Two Distinct Mechanisms Shape the Reliability of Neural Responses

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Abstract

Despite intrinsic noise sources, neurons can generate action potentials with remarkable reliability. This reliability is influenced by the characteristics of sensory or synaptic inputs, such as stimulus frequency. Here we use conductance-based models to study the frequency dependence of reliability in terms of the underlying single-cell properties. We are lead to distinguish a mean-driven firing regime, where the stimulus mean is sufficient to elicit continuous firing and a fluctuation-driven firing regime, where spikes are generated by transient stimulus fluctuations. In the mean-driven regime, the stimulus frequency that induces maximum reliability coincides with the firing-rate of the cell, whereas in the fluctuation-driven regime, it is determined by the resonance properties of the subthreshold membrane potential. When the stimulus frequency does not match the optimal frequency, the two firing regimes exhibit different "symptoms" of decreased reliability: reduced spike-time precision and reduced spike probability, respectively. As a signature of stochastic resonance, reliable spike generation in the fluctuation-driven regime can benefit from intermediate amounts of noise that boost spike probability without significantly impairing spike-time precision. Our analysis supports the view that neurons are endowed with selection mechanisms that allow only certain stimulus frequencies to induce reliable spiking. By modulating the intrinsic cell properties, hence, the nervous system can tune individual neurons to pick out specific input frequency bands with enhanced spike precision or spike probability.

Keywords: subthreshold resonance, spike precision, cell-intrinsic noise, frequency preference, stochastic resonance
1 Introduction

The responses of a neuron to a given stimulus largely depend on the cell’s mean depolarization level. A time-dependent stimulus may therefore either (1) elicit no spikes at all, (2) generate occasional spikes triggered by transient stimulus elevations, or (3) generate a continuous stream of spikes. In the first case, the cell depolarization always remains below threshold. In the second case, the average depolarization is near but still below threshold, so that large stimulus fluctuations can induce firing from time to time. In the third case, the average depolarization is sufficiently high to maintain the cell above threshold.

From a dynamical-systems point of view, it makes a difference whether the mean value of the input signal (for example, an electric current) is below threshold and spikes are only driven by stimulus fluctuations (we term this the fluctuation-driven regime), or whether the neuron is in a continuous firing mode even in the absence of stimulus fluctuations (here termed the mean-driven regime). Below threshold, there is typically a single global attractor corresponding to the unique subthreshold resting state. For constant input, this state is a fixed point. Above threshold, the fixed point becomes unstable, and all trajectories converge to a stable limit cycle, representing continuous firing. Although spikes can be generated in both cases, the different attractor structures lead to distinct firing characteristics. In this study, we therefore investigate the influence of the mean depolarization on spike reliability. To that end, we systematically vary the stimulus mean, traversing from subthreshold to suprathreshold values, and disclose the mechanisms that shape reliability.

Because of their abundance in the nervous system (Buzsaki and Draguhn, 2004), we use oscillatory signals as stimuli. Rhythmic inputs result from periodic sensory stimulation, correlated activity of presynaptic neurons, such as pacemaker cells (see for example Marder and Calabrese (1996)), or collective network oscillations identifiable as large-scale field potentials in EEG (see for example Katz and Cracco (1971); Buzsaki (2006)). Here, we use sinusoidal stimuli and denote by “stimulus” the electric current arriving at the spike-initiation zone. This effective stimulus represents the spike-triggering action of external inputs after synaptic, dendritic and somatic filtering. Since information can be carried by the timing of individual action potentials (Rieke et al., 1997; Reinagel and Reid, 2000) and since synaptic plasticity depends on spike-time precision (Bi and Poo, 2001), we seek to understand the mechanisms that allow neurons to optimize spike-time precision and/or spike probability. Note that throughout this study, the term reliability summarizes both, spike probability and spike-time precision. This definition differs from that used by Tiesinga et al. (2008) and other authors who identify spike reliability with spike probability alone. In our view, however, imprecise spikes (and not only missing spikes) also diminish reliability – hence the choice of terms.

The reliability of single neurons is challenged by the presence of external and intrinsic noise sources, such as the stochastic opening of ionic channels (Schneidman et al., 1998). Yet, spikes can be surprisingly reproducible to repeated stimulus presentations, see for example (Mainen and Sejnowski, 1995; Bair, 1999; Bryant and Segundo, 1976). Certain stimuli, however, are far more efficient than others in eliciting reliable responses (Hunter et al., 1998; Ritt, 2003; Rokem et al., 2006; Galán et al., 2007), and several stimulus attributes, such as stimulus mean, variance, and frequency content, have been shown to influence neural reliability (Hunter and Milton, 2003; Gutkin et al., 2003). However, the detailed dependence of reliability on stimulus properties has
primarily been addressed in the mean-driven firing regime. In this regime, a resonance mechanism between the limit-cycle frequency \( f_{DC} \) and the stimulus frequency significantly enhances reliability when the two frequencies match (Hunter et al., 1998; Hunter and Milton, 2003; Schreiber et al., 2004b).

Neuronal signal transmission often occurs in the fluctuation-driven firing regime. Experimental data indicate that in this case, too, neuronal reliability is frequency-dependent (Fellous et al., 2001; Houweling et al., 2001; Haas and White, 2002). Here, using theoretical and computational techniques, we characterize the fluctuation-driven regime by deducing a relationship between subthreshold membrane properties and the input frequency inducing the most reliable spike timing. We find that the nonlinear behavior of subthreshold neural dynamics needs to be taken into account to predict the optimal input frequency. Our results show that the mechanisms governing the fluctuation-driven regime are distinct from those of the mean-driven regime. They emerge from the properties of the stable fixed point, as opposed to those of the firing limit cycle. It therefore matters whether a stimulus has a mean value below or above firing threshold. In particular, the two firing regimes induce different characteristic “symptoms” of unreliability. Specifically, reliability in response to rhythmic stimulation in the mean-driven regime is limited by decreased spike-time precision, while reliability in the fluctuation-driven regime is predominantly bounded by reduced spike probability. This implies that input noise has markedly different effects on output reliability in these two regimes.

### 2 Materials and Methods

#### 2.1 Conductance-based model cells

Single-compartment conductance-based model neurons were implemented in NEURON (Hines, 1993). The neurons contained fast sodium channels (\( N_a \)), delayed-rectifier potassium channels (\( K_{dr} \)), leak channels (\( L \)), persistent sodium channels (\( N_aP \)), and muscarinic potassium channels (\( M \)). The dynamic equations and values of kinetic parameters of all conductance types and reversal potentials were taken from a model of a cortical pyramidal cell (Golomb and Amitai, 1997), with the exception of the reversal potential of the leak channels and the \( M \) conductance. The leak reversal was set to \(-80 \text{ mV}\). The muscarinic potassium conductance \( M \) was modelled as a slow noninactivating potassium channel with Hodgkin-Huxley style kinetics (Yamada et al., 1989; Gutfreund et al., 1995):

\[
\begin{align*}
I_M &= g_M n (V - V_K) \\
\frac{dn}{dt} &= \frac{(n_\infty - n)}{\tau_n} \\
n_\infty &= \left\{ 1 + \exp\left[ -(V - \theta_n) / \sigma_n \right] \right\}^{-1} \\
\tau_n &= (1000/3.3) T_{adj}^{-1} \left\{ \exp\left[ (V - \theta_{\tau_n}) / \sigma_{1\tau_n} \right] + \exp\left[ -(V - \theta_{\tau_n}) / \sigma_{2\tau_n} \right] \right\}^{-1} \\
T_{adj} &= 3.0(T - 22\text{°C})/10\text{°C},
\end{align*}
\]

where \( g_M \) is the peak muscarinic conductance, \( V_K = -90 \text{ mV} \), \( \theta_n = -35 \text{ mV} \), \( \sigma_n = 10 \text{ mV} \), \( \theta_{\tau_n} = -35 \text{ mV} \), \( \sigma_{1\tau_n} = 40 \text{ mV} \), \( \sigma_{2\tau_n} = 20 \text{ mV} \), and \( T = 36\text{°C} \). The muscarinic potassium conductance has slow dynamics, opposes deviations from the steady-state voltage, and is activated at more depolarized levels of the membrane.
potential. It induces a subthreshold resonance of the membrane potential that becomes increasingly pronounced as the mean depolarization approaches threshold. The model cell presented in the right column of Fig. 5 contains an additional $H$ conductance, which also has slow dynamics and opposes voltage deviations from the steady state. Due to its activation range at lower voltages, it contributes to a subthreshold resonance at less depolarized levels.

The model equations for the $H$ conductance are:

$$I_H = \bar{g}_H(0.8h_1 + 0.2h_2)(V - V_H)$$

$$\frac{dh_1}{dt} = (h_\infty - h_1)/\tau_1$$

$$\frac{dh_2}{dt} = (h_\infty - h_2)/\tau_2$$

$$h_\infty = \{1 + \exp[(V + \theta_H)/\gamma]\}^{-1},$$

where $\theta_H = 82$ mV, $\tau_1 = 40$ ms, and $\tau_2 = 300$ ms. The equations are based on Spain et al. (1987), see also (Bernander et al., 1994; Hutcheon et al., 1996).

Kinetic parameters of all conductances used were set to 36°C. The value of the membrane capacitance was $C_m = 1 \mu F/cm^2$. Peak conductances for individual model neurons were chosen to obtain resonant or nonresonant subthreshold membrane impedances. The peak sodium and delayed rectifier potassium conductances in all model cells were $\bar{g}_{Na} = 24 \text{mS/cm}^2$, $\bar{g}_{Kdr} = 3 \text{mS/cm}^2$. The other peak conductances (leak $\bar{g}_L$, persistent sodium $\bar{g}_{NaP}$, muscarinic $\bar{g}_M$, and $H \bar{g}_H$) are stated in Table 1.

Morris-Lecar model neurons were implemented in their two-dimensional reduction. Using the same nomenclature as Rinzel and Ermentrout (1998), model parameters were: $C_m = 1 \mu F/cm^2$, $V_1 = -1 \text{mV}$, $V_2 = 15 \text{mV}$, $\bar{g}_{Ca} = 1.1 \text{mS/cm}^2$, $\bar{g}_{K} = 2.0 \text{mS/cm}^2$, $\bar{g}_L = 0.5 \text{mS/cm}^2$, $V_{Ca} = 100 \text{mV}$, $V_K = -70 \text{mV}$, and $V_L = -50 \text{mV}$. Neurons with type I and type II dynamics differed in the following three parameters: $V_3 = 10 \text{mV}$, $V_4 = 14 \text{mV}$, $\phi = 1/3$ (type I), and $V_3 = 0 \text{mV}$, $V_4 = 30 \text{mV}$, $\phi = 1/5$ (type II). Although the Morris-Lecar system has only two dimensions, it is still highly nonlinear and in general, exact analytical solutions are not possible. The data for spike timing reliability are therefore obtained numerically. For subthreshold values of $I_{DC}$, however, linearization of the system allows analytical calculation of the subthreshold resonance frequency.

### 2.2 Neural reliability

#### 2.2.1 Stimuli

Each neuron was first stimulated by a constant input current $I_{DC}$. Depending on whether $I_{DC}$ was below or above threshold, the cell was classified to be in the fluctuation-driven regime, or in the mean-driven regime. Next, a small oscillatory input of amplitude $A$ and frequency $f$ was added to $I_{DC}$ (see Fig. 1A). In order to test the reliability of neural responses to different amplitudes and frequencies, intrinsic noise was modelled as an additional stochastic input current $\eta(t)$ obtained from a Gaussian distribution filtered with an alpha function of time constant $\tau = 3$ ms (noise SD=0.02 nA, except Figs. 2, 7 and 9). Hence, the total input current
driving the cell is

\[ \dot{I}(t) = I_{DC} + A \sin(2\pi ft) + \eta(t). \]

In the fluctuation-driven regime, \( I_{DC} \) alone is not sufficient to induce firing. Spike generation will thus occur either when the amplitude \( A \) is large enough to drive the cell across threshold, or when \( I_{DC} + A \) is still below threshold, but the noise \( \eta(t) \) provides the necessary transient excitation. In principle, \( I_{DC} \) represents all time-independent contributions, so that constant modulatory synaptic input from other cells can also be viewed as part of \( I_{DC} \). The frequency dependence of reliability at fixed values of \( I_{DC} \) was characterized by analyzing the responses to a set of sinusoidal stimuli of different frequencies \( f \) (1 to 80 Hz in increments of 1 Hz) and four different amplitudes \( A \).

Each individual stimulus was presented \( N = 20 \) times (\( N = 60 \) for the noise study of Sect. 3.4). Different trials were generated by producing different realizations of the noise \( \eta(t) \), other parameters remaining fixed. Thus \( N \) different responses were obtained whose trial-to-trial variability was caused by the intrinsic noise \( \eta \). Reliability, as well as spike-time precision and probability were calculated based on spiking responses over a two-second window, discarding the initial transient (500 ms) following stimulus onset. Spike times were determined as the time when the voltage crossed \(-20 \) mV from below.

2.2.2 Definition of neural reliability

Neural reliability was quantified by a correlation-based measure that captures impairment in both spike-timing precision and spike probability; for a detailed discussion see Schreiber et al. (2003). Spike trains obtained from \( N \) repeated presentations of a stimulus were smoothed with a Gaussian filter of width \( 2\sigma \), and then pairwise correlated. The normalized value of the correlation was averaged over all pairs. The correlation measure, \( R_{corr} \), based on the smoothed spike trains, \( \vec{s}_i \) (\( i = 1, ..., N \)), is given by

\[ R_{corr} = \frac{2}{N(N-1)} \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} \frac{\vec{s}_i \cdot \vec{s}_j}{||\vec{s}_i|| ||\vec{s}_j||}. \]

The normalization factor guarantees that \( R_{corr} \in [0; 1] \). \( R_{corr} = 1 \) indicates perfect reliability and \( R_{corr} = 0 \) lowest. For all model cell studies, \( \sigma = 1.8 \) ms, chosen to allow for a clear illustration of the different reliable regions (Fig. 3E), without saturating at too low or too high values. Also, \( \sigma = 1.8 \) ms is on the order of the spike-timing jitter observed (Fig. 8A). The qualitative observations discussed here, however, hold for a broad range of sigma (also see Supplemental Fig. 2). Error bars were calculated as the standard error of the mean (SEM) of reliability estimated for at least three independent response subsets with an identical number of trials (\( N = 20 \)).

The stimulus frequency eliciting most reliable responses \( f_{reliab} \) was estimated from the position of the tip of reliable regions in the frequency-amplitude space (see Figs. 3E and 4E). In the mean-driven regime, where model cells fired at all stimulus amplitudes, the most reliable frequency was estimated at \( A = 0.03 \) nA. In the fluctuation-driven regime, however, cells do not fire at small amplitudes. Therefore, the amplitude of the sinusoidal stimulus that corresponds to the tip of the reliable region depended on \( I_{DC} \), as larger amplitudes
are required to cause a cell to fire from rest than from just below threshold. Hence, the amplitude of the sinusoidal input was adapted with $I_{\text{DC}}$, as 10 to 120% (in steps of 10) of the difference between $I_{\text{DC}}$ and the current threshold $I_{\text{th}}$. The most reliable frequency was determined for the smallest stimulus amplitude, where the ratio of reliability and corresponding SEM of reliability exceeded 3.

$I_{\text{th}}$ was estimated by the smallest value of a step current initiated at rest that was able to elicit continuous spiking (as the presentation of sine stimuli was also accompanied with a step in the mean current, see for example Fig. 3A). $I_{\text{th}} = 0.55\, \text{nA}$ for both resonant cells and $I_{\text{th}} = 0.33\, \text{nA}$ for the nonresonant cell in Fig. 5. Note, for completeness, that resonant model cells exhibited a bistable range of currents, where for constant stimuli, depending on initial conditions, the cell can settle on a steady-state voltage or on a spiking limit cycle. This range was $0.53-0.64\, \text{nA}$ and $0.52-0.63\, \text{nA}$ for the resonant (type II) cells in Fig. 5 (middle and right column, respectively).

### 2.2.3 Definition of spike-time precision and spike probability

To quantify spike-time precision and spike probability, individual spike events were identified on the basis of the peri-stimulus time histogram (PSTH) obtained from the trial average of the $N$ responses. Maxima in the PSTH were used to define spike events. To this end, the PSTH was smoothed by a Gaussian filter ($\sigma=1.8\, \text{ms}$, as for the reliability estimate). Then the PSTH was divided into adjacent time windows defining spike events, such that the window borders were located at local minima of the PSTH, while local maxima were found within individual time windows (Fig. 1).

As the neural responses were approximately periodic (see, for example, Figs. 1C, 3C/D, and 4C/D), it was our aim to create windows of approximately equal size $T$. Therefore, given the left border, $t_\ell$, of an event window, the right border was defined as the time of the lowest PSTH value assumed within the time interval $[t_\ell + 0.9T; t_\ell + 1.3T]$. For stimuli of suprathreshold mean extended time intervals were used: $[t_\ell + 0.7T; t_\ell + 1.3T]$ for $f \leq 45\, \text{Hz}$ and $[t_\ell + 0.6T; t_\ell + 1.1T]$ for $f > 45\, \text{Hz}$. Even in the absence of noise, spikes obtained with sinusoidal stimulation are not always regularly spaced. An example are slow stimuli that elicit two spikes per cycle (2:1 mode locking), where the distance between the spikes caused by the same stimulus elevation is smaller than the distance between spikes caused by different stimulus elevations. To account for these deterministic irregularities, we allow for some flexibility in the position of the right border. The adequacy of our event-window definition was also checked manually.

In order to evaluate precision and probability of firing events, the window size $T$ was set to the period of the stimulus in the fluctuation-driven regime, and to the period corresponding to the firing rate $f_{\text{DC}}$ in response to the stimulus mean in the mean-driven regime. This choice was made, because we aim at a spike-event-related analysis of precision and probability: In the fluctuation-driven regime the number of firing events roughly scales with the stimulus frequency, as spikes are caused by stimulus elevations. In the mean-driven regime, the frequency of firing events is largely determined by the average firing rate $f_{\text{DC}}$ and does not vary strongly
with the stimulus frequency. The alternatives, either a stimulus-frequency-related or a constant window size \( T \) for evaluation of both firing regimes would not reflect spike-event-related precision and probability.

Spike jitter was quantified as the SD of spike times within one event window and averaged across all event windows. If, rarely, in the same trial two spikes occurred within one event window, only the spike closest to the mean of all spike times within the event window was considered. Spike precision was defined as the inverse of the averaged jitter. Spike probability was quantified as the percentage of trials with at least one spike within the event window. Probability values presented in the paper correspond to the average across event windows.

### 2.3 Estimation of impedance curves

For computational efficiency, frequency-dependent impedance curves in the subthreshold regime were estimated through the injection of a ZAP current (Impedance(Z) Amplitude Profile) (Gimbarzevsky et al., 1984; Puil et al., 1986):

\[
I_{ZAP}(t) = I_{DC} + \sin[2\pi f(t)t], \quad \text{with} \quad f(t) = f_m t / 2T_0.
\]

As for the analysis of spike reliability, several levels of depolarization were investigated by fixing the constant holding current \( I_{DC} \) to different values.

The time-dependent frequency \( f(t) \) of the ZAP current was increased from 0 Hz to the maximum frequency \( f_m = 60 \) Hz. The overall duration of the ZAP stimulus was \( T_0 = 100 \) seconds, so that the ZAP current varied slowly enough to obtain a similar precision of the impedance estimate as upon injecting sinusoidal currents, as verified in test simulations. The frequency-dependent impedance was obtained as the Fourier transform of the time-dependent response to a ZAP input divided by the Fourier transform of the ZAP current,

\[
Z(f) = \frac{\text{FFT}[V_{ZAP}(t)]}{\text{FFT}[I_{ZAP}(t)]} \quad \text{(Gimbarzevsky et al., 1984; Puil et al., 1986, 1988).}
\]

The position of the peak in the upper response envelope of large-amplitude ZAP stimulation, \( f_{upp} \), was approximated by the position of the global maximum of the ZAP response.

### 3 Results

To study the mean- and fluctuation-driven firing regimes under well defined conditions, we use a computational approach. Numerical simulations allow us complete freedom to precisely and systematically modify even fine details of the deterministic neuronal dynamics and noise characteristics. Neither experimental studies nor purely analytical investigations provide this level of control.

Upon stimulation with a constant current \( I_{DC} \) and in the absence of noise, the model cells either generate no spikes at all or they fire regularly (Fig. 2). In the first case, the cells are in a subthreshold regime, though they may produce spikes in the presence of noise or additional time-dependent stimulation (fluctuation-driven firing).

Fig. 2 goes here.
3.1 Reliability in the mean-driven regime

We first illustrate the firing-rate resonance effect in the mean-driven regime described previously (Hunter et al., 1998; Schreiber et al., 2004b) with conductance-based cortical model neurons that include a sodium, delayed rectifier potassium, leak, persistent sodium, and muscarinic potassium conductance. Suprathreshold stimuli of given amplitude, mean and noise level elicit spikes that range between markedly reliable or unreliable, depending on the dominant frequency of the stimulus. (Fig. 3A–D).

For systematic analysis each model cell was stimulated with a set of sine waves of different frequencies and amplitudes, and fixed suprathreshold mean, to which a stochastic input was added. For each sine-wave stimulus, reliability values were obtained from responses to 20 stimulations, each corresponding to a different realization of the noise. As a function of stimulus frequency and amplitude, several regions of increased reliability are apparent (Fig. 3E). The most reliable spike trains were observed for stimulus frequencies close to 30 Hz. However, 30 Hz is also the firing rate $f_{DC}$ of the cell when stimulated by a constant current equal to the stimulus mean $I_{DC}$. We thus speak of a firing-rate resonance. In this region spikes are generated in a 1:1 phase locking mode, i.e., exactly one spike is fired per stimulus cycle.

The mean-driven regime is characterized by the existence of several stimulus regions of increased reliability at multiples of $f_{DC}$, where one spike is elicited every second (1:2 phase locking, first harmonic) or every third (1:3 phase locking, second harmonic) stimulus cycle. For example, a 1:2 phase-locking mode appears at input frequencies of $\approx 60$ Hz. In addition, a 2:1 phase-locking mode can be obtained for stimulus frequencies around $f_{DC}/2$ (first subharmonic). Here, two spikes are generated per stimulus cycle (see Fig. 3E, reliable region at $\approx 14$ Hz). To emphasize the analogy with resonance effects in classical mechanics, the regions of increased reliability are called Arnold tongues (Coombes and Bressloff, 1999; Tiesinga, 2002). The width of the tongues and their peak reliability value strongly depend on density, conductance and kinetics of the ionic channels in the cell membrane (Schreiber et al., 2004b).

Larger amplitudes of the time-dependent stimulus component yield higher reliability values. Consequently, the reliable regions broaden with stimulus amplitude. Note that the firing-rate resonance effect is only useful to predict the optimal input frequency for small and medium stimulus amplitudes. For larger amplitudes, nonlinear effects modify the shape of the reliable regions.

3.2 Reliability in the fluctuation-driven regime

In the absence of noise, neurons do not spike in response to the subthreshold current $I_{DC}$. Therefore, the firing-rate resonance effect cannot explain the frequency preference of neural reliability. However, also this firing regime exhibited a frequency preference.
In Fig. 4E only a single Arnold tongue appears in the fluctuation-driven regime. The most reliable input frequencies were found at around 17 Hz. As in the mean-driven regime, the reliable frequency range widened with increasing amplitude. At the most reliable frequency, spikes were again 1:1 mode-locked to the stimulus. To the left and right of this frequency, reliability decreased because more and more spikes were missing from the 1:1 mode-locking pattern (Fig. 4C). At large stimulus amplitudes, responses to frequencies smaller than the best frequency also showed a number of additional spikes (see doublets in Fig. 4C).

3.2.1 Membrane impedance and reliability

The reliability profile is reminiscent of the subthreshold membrane impedance obtained for the same \( I_{\text{DC}} \) value (Fig. 4F). The impedance characterizes how well—in terms of its voltage response—a neuron responds to subthreshold inputs of different frequencies (Hutcheon and Yarom, 2000). Usually, cells are classified as resonant or nonresonant, depending on whether the membrane impedance peaks at non-zero frequencies (resonant) or at 0 Hz (nonresonant). Resonance at threshold determines whether the neuron shows type I or type II firing dynamics, i.e., whether the limit cycle is born through a saddle-node or a Hopf bifurcation (Rinzel and Ermentrout, 1998; Izhikevich, 2000).

We performed a systematic analysis of impedance and reliability in resonant and nonresonant cells using conductance-based model neurons. Both impedance and reliability were estimated over a broad range of \( I_{\text{DC}} \) values. This is important, because the frequency-dependence of the membrane impedance can change with the mean level of depolarization in a cell-type specific manner, influenced by the composition of ionic conductances and their voltage dependence. Here, we discuss in detail three examples with a different profile of subthreshold resonance across depolarization: (1) a cell that is nonresonant across all subthreshold levels of depolarization, (2) a cell that is nonresonant at rest but exhibits resonance at more depolarized voltage levels, and (3) a cell that is resonant for hyperpolarized as well as depolarized membrane potentials (Fig. 5A). Before doing so, we briefly review how the depolarization-dependence in these cells was shaped.

Subthreshold resonance properties and their dependence on depolarization arise from the interplay of ionic conductances and passive membrane properties (Hutcheon and Yarom, 2000). In particular, M conductances can give rise to resonant characteristics at more depolarized levels, while H conductances shape resonances at more hyperpolarized levels (Hu et al., 2002). If there are no specific resonant conductances that oppose voltage changes with slow dynamics (Hutcheon and Yarom, 2000), nonresonant characteristics result. The three model cells presented here contained (1) neither H nor M conductances (nonresonant), (2) an M conductance (resonant), and (3) the same M conductance as cell (2) together with an additional H conductance. In particular, cells (2) and (3) had almost identical properties close to threshold, where the activation of the H conductance was marginal, though they differed in their impedance profile at more hyperpolarized membrane potentials. Cell (2) corresponds to the cell discussed in the previous sections (Fig. 3 and Fig. 4).
Systematic comparison of subthreshold resonance profiles with the most reliable frequency across different depolarization levels set by $I_{DC}$ confirmed that the frequency dependence of the membrane impedance correlates with the frequency preference of neural reliability. For the nonresonant cell (1), the most reliable stimulus frequency was close to zero at all subthreshold $I_{DC}$ and thus coincided with the impedance peak (Fig. 5B, left panel). For the resonant cells (2) and (3), too, the frequency of maximal impedance correlated with the tip of the most reliable region for values of $I_{DC}$ close to threshold.

Nevertheless, at lower $I_{DC}$, the frequency of maximal impedance tended to systematically underestimate the most reliable frequency (Fig. 5B, middle and right panel). This trend was most apparent for the resonant cell (2) and was confirmed by a systematic investigation of many resonant and nonresonant model cells (data not shown). To understand this finding, it is essential to analyze the ZAP responses on which impedance estimates are based, as shown in the following section.

3.2.2 Nonlinearities at large amplitudes

For each input frequency, the membrane impedance quantifies the amplitude of voltage oscillations obtained in response to a small sinusoidal input current added to a constant (DC) current. As a linear measure, the membrane impedance can be well estimated using small-amplitude ZAP stimuli. However, to assess neural reliability, neural responses need to contain spikes. For low $I_{DC}$ values (resulting in average membrane potentials far below threshold), the amplitude $A$ of the sinusoidal stimulation has to be large to elicit spikes. Therefore the question arises, whether impedance estimates, which are based on small-amplitude ZAP stimulation, can account for reliability measures in response to large-amplitude stimulations. These trigger nonlinear dynamics, so any reliability measure based on the (linear) impedance might deviate from the observed reliability. As explained below, this is the case when the impedance profile varies strongly with depolarization.

Fig. 6 goes here.

In Fig. 6, the subthreshold response properties of two example cells are compared. The impedance profile of the cell in A is highly sensitive to $I_{DC}$, in contrast to the stable behavior seen in B. In Fig. 6A1–6A3 the responses to ZAP currents are shown to change with stimulus amplitude. For the small-amplitude ZAP, the envelope of the voltage responses reproduces the frequency dependence of the impedance. Moreover, both the upper and lower envelope are symmetric with respect to the mean voltage. The ZAP stimulus in panel A2 has almost the largest possible amplitude not eliciting spikes. Here – despite the same $I_{DC}$ – the upper and the lower response envelopes look significantly different: a global maximum around 4 Hz is evident for the upper part of the response, whereas the envelope of the lower part is monotonic. The upper envelope reflects the trend of the impedance towards threshold; in fact, this cell has a strong subthreshold resonance close to threshold (Fig. 6A4 and 6A5). The monotonic behavior of the lower envelope, on the other hand, is consistent with the impedance profile near rest.

Only the upper response envelope is useful to predict the stimulus frequency eliciting spikes: if the ZAP amplitude is slightly increased, action potentials are generated at frequencies around the maximum of the upper
response envelope (Fig. 6A3). It should be noted that this maximum may not be visible in the impedance profile. For example, for the resonant cell shown here, the impedance function based on small- and large-amplitude ZAP responses was monotonically decreasing (Fig. 6A6). Linear impedance, hence, is not sufficient to predict the best stimulus frequency to initiate spiking: the non-linear, large-amplitude ZAP voltage response needs to be evaluated directly. Only when the impedance profile does not vary strongly with the membrane depolarization do ZAP responses remain symmetrical, and similar to the impedance curve.

Spikes are triggered when the membrane potential crosses the firing threshold. We therefore conjectured that the input frequency corresponding to the maximum in the upper envelope of the ZAP response provides a good prediction of the most reliable stimulus frequency. To test this hypothesis, for each $I_{DC}$, the largest ZAP amplitude not eliciting spikes was chosen. Consequently, the amplitude of these large ZAP stimuli decreased with $I_{DC}$ and close to threshold the amplitudes were rather small. The frequency $f_{upper}$ corresponding to the maximum in the upper response envelope was determined for each cell as a function of $I_{DC}$. This frequency was compared to the input frequency eliciting most reliable spiking.

Fig. 5B shows $f_{upper}$ as a function of $I_{DC}$ in the nonresonant and the two resonant cells. For the nonresonant cell, this frequency was equal to the frequency obtained from the linear impedance analysis (Fig. 5B, left panel). In the resonant cells, however, the two frequencies differed (Fig. 5B, middle and right panel). As predicted, further below threshold, where stimulus amplitudes have to be large to elicit spikes, $f_{upper}$ tends to deviate from the subthreshold resonance frequency $f_{res}$, and closely follows the frequency inducing maximal reliability. Hence, unlike a prediction based on a purely linear impedance estimate, $f_{upper}$ provides a better account of the nonlinear phenomena prevailing at low values of $I_{DC}$.

For comparison, the frequency preferences of the three example neurons are presented in Fig. 5C. Two different behaviors are visible: Below threshold $f_{reliab}$ (the most reliable input frequency) coincides with $f_{upper}(I_{DC})$; above threshold $f_{reliab}$ is predicted by the firing-rate-$I_{DC}$ curve. The transition at threshold is not always smooth. In the nonresonant cell of Fig. 5, for example, the derivative of $f_{reliab}(I_{DC})$ is discontinuous. Moreover, in resonant cells, sometimes $f_{reliab}$ itself exhibits a jump, as shown below.

From a dynamics-systems point of view, cells can be classified according to the bifurcation type at threshold (Rinzel and Ermentrout, 1998): for example, a limit cycle corresponding to regular firing emerges either through a Hopf bifurcation (type II cells) or a saddle-node bifurcation (type I cells). At threshold, type II cells are resonant and type I cells are nonresonant.

For type II neurons, the stable limit cycle usually appears before the fixed point looses stability. As a consequence there is a range of input currents where two different attractors coexist, and the frequency of damped subthreshold oscillations around the fixed point need not coincide with the frequency associated with the limit cycle. The stimulus frequency eliciting most reliable responses can reflect this jump, as exemplified by the Morris-Lecar neurons in Fig. 7B. Although this discontinuity may be hidden by noise or large-amplitude stimuli, it is nevertheless of conceptual relevance. The jump in $f_{reliab}$ demonstrates that there are indeed two different resonance phenomena determining the most reliable input frequency below and above threshold – associated with the fixed point and the limit cycle, respectively.
For nonresonant neurons, instead, $f_{\text{reliab}}$ is always continuous (Fig. 7A). Here the fixed point loses stability at the same $I_{DC}$ where the limit cycle appears. Initially, the frequency of the limit cycle is small and then gradually increases with $I_{DC}$. Hence, at threshold, both the frequency of maximal impedance and the firing rate are zero.

### 3.3 Precision and Probability

In the fluctuation-driven regime, spike probability is maximal if the input frequency matches $f_{\text{upp}}$. In addition, the most reliable stimulus frequency resembles $f_{\text{upp}}$, too. Hence, in the fluctuation-driven regime, optimal reliability closely coincides with peak spike probability. This contingency is not to be expected in the mean-driven regime, where the stable limit cycle guarantees regular firing. Hence, to characterize the different facets of reliability in the two dynamical regimes, we separately examined the frequency dependence of spike probability and spike-time precision in both regimes. To that end, we identified individual firing events. In the fluctuation-driven regime, the events were associated with high values of the stimulus. In the mean-driven regime, firing events occurred at intervals determined by the firing frequency in response to the stimulus mean, $f_{DC}$. Based on the smoothed PSTH, time windows locked to individual spike events were defined and temporal jitter (SD of spikes within each event) as well as spike probability (number of responses with at least one spike in each event) inside each window were quantified (see Methods). Spike-time precision was defined as the inverse of the temporal jitter.

We found that precision and probability showed different trends, for stimuli with sub- and suprathreshold mean. In the mean-driven regime, spike probability was relatively insensitive to stimulus frequency (Fig. 8A, middle panel); overall, probability values were high (80% or more, for most frequencies and amplitudes). In the fluctuation-driven regime, however, spike probability strongly depended on the stimulus frequency (Fig. 8B, second panel from the top). Here, only a single region of high spike probability was observed, which coincided with the region of high reliability (shown in Fig. 4). Towards the margins of this region spike probability decreased dramatically. Outside the region no spikes were generated, despite the presence of noise.

Spike-time precision showed a strong dependence on stimulus frequency in both firing regimes (Fig. 8, top panels). Mean-driven firing was characterized by several regions of increased precision, which coincided with the regions of high reliability (shown in Fig. 3). In the fluctuation-driven regime, precision is only well defined in the region where spike probability was not zero (i.e. outside the striped pattern shown in the top panel of Fig. 8B). Within this region, precision increased slightly with the stimulus amplitude and fell off towards the margins in frequency space.

In both firing regimes, the dependence of the average firing rate on stimulus frequency mimicked the trend observed in spike probability (Fig. 8, third panels from the top). Highest reliability (i.e. both high spike probability and high spike-time precision) was achieved in a 1:1 mode locking between stimulus and response.
The firing rate therefore followed the stimulus frequency in these regions, as indicated by the concurrence of firing rate and the dashed identity line (Fig. 8, bottom panels).

A comparison of both regimes shows that the major factor limiting reliability is distinct in both regimes: spike-time precision in the mean-driven regime in contrast to spike probability in the fluctuation-driven regime. This finding is readily explained by the different attractor structure of the respective dynamical systems. In the presence of a stable limit cycle, the most prominent effect of noise is a temporal displacement of individual spikes, i.e., spike jitter. In the absence of a stable limit cycle, outside the resonance frequency band, the stimulus is not effective enough to initiate spiking, leading to a decrease in spike probability.

### 3.4 Influence of noise

This interpretation substantiates a different role of noise in both firing regimes, at least close to the tip of the most reliable regions. As an example we consider the resonant model cell (as in Fig. 3 and Fig. 4).

In the mean-driven regime, noise did not strongly impair spike probability, but decreased spike-time precision (Fig. 9A and B, left panels). Consequently, reliability decreased monotonically with increasing noise levels (Fig. 9C, left panel) due to a reduction in precision. Note that the noise amplitude was still small compared to the distance between the stimulus mean and threshold.

Although noise also reduced spike-time precision in the fluctuation-driven regime, it enhanced spike probability (Fig. 9A and B, right panels). The tradeoff between these two effects can even lead to a peaked reliability at non-zero noise levels (Fig. 9C, right panel). First, reliability increased with noise, because spike probability increased, but then noise progressively impaired spike-time precision so that reliability decreased again. Such a positive effect of noise on spike probability and consequently also spike reliability can be expected to be crucial for stimuli close to the border of the reliable region, where reliability is critically limited by impaired spike probability.

### 4 Discussion

Experimental studies have revealed a strong frequency preference of neural reliability in various systems, including aplysia motoneurons (Hunter et al., 1998), prefrontal cortex (Nowak et al., 1997; Fellous et al., 2001), spinal cord (Beierholm et al., 2001), and hippocampus (Lawrence et al., 2006). Hunter and colleagues (Hunter et al., 1998) were the first to describe the resonance mechanism between the intrinsic DC firing rate $f_{DC}$ and the most reliable stimulus frequency. This mechanism is relevant for the mean-driven regime. There is, however, experimental evidence that a frequency dependence of neural reliability also exists in a regime
where the stimulus mean alone would not be sufficient to elicit action potentials (Haas and White, 2002). Subthreshold oscillations have been associated with precise spike timing in this region (Desmaisons et al., 1999). In prefrontal cortical neurons, the dominant frequency of these oscillations has been shown to coincide with the best spike-timing frequency (Fellous et al., 2001). This state of affairs has lead us to distinguish two different firing regimes, depending on the underlying attractor dynamics.

4.1 Separation of two regimes

Our results provide evidence that the attractor structure of the single-neuron dynamics explains the frequency preference of neural reliability both in cells with type I and with type II excitability. For type I neurons, the transition of \( f_{\text{reliab}} \) from the fluctuation-driven to the mean-driven regime is smooth. For type-II neurons, i.e., neurons that are resonant at the firing threshold, the transition of \( f_{\text{reliab}} \) may be discontinuous. This jump is likely to be of limited biological significance, as the presence of noise and/or nonvanishing stimulus amplitudes tends to smooth the discontinuities in frequency preference. However, its mere existence clearly hints at the nontrivial underlying attractor structure that explains the differential symptoms of reliability in the fluctuation- and the mean-driven firing regimes.

In our view, the distinction between the dynamical phenomena shaping reliability in the two firing regimes has not been sufficiently addressed in the literature. For example, Fellous and colleagues (2001) changed the amplitude of time-dependent stimuli together with their mean. Because of this experimental paradigm, large stimuli automatically shifted the cell from the fluctuation- to the mean-driven regime. Note in this context that the influence of the subthreshold membrane impedance on the cells firing properties decreases with the distance of the stimulus mean from the firing threshold: subthreshold resonance is a property related to the fixed point losing stability at the threshold. This insight is also needed to correctly interpret previous results connecting subthreshold resonance and spiking properties, as these results may only apply to the fluctuation-driven firing regime. For example, the relation between subthreshold resonance and the average firing rate or characteristics of firing patterns in the entorhinal cortex have only been shown in the fluctuation-driven regime (Schreiber et al., 2004a; Engel et al., 2008).

Previously, Richardson et al. (2003) distinguished two firing regimes in terms of the noise: regular firing (at low noise levels) and noise-driven firing (at high noise levels). The authors evaluated the modulation depth of the instantaneous firing rate, which also reflects the synchrony of the single-cell response with the periodic stimulus. They found that the modulation depth was maximal at a specific input frequency, whose value depended on the input noise. For low noise, the optimal input frequency coincided with the firing rate of the cell; for high input noise it was equal to the subthreshold resonance. Hence, the two frequencies achieving optimal responses in their study coincide with the two frequencies that we report here.

In contrast to our approach, the firing rate of the cell was kept constant in the study of Richardson et al., so whenever the amount of noise was increased, a compensating reduction in the DC level was introduced. Therefore, their paradigm implied that low noise was always accompanied by a higher DC, and high noise was concurrent with a lower DC. In this framework, a separation of two regimes that depends on the amount of
noise coincides with a separation that depends on the DC level. We took a different line and independently manipulated the DC level and amount of noise. This allowed us to show that the two firing regimes need not differ in the amount of noise to exhibit different symptoms of impaired reliability.

The extent to which differential symptoms of reliability in the two firing regimes hold for nonrhythmic stimuli has not been a focus of the present study. We have, however, previously shown in cells of the entorhinal cortex and in model cells that frequency-specific filtering by subthreshold resonance equally affects the effective amplitude of responses to nonrhythmic frozen-noise signals in terms of their SD (Schreiber et al., 2004a). When comparing nonrhythmic stimuli of the same total power, but a differential distribution of power across frequencies, it is hence likely that spike probability in response to stimuli with more power in a frequency band around the resonant frequency is less impaired than spike probability in response to stimuli with less power in this frequency band.

4.2 Reliability in the fluctuation-driven regime

Our results help to understand frequency preference in the fluctuation-driven regime on both a qualitative and quantitative level. Qualitatively, the most reliable stimulus frequency is determined by a resonance with the subthreshold voltage oscillations. This finding agrees with the experimental observations of Fellous et al. (2001), whose study at low current amplitudes was presumably conducted in the fluctuation-driven regime. In particular, their data show clearly that spike probability is impaired (their Fig. 2B). However, impedance values determined at the stimulus mean are often not sufficient to quantitatively predict the most reliable frequency. In fact, Fellous et al. (2001) already pointed out that the subthreshold oscillation frequency is only a good predictor of the frequency of best reliability if input amplitudes are small or if the oscillation frequency does not depend on voltage. If, however, the stimulation amplitude is large enough to almost elicit spikes, the neural responses capture the non-linearities arising from the voltage dependence of ion-channel activation. A strong dependence of the impedance profile on depolarization produces an asymmetry between the upper and lower response envelopes (see Fig. 6). The upper envelope is mainly influenced by the impedance properties close to threshold, while the lower envelope is affected by the impedance properties at more negative membrane potentials. Hence, cells whose resonance frequency does not change with depolarization exhibit upper and lower envelopes that do not differ in the position of their extrema, even at large stimulus amplitudes. For small-amplitude stimuli close to threshold or for cells with a depolarization-independent resonance frequency, \( f_{\text{upp}} \) coincides with the linear impedance prediction.

4.3 Comparing the fluctuation- and mean-driven regimes

In both the fluctuation- and the mean-driven regime, the most reliable responses are obtained in a 1:1 firing mode, where the neuronal firing rate coincides with the stimulus frequency. Nevertheless, there are fundamental differences between the two regimes.
1. The effect of spike-time precision and spike probability on neural reliability. In the mean-driven regime, the only stable attractor is a limit cycle corresponding to periodic spiking. Therefore, the highest possible reliability is governed by the sensitivity of the regular firing mode to time-dependent stimulus perturbations, as shown by the size of spike-timing jitter. Phase-response curves (Hansel et al., 1995; Kuramoto, 2003) can be used to quantify this sensitivity. In the fluctuation-driven regime, however, the only stable attractor is a fixed point. In this regime, spiking requires a temporary escape from this state. Accordingly, spike probability becomes a crucial factor determining spike reliability.

2. The effect of noise on neural reliability. In the mean-driven regime, noise always decreases reliability. In contrast, small amounts of noise can increase reliability in the fluctuation-driven regime, by helping the system to escape from the fixed point. Indeed, below threshold maximal reliability may be obtained for intermediate noise levels, as expected from the general framework of stochastic- and coherence resonance (Longtin, 1993; Pikovsky and Kurths, 1997; Lindner et al., 2004). Lower noise levels result in impaired spike probability. Larger noise levels, in turn, may increase the firing rate beyond the input frequency, generating spikes that are poorly locked to the stimulus. Similar results have also been obtained in several sensory (Longtin et al., 1991; Douglass et al., 1993; Levin and Miller, 1996), motor (Martínez et al., 2007) and central (Reinker et al., 2004; Tateno et al., 2004) neurons.

3. The existence of additional reliable frequencies at harmonics and subharmonics of the optimal frequency. In the mean-driven regime, additional reliable frequencies can exist because reliability is determined by a resonance between the limit-cycle frequency and the stimulation frequency. For example, in the 1:2 firing mode, the precision of individual spikes is high, as spike events coincide with every second stimulus cycle. In the fluctuation-driven regime, on the other hand, harmonics do not play a role, because escaping the fixed point is most probable if the stimulation frequency matches the resonance frequency associated with the fixed point. At harmonic or subharmonic frequencies the membrane impedance is lower, so reliability decreases. Multiple frequencies of increased reliability could only be expected if the membrane impedance exhibited several peaks, or potentially, at very large stimulus amplitudes so that the system can easily jump onto the firing trajectory.

In the mean-driven regime, close to the harmonic frequencies of $f_{\text{reliab}}$, i.e., in a 1:n firing mode, noise can shift the firing phase by a full stimulus period (or approximately $1/n^{th}$ of the average firing rate). Such single-neuron firing states may occur in a network in the state of clustered synchrony, where individual neuronal firing is relatively regular, but the population frequency is n-times higher than the frequency of individual neurons (Golomb et al., 1992; Brunel and Hansel, 2006). In a fluctuation-driven regime, such a clustered state is not to be expected according to our analysis.

The mechanisms that shape the frequency selectivity of spike-time reliability described here are valid in a regime of moderate stimulus amplitudes. If the stimulus amplitude is too small, resonance effects may be masked by noise (Hunter and Milton, 2003). On the other hand, if the amplitude is too large, the original attractor structure is destroyed. Strictly speaking, stable attractors, such as fixed points or limit cycles, exist only for constant stimulation currents. When the time-dependent stimulation is small or moderate, the description in terms of attractors still applies, since the variable stimuli only perturb the attractors slightly, without challenging their stability. If, however, the temporal fluctuations in the input current become too
large, they dominate the attractor structure, and one can no longer explain neural reliability in terms of the
original attractor frequencies.

Besides, a clear distinction between fluctuation- and mean-driven regime is only possible for stimulus means
sufficiently far away from threshold. If $I_{DC}$ is close to threshold and the time-dependent stimulus component
has a relatively large amplitude, both regimes interfere and the clear separation of reliability characteristics
between both firing regimes is no longer possible.

4.4 Role of ionic conductances

Neural reliability and its dependence on stimulus characteristics can be modulated in various ways. First, the
stimulus frequency that elicits most reliable responses can be altered. Second, the absolute size of neural
reliability can be up- or down-regulated, for a fixed optimal stimulus frequency. Third, and most generally, the
entire shape of the reliability curve can be modified.

These different variants of modulating neural reliability can all be implemented on the level of ionic conduc-
tances and their dynamics. In the fluctuation-driven regime, conductances shaping subthreshold resonance,
e.g., H- or M-type conductances, can change the stimulus frequency that is transmitted most reliably. In the
mean-driven regime, all conductances exerting a strong influence on the DC firing rate, such as slow potas-
sium channels involved in spike-frequency adaptation, are prime candidates for the adjustment of the stimulus
frequency resulting in most reliable responses.

The mechanisms changing absolute reliability values lead to the following hypothesis: In the fluctuation-
driven regime, conductances that modify the impedance profile beyond the position of the maximum are likely
to influence the maximum value and/or tuning width of reliability. The former could, for example, be expected
for persistent sodium channels, which are known to amplify subthreshold resonance (Hutcheon and Yarom,
2000). Similarly, in the mean-driven regime, parameters of individual conductances influencing attractor
robustness, such as the peak conductance or the time constant of slow potassium channels, have been shown
to improve the absolute values of neural reliability at the most reliable frequency (Schreiber et al., 2004b).
Since ionic conductances and their properties can be changed on short time scales by neuromodulators, our
study suggests a mechanism for rapid large-scale adjustments of neural reliability in both the fluctuation- and
mean-driven firing regimes.
References


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Table 1: Parameters of the conductance-based model neurons.

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Table 1: Parameters of the conductance-based model neurons.
Figure 1: Definition of firing events.

**A** Sinusoidal stimuli of 9 Hz used to drive model cells in the presence of noise. The dashed line marks the current threshold. Left column: $I_{DC} = 0.4 \text{nA}$ (below threshold), right column: $I_{DC} = 0.7 \text{nA}$ (above threshold). **B** The corresponding raster plots, with windows marking the borders of firing events (gray vertical lines). **C** The corresponding PSTHs, whose minima are used to define the window borders.
Figure 2: Neurons exhibit two different firing modes. Firing rate as a function of the stimulus mean for a constant current (black solid line), and a current with a time-dependent component (dashed line, sinusoidal stimulation at $f=5\text{Hz}$; amplitude $0.06\text{nA}$ plus Gaussian noise with $SD = 0.06\text{nA}$ and filtering time constant $= 3\text{ms}$). While the model neuron does not fire at all in response to the constant current below threshold, it generates spikes at current means below threshold in the presence of stimulus- and noise-induced fluctuations. The stimulus mean and its relation to the spike threshold define two distinct firing regimes, where spikes are either driven by the mean current (here termed mean-driven, i.e. for stimulus means above threshold) or current fluctuations (here termed fluctuation-driven, i.e. for stimulus means below threshold). We only call the response regime subthreshold, if no spikes are present at all.
Figure 3: Neural reliability in the mean-driven firing regime. Data from the same model cell as in Fig. 2. (A and B) Two example stimuli with equal strength (\(I_{DC}=0.7\,\text{nA}\)), noise level (0.02 nA) but different frequency. The dashed line marks the DC current needed to reach the firing threshold. (C and D) Raster plots of responses to repeated presentations of the stimuli in A and B. Although the only difference is the stimulus frequency, neural reliability differs significantly. (E) Correlation-based reliability as a function of stimulus frequency and amplitude of the sine-wave component. Several regions of increased reliability are visible. C and D mark the values corresponding to the raster plots shown above.
Figure 4: Neural reliability in the fluctuation-driven firing regime.
Data from the same model cell and noise level as in Fig. 3, but for a lower value of $I_{DC}=0.4\,\text{nA}$.
(A and B) Two example stimuli with subthreshold mean, that differ only in their frequency. 
(C and D) The corresponding spike rasters. (E) Reliability as a function of stimulus frequency and amplitude. The region of high reliability around 17Hz is clearly visible. C and D mark the values corresponding to the raster plots above. (F) The peak in the membrane impedance measured at the subthreshold holding current $I_{DC}$ coincides with the frequency of highest reliability.
Figure 5: Membrane impedance influences neural reliability in resonant and nonresonant neurons. Analysis of a nonresonant (left column) and two resonant (middle and right columns) model cells. These correspond to the cells (1)–(3) described in the text. (A) Membrane impedances at four different depolarization levels, from rest to threshold ($I_{DC} = 0$, 0.1, 0.2, and 0.3 nA for the nonresonant cell (left column); $I_{DC} = 0$, 0.15, 0.3, 0.45 nA for the resonant cells (middle and right columns); line color darkens with depolarization). Impedance is estimated using small-amplitude ZAP stimuli. While the nonresonant cells shows low-pass-filter characteristics across all subthreshold levels of $I_{DC}$, the impedance characteristics of the resonant cells change with depolarization from nonresonant to resonant (middle panel) due to the voltage-dependent activation of a muscarinic potassium conductance, or are resonant across the whole depolarization range due to an additional H conductance. (B) Subthreshold resonance frequency $f_{res}$ based on small-amplitude ZAP responses (dashed line), the frequency of best reliability $f_{reliab}$ estimated at the tip of the most reliable region in the frequency-amplitude space (circles), see also Fig.4E, and the peak position $f_{upp}$ of the upper response envelope to large-amplitude ZAP stimuli (solid line) as a function of $I_{DC}$ between zero and firing threshold. While close to threshold ($I_{DC} \approx 0.55$ nA) $f_{res}$ and $f_{reliab}$ coincide, larger deviations at low values of $I_{DC}$ occur for cells whose resonance frequency varies strongly with membrane depolarization (middle and right panels). $f_{upp}$ predicts $f_{reliab}$ well across the whole range of membrane depolarizations. (C) Most reliable frequencies depicted over the whole range of $I_{DC}$ (subthreshold: gray circles, suprathreshold: black circles). The solid line shows the DC firing rate in the mean-driven regime. While the best frequency increases continuously in the resonant cell, it remains close to zero across the whole fluctuation-driven range for the nonresonant cell.
Figure 6: Responses to large-amplitude ZAP stimuli are asymmetric for model cells whose subthreshold resonance depends strongly on depolarization.

(A1–A3) Responses to ZAP stimuli with three different amplitudes \( A \) (as indicated), \( I_{DC} = 0.09 \, \text{nA} \), current threshold at \( \sim 0.3 \, \text{nA} \). While upper and lower response envelopes to the small-amplitude stimulus are symmetric (A1), this is no longer true for the large-amplitude ZAP stimulus (A2), where the upper response envelope exhibits a pronounced peak. If \( A \) is increased slightly further, spikes are elicited close to this peak (A3). (A4) Impedance profiles of this cell across different levels of depolarization (\( I_{DC} = 0.02, 0.08, 0.14, 0.2, 0.24, \) and \( 0.26 \, \text{nA} \)). (A5) \( f_{res} \) as a function of \( I_{DC} \). (A6) Membrane impedance calculated on the basis of responses in the top and middle panels of A1. Because of the strong attenuation seen in the lower response envelope, the peak of the upper response envelope for \( A = 0.18 \, \text{nA} \) does not translate into an obvious peak in the impedance. (B1–B6) Corresponding data for a cell whose subthreshold resonance frequency varies little with depolarization. Large-amplitude ZAP responses exhibit no significant asymmetries with respect to the extrema in their upper and lower response envelopes. \( I_{DC} = 0 \, \text{nA} \), current threshold at \( \sim 0.21 \, \text{nA} \) for panels B1–B3, and B6. In B4, \( I_{DC} = -0.3 \, \text{nA} \) to \( 0.2 \, \text{nA} \), in steps of \( 0.1 \, \text{nA} \).
Figure 7: Frequency dependence of neural reliability in Morris-Lecar neurons.

(A) Type I Morris-Lecar model neuron (nonresonant): The stimulus frequency resulting in maximal reliability \( f_{\text{reliab}} \) (gray and black circles, in the fluctuation- and mean-driven regime, respectively) estimated at the tip of the reliable region in frequency-amplitude space (see, for example, Fig.4E) is approximately zero below threshold and increases with DC firing rate \( f_{\text{DC}} \) (solid line) above threshold. (B) Corresponding data in a type II Morris-Lecar model neuron (resonant): \( f_{\text{reliab}} \) (gray circles) coincides with the frequency at the peak of the upper response envelope \( f_{\text{upp}} \) (thick dashed line). In the fluctuation-driven regime, \( f_{\text{reliab}} \) is distinct from the subthreshold resonance frequency \( f_{\text{res}} \) obtained analytically from the linearized Morris-Lecar model (dotted line). In the mean-driven regime, \( f_{\text{reliab}} \) (black circles) correlates with \( f_{\text{DC}} \) (solid line). Note that for the (resonant) type II model in B, the threshold region is marked by a discontinuity between \( f_{\text{res}} \) and \( f_{\text{DC}} \). Also \( f_{\text{reliab}} \) exhibits a jump. In contrast, the transition in the threshold region is smooth for the (nonresonant) type I neuron in A. Noise SD is 0.5 \( \mu A/cm^2 \) in both panels.
Figure 8: Comparison of spike-time precision and spike probability in both firing regimes. Data for the same model cell as in Figs. 3 and 4. (A) Mean-driven firing ($I_{DC} = 0.7\; \text{nA}$): While spike-time precision shows a similar structure as reliability (compare Fig. 3E), the dependence of spike probability on frequency is small. The average firing rate (at $I = 0.05\; \text{nA}$) does not vary much with frequency. For the most reliable region, the firing rate briefly deviates and follows the stimulus frequency due to a 1:1 mode locking between stimulus and neuronal response. Dashed line: equality between the average firing rate and the stimulus frequency. (B) Fluctuation-driven firing ($I_{DC} = 0.4\; \text{nA}$): Here, both spike-time precision and spike probability depend on the frequency and are related to the frequency-dependence of reliability (compare to Fig. 4). Outside the black probability region no spikes are fired at all (striped pattern). This is also reflected in the average firing rate ($A = 0.12\; \text{nA}$). As in the mean-driven regime, for the most reliable responses the firing rate follows the stimulus frequency in a 1:1 mode-locking pattern.
Figure 9: Influence of intrinsic noise on spike reliability. Data from the same model cell as in Figs. 3 and 4. Left column: mean-driven firing regime, right column: fluctuation-driven firing regime. The stimuli are close to the tip of the most reliable region (mean-driven: \(I_{\text{DC}}=0.4\, \text{nA}, A=0.08\, \text{nA}, f=18\, \text{Hz}; \) fluctuation-driven: \(I_{\text{DC}}=0.7\, \text{nA}, A=0.05\, \text{nA}, f=30\, \text{Hz}, \) see also Fig. 3E and Fig. 4E). (A) Raster plots for three different noise levels (noise SD as indicated). (B) Mean-driven: spike-time precision decreases with noise, while spike probability is not strongly impaired. Fluctuation-driven: spike precision decreases, while spike probability increases with noise. (C) Reliability as a function of the noise level. While reliability in the mean-driven regime decreases with noise, reliability in the fluctuation-driven regime initially increases. Marked circles indicate positions where raster plots are presented in A. In the fluctuation-driven regime the opposite trends of spike precision and spike probability lead to an optimal reliability at intermediate noise levels.