reliability of some intrinsically bursting neurons because they possess clearly separated, but coupled time scales (slow bursts and fast spikes). The estimate that the optimal time-scale for reliability is  $\sim 16\%$  of the period follows from the assumption that the phase-resetting curve of the neuron is dominated by the first term in its Fourier expansion. This assumption is generally true with tonically spiking neurons but not for neurons with complex waveforms like bursts. Despite not being universal, the applicability of our theory is broad enough to be relevant for sensory coding, like in mitral cells, and other cognitive functions, like in pyramidal cells.

In our experiments, the input has been provided as current injections through standard whole cell patch-clamp techniques. The same experiments could be generalized for dynamic-clamp techniques, in which inputs are given as conductance changes. In this case, the driving force of the conductance is likely to increase reliability by quickly amplifying the input at specific points of the spike’s waveform. This would be similar to the effect that we have seen previously with computer models in which we compared current and conductance injection in the case of noise-induced synchronization (Galán et al. 2006b). In other words, our quantification of reliability may underestimate the reliability measured with conductance clamp techniques.

Our findings on spike-time reliability and its optimal time scale are immediately applicable to stochastic synchronization (Galán et al. 2006b), because both phenomena are closely related. In the former case, the timing of the spikes is preserved in repeated trials with the same fluctuating stimulus. In the latter case, identical neurons receiving similar (correlated) fluctuating stimuli trigger synchronous spikes. In particular, barrages of spatially correlated synaptic input currents will synchronize postsynaptic neurons quickly. Analogously, in the case of a single neuron, a reproducible barrage of synaptic pulses will trigger highly reliable responses.

In conclusion, we showed that neurons have a preferred time scale in which the fidelity of the response, quantified as spike-time reliability, is maximal. In real neurons, this time scale is in the range of a few (2–5) milliseconds, suggesting that neurons are adapted to optimally respond to their most natural input signal: fast synaptic currents.

#### GRANTS

This work was supported by National Institute of Health Grants R01-DC-005798 and R01-MH-079504 and National Science Foundation Grant DMS 0513500.

## REFERENCES

- Bryant HL, Segundo JP.** Spike initiation by transmembrane current: a white-noise analysis. *J Physiol* 260: 279–314, 1976.
- Destexhe A, Rudolph M.** Extracting information from the power spectrum of synaptic noise. *J Comput Neurosci* 17: 327–345, 2004.
- Galán RF, Ermentrout GB, Urban NN.** Efficient estimation of phase-resetting curves in real neurons and its significance for neural-network modeling. *Phys Rev Lett* 94: 158101, 2005.
- Galán RF, Ermentrout GB, Urban NN.** Reliability, discriminability and stochastic synchronization of olfactory neurons. *Sensors Actuators B Chem* 116: 168–173, 2006a.
- Galán RF, Fourcaud-Trocmé N, Ermentrout GB, Urban NN.** Correlation-induced synchronization of oscillations in olfactory bulb neurons. *J Neurosci* 26: 3646–3655, 2006b.
- Hodgkin AL, Huxley AF.** A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol* 117: 500–544, 1952.
- Hunter JD, Milton JG.** Amplitude and frequency dependence of spike timing: implications for dynamic regulation. *J Neurophysiol* 90: 387–394, 2003.
- Hunter JD, Milton JG, Thomas PJ, Cowan JD.** Resonance effect for neural spike time reliability. *J Neurophysiol* 80: 1427–1438, 1998.
- Izhikevich EM.** Which model to use for cortical spiking neurons? *IEEE Trans Neural Netw* 15: 1063–1070, 2004.
- Kuramoto Y.** *Chemical Oscillations, Waves, and Turbulence*. Mineola, New York: Dover Publications, 2003.
- Mainen ZF, Sejnowski TJ.** Reliability of spike timing in neocortical neurons. *Science* 268: 1503–1506, 1995.
- Mancilla JG, Lewis TJ, Pinto DJ, Rinzel J, Connors BW.** Synchronization of electrically coupled pairs of inhibitory interneurons in neocortex. *J Neurosci* 27: 2058–2073, 2007.
- Movshon JA.** Reliability of neuronal responses. *Neuron* 27: 412–414, 2000.
- Rieke F, Warland D, de Ruyter van Stevenick R, Bialek W.** *Spikes. Exploring the Neural Code*. Cambridge, MA: MIT Press, 1997.
- Rodriguez-Molina VM, Aertsen A, Heck DH.** Spike timing and reliability in cortical pyramidal neurons: effects of EPSC kinetics, input synchronization and background noise on spike timing. *PLoS ONE* 2: e319, 2007.
- Rudolph M, Destexhe A.** Inferring network activity from synaptic noise. *J Physiol Paris* 98: 452–466, 2004.
- Schreiber S, Fellous JM, Tiesinga P, Sejnowski TJ.** Influence of ionic conductances on spike timing reliability of cortical neurons for suprathreshold rhythmic inputs. *J Neurophysiol* 91: 194–205, 2004.
- Tateno T, Robinson HP.** Rate coding and spike-time variability in cortical neurons with two types of threshold dynamics. *J Neurophysiol* 95: 2650–2663, 2006.
- Tateno T, Robinson HP.** Phase resetting curves and oscillatory stability in interneurons of rat somatosensory cortex. *Biophys J* 92: 683–695, 2007.
- Teramae J, Tanaka D.** Robustness of the noise-induced phase synchronization in a general class of limit cycle oscillators. *Phys Rev Lett* 93: 204103, 2004.
- Thomas PJ, Tiesinga P, Fellous JM, Sejnowski TJ.** Reliability and bifurcation in neurons driven by multiple sinusoids. *Neurocomp* 52–54: 955–961, 2003.
- Tsubo Y, Takada M, Reyes AD, Fukai T.** Layer and frequency dependencies of phase response properties of pyramidal neurons in rat motor cortex. *Eur J Neurosci* 25: 3429–3441, 2007.
- Urban NN, Sakmann B.** Reciprocal intraglomerular excitation and intra- and interglomerular lateral inhibition between mouse olfactory bulb mitral cells. *J Physiol* 542: 355–367, 2002.