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Optimal time scale for spike-time reliability:

Theory, simulations and experiments

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Abstract

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 have investigated how spike-time reliability depends on the time scale of fluctuations of the input stimuli in real neurons (mitral cells in the olfactory bulb and pyramidal cells in the neocortex) as well as in neuron models (integrate-and-fire and Hodgkin-Huxley) with intrinsic noise. In all cases we found that for firing frequencies in the beta/gamma range, spike reliability is maximal when the input includes fluctuations on the time scale of a few milliseconds (2–5 ms), coinciding with the time scale of fast synapses, and decreases substantially for faster and slower inputs. In addition, we show mathematically that the existence of an optimal time scale for spike-time reliability is a general feature of neurons. Finally, we comment how these findings relate to the mechanisms that cause 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) 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 rate at which stimuli fluctuate. 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 non-reproducible 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.

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 olfactory bulb and coronal slices from the somatosensory 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 μ M, CNQX 10 μ M, bicuculline 10 μ M). 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 τ and then rescaling to the desired variance, so that the amplitude of the fluctuations was the same for all τ . Each stimulus was presented 6 times to study the reliability of the response. The firing rate was 30 ± 20 Hz (mean $\pm$ s.d.) in mitral cells and 18 ± 8 Hz in pyramidal cells. Experimental estimation of the background noise level was performed by measuring the standard deviation 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 pair-wise 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. Then, these strings were convolved with a square function of width 2δ , ($\delta = 4$ ms, in Fig. 3) and unitary amplitude. The pair-wise correlation was calculated as the dot product of these signals 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 the measure of synchrony previously used by the authors (Galán et al., 2006a; Galán et al., 2006b).

Simulations

The integrate-and-fire model used a simple equation for an arbitrary membrane potential: $d\psi/dt = -\alpha\psi + \beta I$, where $\alpha = 0.5$ and $\beta = 0.22$ (time in ms; current in pA; integration time step $dt = 0.1$ ms; voltage threshold: $\psi = 0.4$; voltage reset value: $\psi = -10$). The current I consisted of 60% signal and 40% background noise. We also used the conductance model by Hodgkin and Huxley (Hodgkin and Huxley, 1990) (bias current: 6 pA; fluctuations amplitude: 6 pA; background noise amplitude: 2 pA; membrane surface: 1000 μm^2) and the same analysis applied to experimental data.

Results

Several studies have emphasized the importance of fast input fluctuations 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 stimulus fluctuations 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 (stochastic) synchronization (Galán et al., 2006b; Galán et al., 2006a; Galán et al., 2007) - you should cite some others here - perhaps the teramae paper? : In the former, the timing

of spikes is preserved across repeated trials in which the same fluctuating stimulus (frozen noise) is delivered to a single neuron. In the later, a pattern of synchronous spikes is generated across different neurons receiving similar fluctuating inputs. Thus, the study of reliability can be reduced to the study of two identical neurons receiving identical fluctuating inputs in the presence of background noise. Let $y_i(t)$ be the voltage traces of these two neurons (outputs) and $x_i(t)$ the respective inputs received ($i=1,2$). The relationship between the inputs and the outputs is given to a first order approximation by (see e.g., (Rieke et al., 1997)):

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

where the convolution kernel, $K(s)$ is the spike-triggered average of the neuron. As in the experiments and simulations described below, the inputs $x_i(t)$ consist of two components: a fluctuating signal common to both neurons $I(t)$ with autocorrelation time, τ , plus uncorrelated white noise, $\eta_i(t)$, i.e.,

$$x_i(t) = I(t) + \eta_i(t),$$

with

$$\begin{aligned} \langle \eta_1(t) \eta_2(t-s) \rangle &= 0, \quad \langle \eta_i(t) \eta_i(t-s) \rangle = \sigma_\eta^2 \delta(t-s), \\ \langle I(t) I(t-s) \rangle &= \sigma_I^2 \exp(-|s|/\tau). \end{aligned} \quad (1)$$

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

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

Then using (1), we calculate

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

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

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

Thus, $R=R(\tau)$ becomes:

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

Note that in the absence of background noise, i.e. if $\sigma_\eta=0$, then $R=1$ for any τ , whereas in the absence of a fluctuating signal, i.e. if $\sigma_I=0$, then $R=0$ for any τ . Plotting R vs. τ clearly reveals a maximum (Fig. 1a) around 4 ms. This optimal time scale for reliability is much lower than the average inter-spike interval (Fig. 1a, dashed lines), which is 25 ms for the parameters used ($\sigma_I=4$, $\sigma_\eta=1$, $K(s)$ in Fig. 1b). Interestingly, the existence of a maximum does not rely on the

fine details of the spike-triggered average or the parameters chosen, suggesting that this phenomenon is a general property of neurons. In fact, it will be characteristic of any device with a resetting threshold, because their kernel and therefore, their function $Q(u)$ will qualitatively resemble those of real and simulated neurons.

Simulations and Experiments

To test our theory, we have designed the following experiments with simulated and real neurons. We repetitively presented “frozen noise” stimuli (see *Methods*) that consisted of a constant current (such that the neurons fired regularly in the gamma band) plus aperiodic fluctuations $I(t)$ generated by passing white noise through different low pass filters to generate signals with different autocorrelation times, τ (the shorter τ is, the faster are the fluctuations). We performed the experiments (Fig. 2) on mitral cells ($n=4$) of the olfactory bulb and on neocortical pyramidal cells ($n=4$) of mice obtaining similar results: on average, spike-time reliability is maximal for $\tau \approx 3$ ms (Fig. 3a). For this time scale, reliability monotonically increased with increasing amplitude of the fluctuations (Fig. 3b). Interestingly, already 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 Hodgkin-Huxley conductance model (Hodgkin and Huxley, 1990) and even by a simple integrate-and-fire model 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 (see *Methods*) detects spikes that are preserved across trials within a time bin of 2δ ms, i.e. the tolerance to “spike jitter” is $\pm\delta$ ms. In Fig. 4 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. 4. However, the values of reliability should increase overall as we tolerate larger spike jitter across repetitions. This can also be observed in Fig. 4.

Discussion

Although reliable firing to fast fluctuating stimuli was first described some thirty years ago (Bryant and Segundo, 1976; Mainen and Sejnowski, 1995), the mechanisms underlying this phenomenon still are not well understood. Some studies have suggested that the enhanced reliability in response to fast fluctuations requires specific interactions between the membrane potential and the ionic currents (Schreiber et al., 2004). In contrast, based on computational studies and electrophysiological experiments, we have recently hypothesized (Galán et al., 2006a) that reliability is a rather general property of devices with a resetting threshold, like neurons. This hypothesis was based on the following intuition: In devices with a resetting threshold, the average number of threshold crossings (and thus spikes) within a given time window is determined by the steady state input (F-I curve). However, 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 non-reproducible background noise. On the other hand, if the stimulus fluctuations are too fast, threshold crossings will occur only when stimulus and noise (whose power spectrum is roughly constant and therefore contains arbitrarily fast fluctuations) add to pass threshold, so that the neuron will sometimes fire even when the input current is far from threshold. As a result, the precise timing of the spikes will be non-reproducible 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, where a small fluctuation of the stimulus or the noise will be sufficient to make the neuron fire. In this paper, we provide a mathematical proof of this intuitive argument.

Our hypothesis that reliability is a general property of devices with a resetting threshold is also supported by the fact that the optimal time scale of 2-5 ms reported here is inconsistent with

several intrinsic time constants of the neurons: membrane time constants are typically one order of magnitude slower. In mitral cells subthreshold resonance is also much slower occurring between 5 and 15 Hz (RFG et al., unpublished data), whereas pyramidal cells lack a preferred input frequency. 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 pyramidal cells possess type I excitability (Tateno and Robinson, 2006) (neural integrators). Despite these differences the curves of reliability are very similar. [What does determine the time scale of the optimum]

Our findings on spike-time reliability and its optimal time scale are immediately applicable to stochastic synchronization (Galán et al., 2006b), since 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 later 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 have shown that neurons, as devices with a resetting threshold, 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 ms) milliseconds suggesting that neurons are adapted to optimally respond to their most natural input signal: fast synaptic currents.

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Figure 1.

Prediction of the mathematical theory. (a) Spike-time reliability, R as a function of the time scale, τ of the stimulus fluctuations. For a firing rate in the gamma band (40 Hz), the theory predicts a maximum value of reliability around $\tau=4$ ms, which is much smaller than the average inter-spike interval (25 ms, dashed line). (b) Spike-triggered average, $K(s)$ of the neuron used in the simulations. Qualitatively, this shape is prototypical for real and simulated neurons

Figure 2.

Maximal reliability in real cells. Aperiodic frozen currents (top traces; $\tau = 3$ ms) are injected six times into a mitral cell (a) and into a neocortical pyramidal cell (b). In both neurons, virtually all spikes appear in more than one trial and most ($\sim 85\%$) are preserved across all trials.

Figure 3.

Optimal time scale for reliability in real and simulated neurons. (a) On average, reliability (see *Methods*) is maximal between 2 and 5 ms, where ca. 80 % of the spikes are preserved across trials. Lines connect the median of the values (mitral cells: circles; pyramidal cells: diamonds) obtained in all experiments at each τ , for a tolerance to jitter, $\delta = 4$ ms. (b) Dependence of reliability on the amplitude of the stimulus fluctuations for $\tau = 3$ ms. Reliability monotonically increases with the fluctuations amplitude, σ .

Figure 4.

The optimal time scale for spike-time reliability is independent of our choice of tolerance to jitter, δ . The spike-time reliability of the mitral cells in Fig. 3 has been recalculated for several values of δ . As expected, reliability increases overall with increasing tolerance to jitter. However, the peak of reliability remains unchanged at $\tau = 3.3$ ms. The curve for $\delta = 4$ ms is the one plotted in Fig. 3.