Reliability and Bifurcation in Neurons Driven by Multiple Sinusoids

Peter J. Thomas[a,2], Paul H. E. Tiesinga[a], Jean-Marc Fellous[a] and Terrence J. Sejnowski[a]

[a] *Sloan-Swartz Center for Theoretical Neurobiology, Computational Neurobiology Lab, and Howard Hughes Medical Institute, The Salk Institute, 10010 N. Torrey Pines Rd, La Jolla, CA 92037, USA.*

Abstract

We investigated the effect of the phase relationship between two frequency components of a periodic stimulus on cortical neurons *in vitro* and on simulated Integrate-and-Fire (IF) model neurons. It is well established that entrainment to a resonant frequency in a fluctuating stimulus can induce reliable and precise spike trains. Recently, Makeig *et al* (Science, 2002) demonstrated stimulus-evoked phase-resetting of α rhythms in human EEG. We find that varying the phase between two stimulus sinusoids in the α-range (5 and 10 Hz), while holding their power constant, modulated the reliability and precision of a neuron's response. The neuron's output was maximally precise for one phase and maximally imprecise for another. This phenomenon may be understood as a bifurcation between spike-time attractors, which we investigated with IF simulations. Our results suggest phase resetting could switch neurons dynamically between temporal and rate coding.

Key words: neural code, phase locking, precision

1 Introduction

In seminal work on neural reliability, Mainen and Sejnowski showed that while a constant input current led to unreliable spike-times, a small fluctuating component added to a DC current dramatically increased reliability[4]. Hunter et al showed that the frequency content of a low-pass-filtered-Gaussian stimulus

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[2] Corresponding author, `pjthomas@salk.edu`

influenced the reliability of an output spike train: when there was relatively more power near the fundamental harmonic corresponding to the inverse firing rate, the neuron was more reliable, in both IF neurons and in invertebrate motor neurons[3]. Neurons *in vitro* and in simulation showed resonances at frequencies matching the frequencies of sinusoidal drives that induced the most reliable firing, suggesting a phase-locking phenomenon at the root of neuronal reliability.

Fellous *et al* showed that in both pyramidal cells and interneurons in rat frontal cortex, the internal dynamics of neurons could lead to resonance with a periodic signal to enhance reliability of firing[2]. Tiesinga *et al* have shown that reliability is closely related in general to the bifurcation structure of the neuron's dynamics, which is determined both by the neurons internal dynamics and the time course of the input signal[8]. In the vicinity of a spike-time bifurcation point, the reliability of spike times dramatically decreases due to noise-induced transitions between distinct attractors.

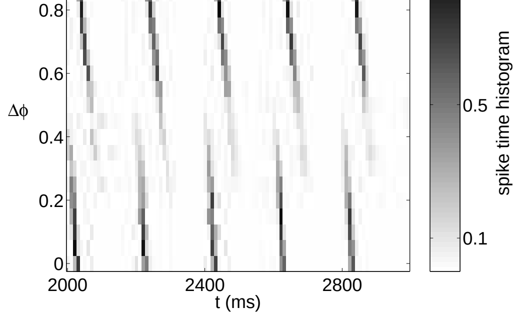
These studies indicate that the reliability of output spike patterns depends on the noise intrinsic to the neuron, its deterministic internal dynamics and the pattern of input current. In the work reported here we systematically varied the shape of a periodic input stimulus while preserving its frequency content. We shifted the relative phase of two component sinusoids, thereby causing a bifurcation in the firing pattern.

Event-related phase-resetting of EEG components recently reported [5] suggests that phase relationships may also be important in neural responses. Makeig *et al* found that event-related changes in EEG signals reflected the realignment of phases of independent EEG components without increasing their power. We consider here an analog situation in which the phase between two sinusoids (of commensurate frequency) composing the fluctuating stimulus is varied. We find an optimal phase at which the neuron is most reliable and also a phase at which the neuron is *least* reliable. This effect was observed in both cortical pyramidal neurons *in vitro* and in simulated neurons.

2 Results

To test the effect of correlated synaptic inputs with power in multiple frequencies, we injected a periodic current signal that was a sum of two sinusoids, while varying their relative phase from trial to trial. Both model Integrate-and-Fire (IF) neurons and cortical neurons *in vitro* were injected with currents of the form

$$I(t) = I_0 + I_1 sin(\omega t + 2\pi\Delta\phi) + I_2 \sin(2\omega t) \tag{1}$$



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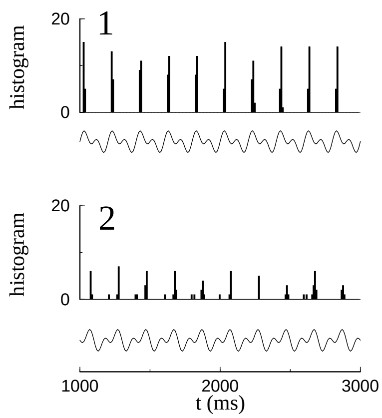

Fig. 1. Spike-time Bifurcation in a cortical neuron. Vertical axis: phase-offsets $\Delta\phi = 0.0, 0.05, \cdots, 0.95$. A 3000 ms long stimulus consisting of two sinusoidal currents with frequencies 5 and 10 Hz, respectively, was injected using current-clamp. For phase offsets around 0.45, there was a bifurcation between two competing dynamical attractors. Where the attractors collided, the spike times were unreliable. (A) Spike-time histogram (normalized by the number of trials) of the last 1000 ms as a function of $\Delta\phi$. (B) Spike-time histogram for two phase-offsets, (1) for $\Delta\phi = 0.0$ and (2) for $\Delta\phi = 0.5$. The injected stimulus waveforms are shown below each histogram.

where $0 \leq \Delta\phi < 1$ determines the phase offset of the sinusoids. We used frequencies in the α-range: $2\pi\omega = 5$ Hz and $4\pi\omega = 10$ Hz.

Figure 1 shows accumulated spike-train data for different phase-offsets $\Delta\phi$ (between 0.0 and 1.0). The horizontal axis shows time after stimulus onset. After an initial transient most phase-combinations settled into a regular 5 Hz firing pattern, with the region of greatest precision centered on a phase-offset of $\Delta\phi \approx 0.9$. As the phase-offset decreased the firing pattern became less robust. In a region between $\Delta\phi \approx 0.35 - 0.55$ there are two competing attractors present, and the firing pattern becomes markedly unreliable. Below $\Delta\phi \approx 0.3$ the second attractor wins out and the firing pattern becomes reliable again.

Note that because the phase-offset is a periodic quantity, the two spike-time-patterns that are in competition at $\Delta\phi \approx 0.45$ vary continuously and wrap around the boundary at $\Delta\phi = 0.0 \equiv 1.0$.

Unreliable spike times can occur when a neuron's response to an input signal lies near a bifurcation of the neuronal dynamics[8]. We simulated IF model neurons driven by two superposed sinusoids with and without additive noise. Periodically-forced IF neurons exhibit a rich structure of mode-locking and bifurcations which has been exhaustively analysed in the case of a sinusoidal drive[1, 7].

Figure 2 illustrates a series of bifurcations in an IF neuron driven by two sinusoids as their phase-offset varies. At a transition between two attractors (for example around $\Delta\phi \approx 0.2$ in Figure 2, noise induces random transitions between the two basins of attraction, leading to reduced precision and reliability.

3 Methods

Protocols for these experiments were approved by the Salk Institute Animal Care and Use Committee and they conform to USDA regulations and NIH guidelines for humane care and use of laboratory animals. Regularly spiking layer five pyramidal neurons in 350 μm-thick coronal slices of rat prelimbic and/or infra-limbic cortex were injected with twenty different phase offsets, in pseudorandom order, over multiple trials. The injected currents were $I_0 = 100$ pA, $I_1 = I_2 = 50$ pA. Whole-cell patch-clamp recordings were achieved using glass electrodes (4-10 MΩ). Patch-clamp was performed under visual control at room temperature. Data were acquired in current clamp mode using an Axoclamp 2A amplifier (Axon Instruments, Foster City, CA). Data acquisition and current injection used standard computer protocols. Programs were written in Labview 6.1 (National Instrument, Austin, TX), and data were acquired with a PCI-16-E1 data acquisition board (National Instrument, Austin, TX). Data acquisition rate was 10 kHz. Data were analyzed offline, and simulations were performed using MATLAB (The Mathworks, Natick, MA).

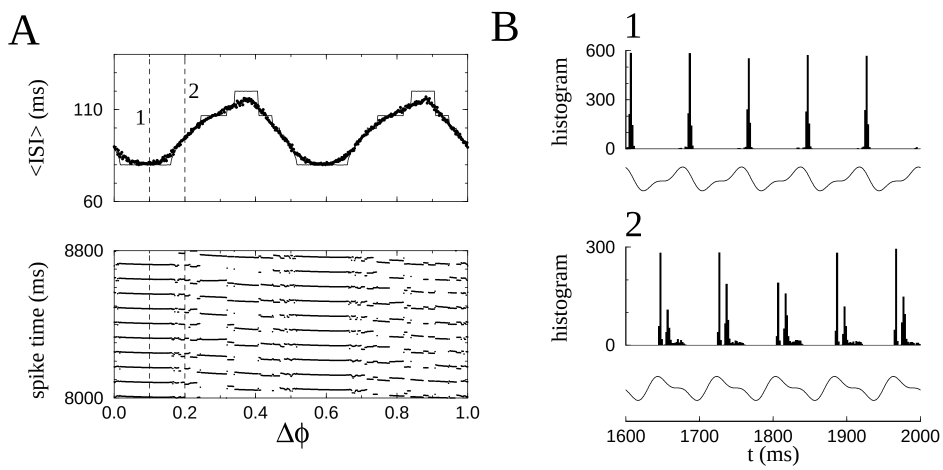

Fig. 2. Bifurcations were induced in an integrate-and-fire model neuron by varying the relative phase $\Delta\phi$ between two superposed sinusoidal currents with periods of 40 ms and 80 ms, respectively. (A,top) average interspike interval (line: $D = 0$; dots: $D = 10^{-4}$.). (A,bottom) spike times as a function of phase-offset $\Delta\phi$. Bifurcations between several attractors occur as $\Delta\phi$ varies. (B): spike-time histograms from two adjacent attractors, labeled by 1 and 2 in A. The injected stimulus waveforms are shown below each histogram.

Model neurons were specified by the differential equation

$$\frac{dV}{dt} = -V + I(t) + \sqrt{D}\eta \tag{2}$$

in dimensionless units. The voltage variable is reset to zero upon crossing a threshold $\theta = 1$. D is the variance of an additive noise source, given by a normalized white-noise process η. The equations were solved numerically using the 4^{th}-order or noise-adapted 2^{nd}-order Runge-Kutta method (Press et al, 1992) implemented in the Fortran programming language. An integration time-step of 0.01 ms yielded stable results.

4 Discussion

Reliability is important for understanding neural coding. The precision of neural response governs the amount of information about the stimulus that can be communicated and influences the flow of information in the network containing the neuron. Just as reliable timing is necessary for neural codes using the detailed temporal structure of spike-trains, unreliable timing erases information about the stimulus. The ability to modulate reliability by moving in and out of resonance with a given frequency component may be an important means of regulating correlation and gating information flow in cortical networks[6].

Our results show that when multiple input frequencies are present, the reliability and precision of the neuronal response is sensitive not only to the frequencies but to their relative phases as well. This finding is of special interest given recent results on stimulus-induced phase-resetting of human EEG rhythms in visual awareness tests[5]. Whatever its cognitive salience may be, rhythmic correlated population activity is a prominent feature of cortical dynamics. Depending on the relative phase relationships of different frequency components, a pyramidal cell can support either a precise spike-time code or a rate code in which spike-times show great variability (but in which spike rate is conserved.)

This transition in behavior may be understood as a bifurcation between dynamical attractors that occurs as the phase-offset varies. The precision and reliability of neural spike-timing depends on the interplay of synaptic input and the internal dynamics of a given neuron. When two dynamical attractors or spike patterns are close enough in phase space that intrinsic neuronal noise can induce transitions between them, the timing of individual spikes becomes unpredictable. Thus bifurcations are a general mechanism controlling neural reliability and unreliability.

5 Conclusions

To understand the effects of varying phase-relationships between different frequency components on neuronal response, we studied phase-locking behavior of *in vitro* and model neurons driven by periodic stimuli containing multiple superposed frequency components. We found that the response of a neuron to an input signal containing multiple frequencies in the α-range (5 and 10 Hz) depended on the relative phase of the frequency components. For some phase-offsets between a pair of frequencies the neuron fired a highly reliable, reproducible spike train while for other phase-offsets the response was unreliable. This effect occurs because shifting the relative phases changes the shape of the stimulus waveform even though the power in the different frequency components remains constant. This change in shape causes a bifurcation in dynamical attractors of the neuron, with reliability lowest in the vicinity of the bifurcation point. Varying the phase relationships between frequency components, which is seen for example in the stimulus-induced phase-resetting of human EEG, could effectively turn a timing code into a rate code or could selectively preserve or erase information contained in incoming spike trains.

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