Modulation of the frequency preference and attractor structure of prefrontal cortical neurons.

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Introduction

- The correct timing of action potentials is critical for many functions in the CNS: interaural time differences in owls, electrosensory capability in electric fish, olfactory coding in the locust, somatosensation with whiskers in rats, long term synaptic dynamics.
- Neuronal discharges in response to repeated presentations of the same stimuli are reliable in vitro (Mainen & Sejnowski 1995; Fellous et. al. 2001) and in vivo (Reinagel & Reid 2002) across animals and across cells. This reliability depends on the intrinsic characteristic of neurons, and on the specifics of the input.
- Neurons in vitro have intrinsic frequency preferences (Fellous et. al. 2001) that match the frequency ranges observed in the EEG.
- We show that the preferred frequency could depend only on the density of a few intrinsic membrane currents, and that a neuron responds to mixture of frequencies by generating a discrete ensemble of spike patterns we call attractors.

Methods

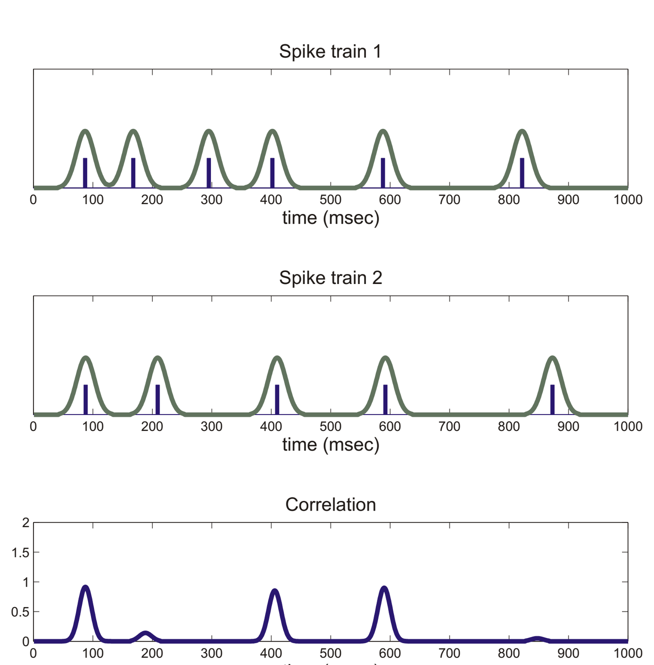
In vitro experiments:
We used layer 5 pyramidal prefrontal cortical cells in 2-3 weeks old Sprague Dawley rats. Cells were recorded using the patchclamp technique and all experiments were conducted at 31 °C, in current clamp mode. In most experiments synaptic transmission was blocked with DNQX (10 M), Bicuculine (20 M) and APV (50 M). Data were acquired with National Instrument hardware and Labview software (Fellous et. al. 2001).

Computational modeling:
Neurons were modeled as single-compartment Hodgkin-Huxley type neurons. The baseline model contained fast sodium channels (Na, 24 mS/cm^2), delayed-rectifier potassium channels (Kdr, 3 mS/cm^2), leak channels (leak, 2 10^{-2} mS/cm^2), slow potassium channels (Kslow, 1 mS/cm^2) and persistent sodium channels (NaP, 7 10^{-4} mS/cm^2) (details are in Golomb and Amitai (1997)). Parameter variations were performed around the baseline parameter values.

Data Analyses:
All analyses were performed using MATLAB.

1. A new reliability measure

1.1 'correlation' measure

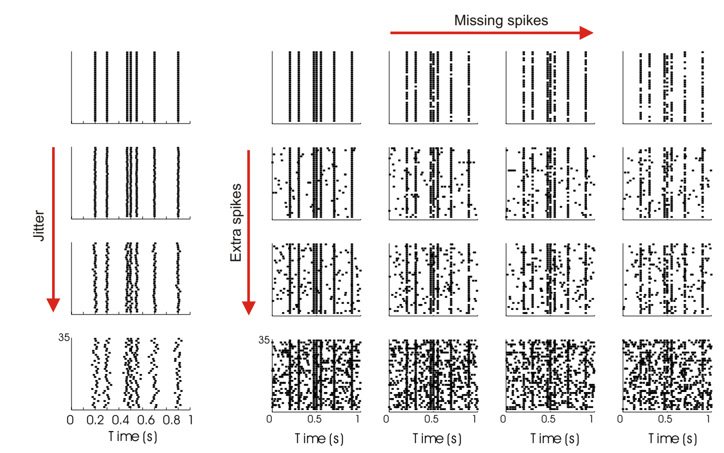


- All spike trains are filtered with a Gaussian of width (3-5 ms).
- The dot product R_{ij} between two trials is computed and normalized (correlation).
- Average "correlation" of all pairs of trials defines reliability.
- Rcorr is in [0;1]

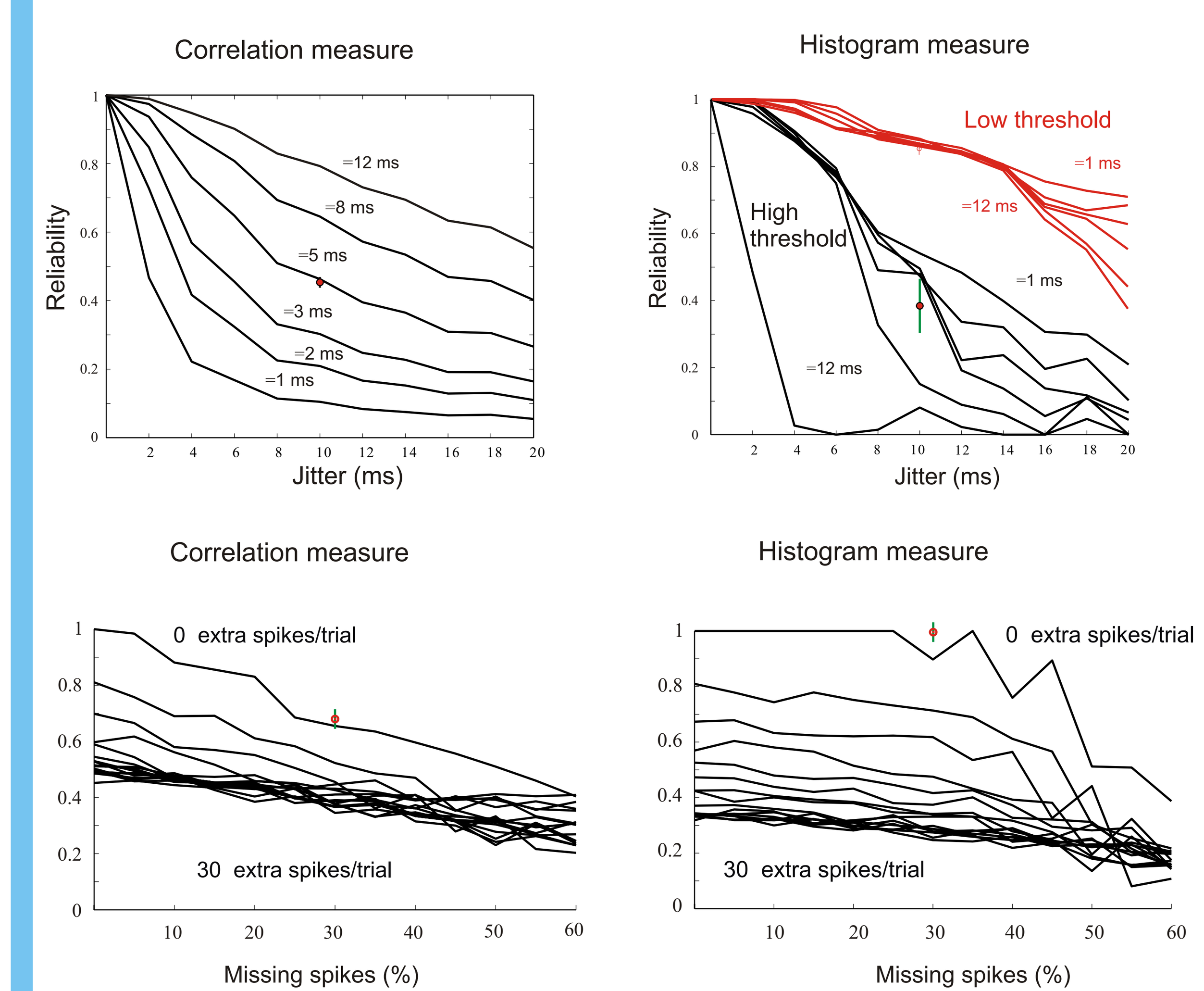
$\vec{s}_i$ … filtered spike trains i (i=1,..N)
N … number of trials

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

1.2 Reliability, jitter, extra and missing spikes.



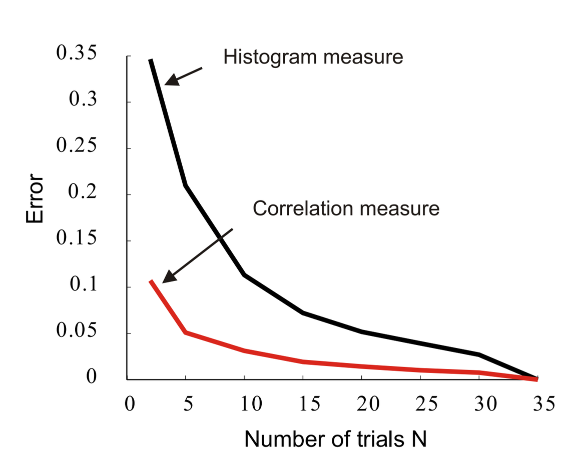
Correlation measure compared to a histogram measure on a surrogate set of data.



The correlation measure degrades smoothly with jitter, should be adjusted according to the expected precision of the data.

The histogram measure suffers from "event skipping" and does not degrade smoothly with extra/missing spikes.

1.3 Reliability and number of trials

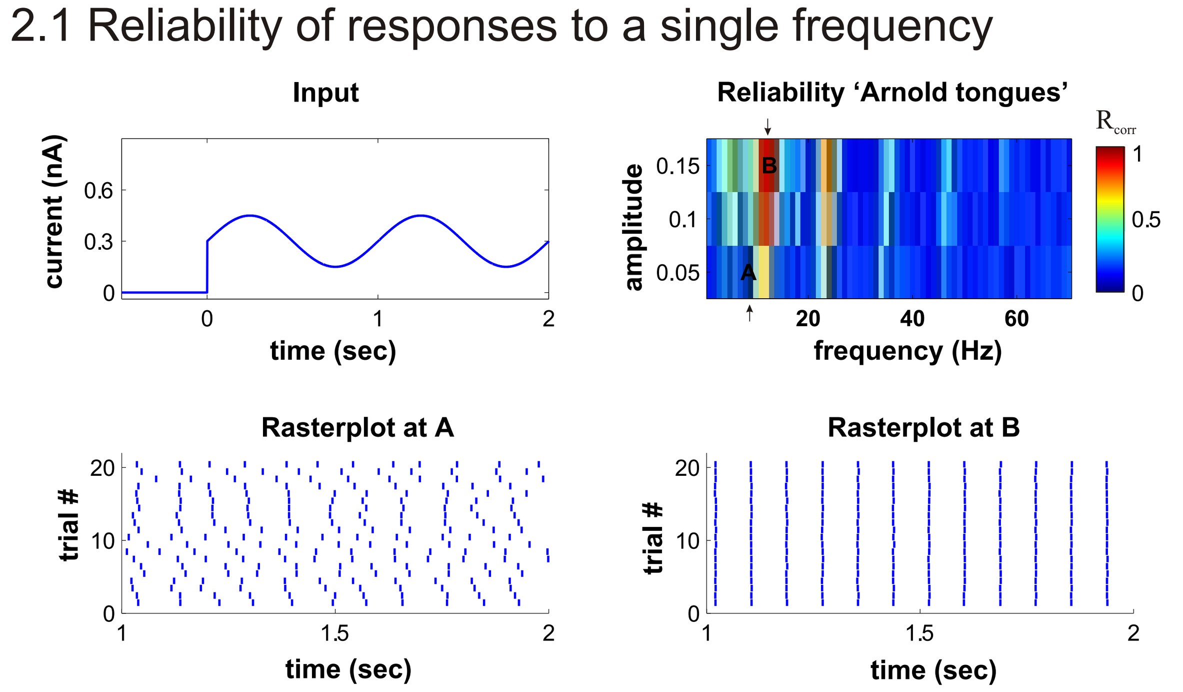


The average error in reliability with only N<35 trials is calculated taking reliability for 35 trials as a reference. (Based on 208 test sets with additional/missing spikes).

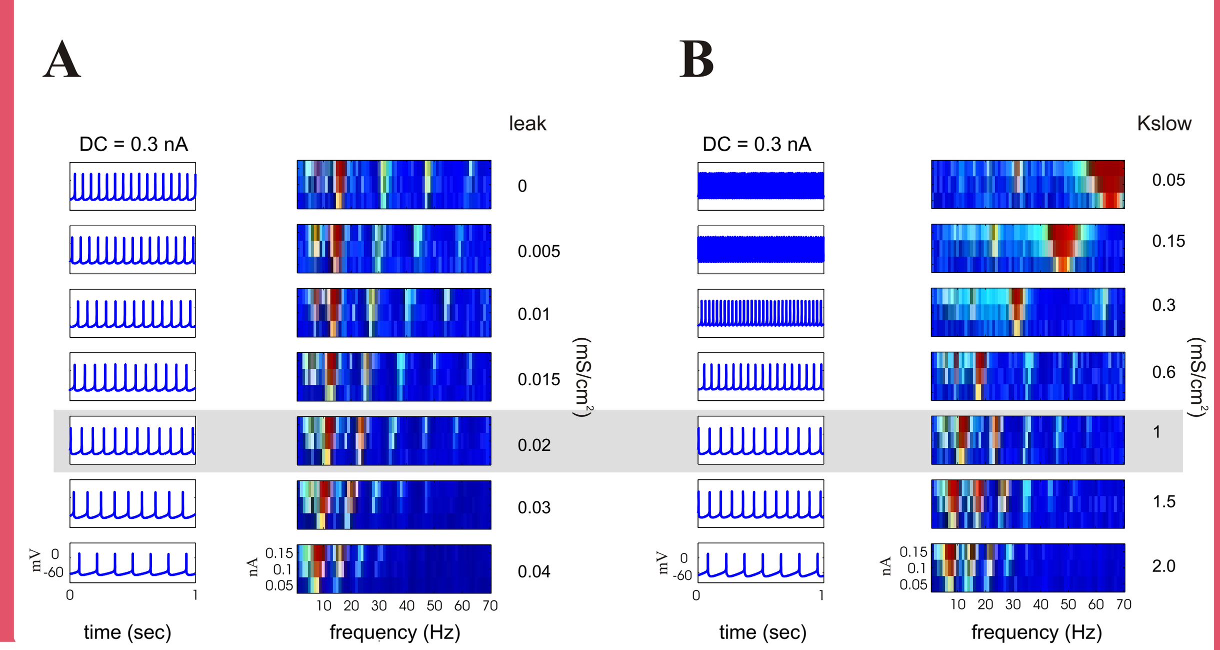
The error in the correlation-based reliability estimate is always more than a factor two lower than the error in the histogram-based reliability estimate.

2. Modulation of frequency preference

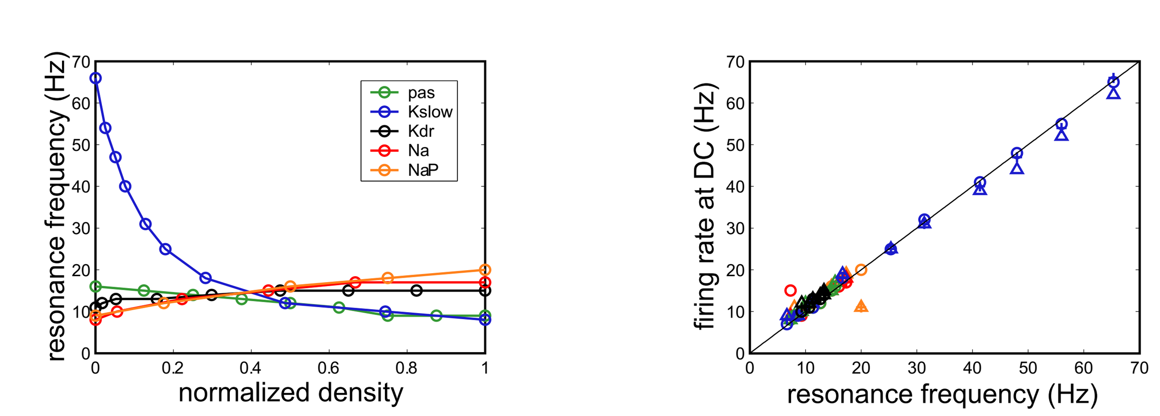
2.1 Reliability of responses to a single frequency



2.2 Frequency preference: Kslow



Modulation of intrinsic frequency preference
For each panel the left column shows the response to a DC pulse (no noise), the right panel shows the reliability in response to a DC plus sinewave of varying frequency and amplitude. A: variation of the leak conductance. B: variation of Kslow. Kslow is effective in modulating the frequency preference of the model cell. Note that the peak of reliability occurs for driving frequencies corresponding to the firing rate at DC. Shaded area is the baseline model.

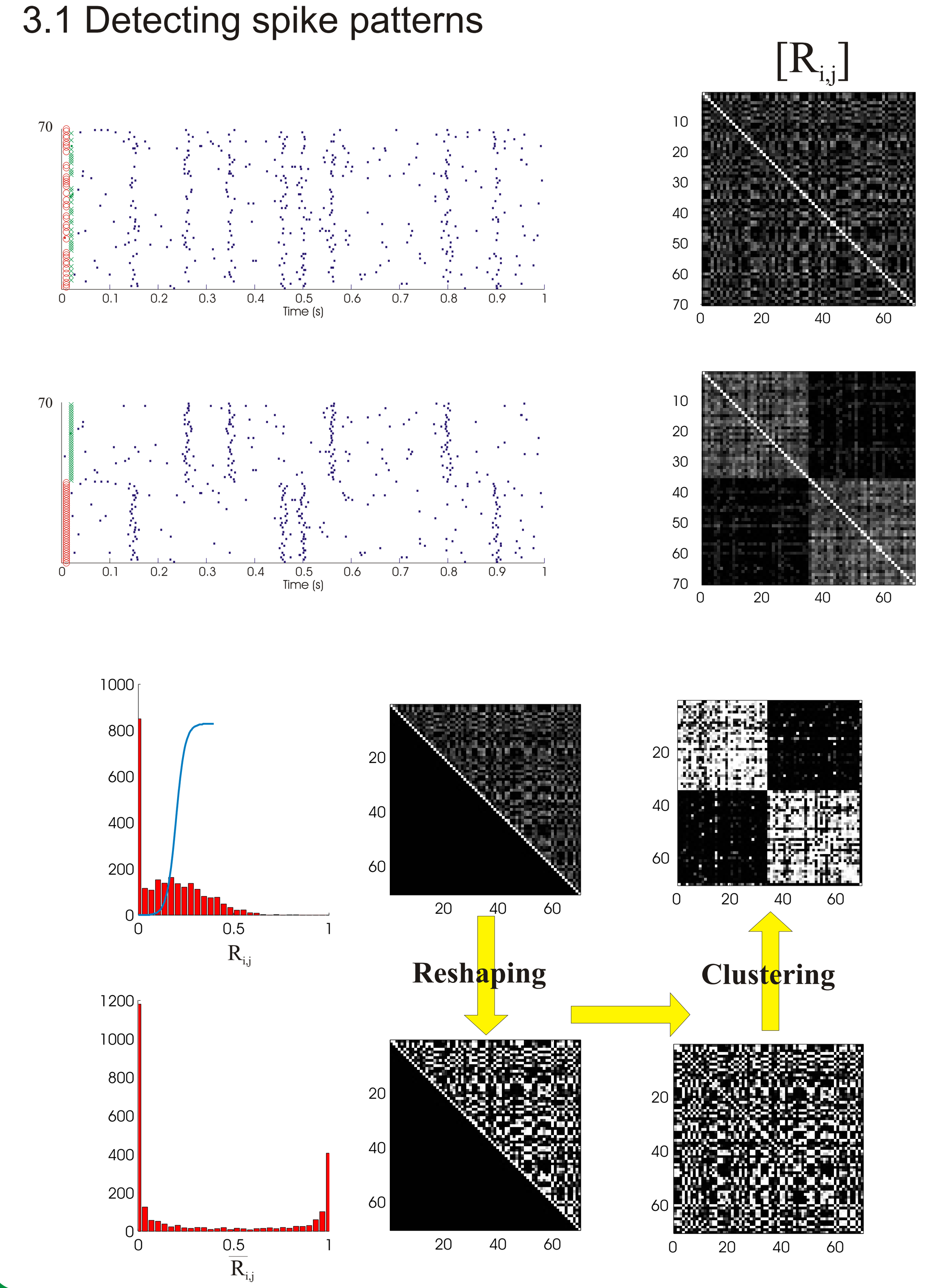


Kslow is the most effective modulator of resonant frequency.

The DC firing rate is a good predictor of resonant frequency.

3. Multiple frequencies, multiple spike patterns?

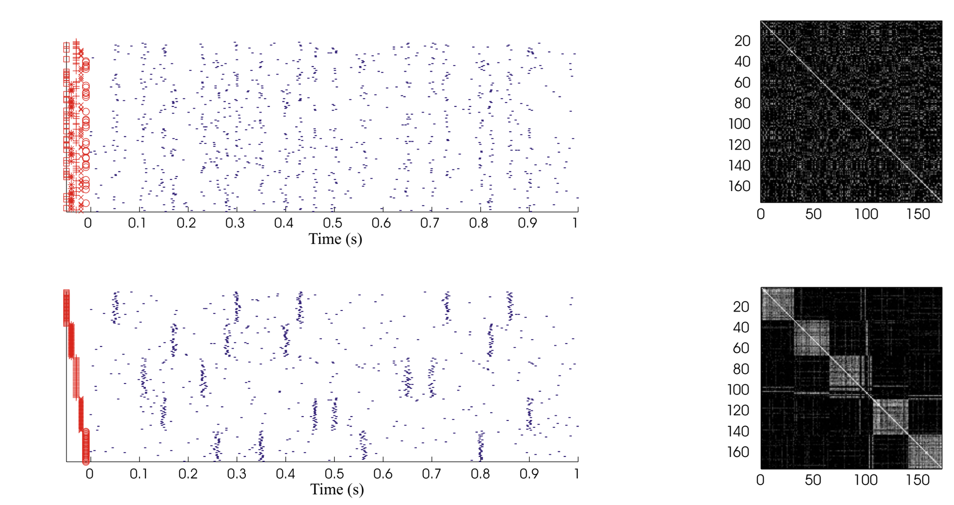
3.1 Detecting spike patterns



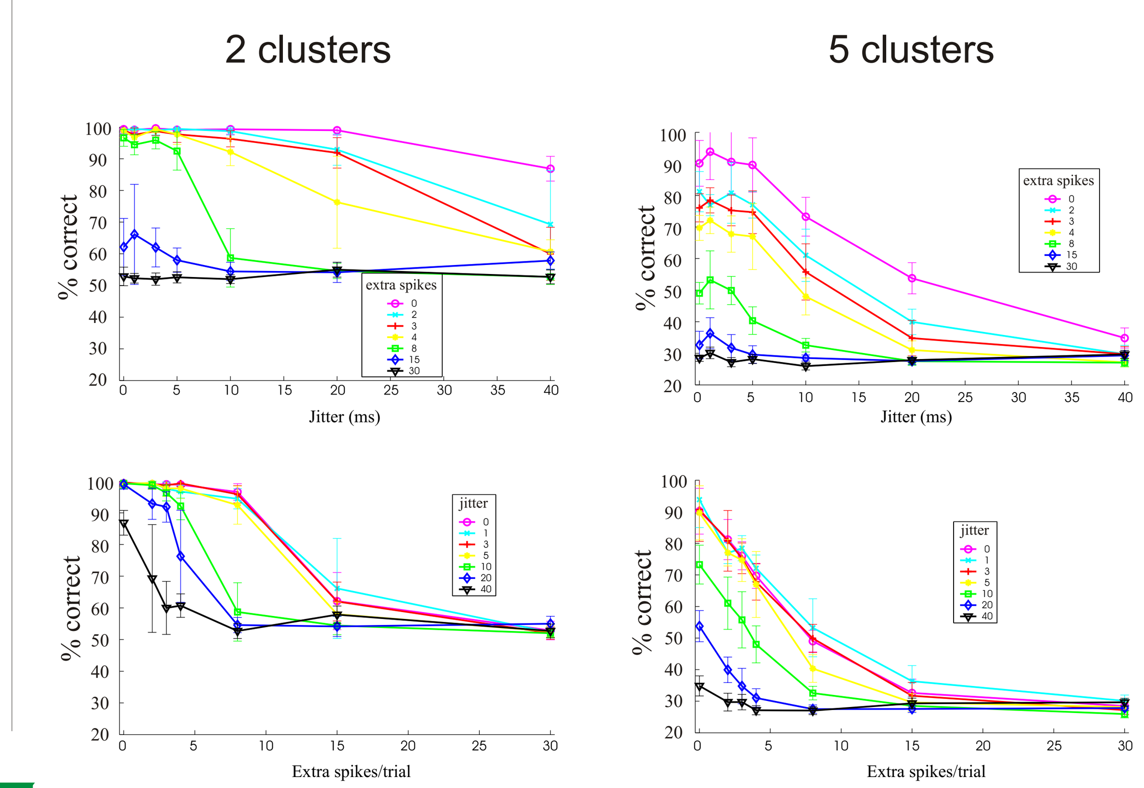
Fuzzy K-means algorithm

Iterative procedure aimed at minimizing the objective function $O_f(U,V)$ for K clusters, N data points. C_j are the cluster centers, V_i are the data points (vectors), u_{ij} are the membership weights, and f is the fuzzy factor (>1).

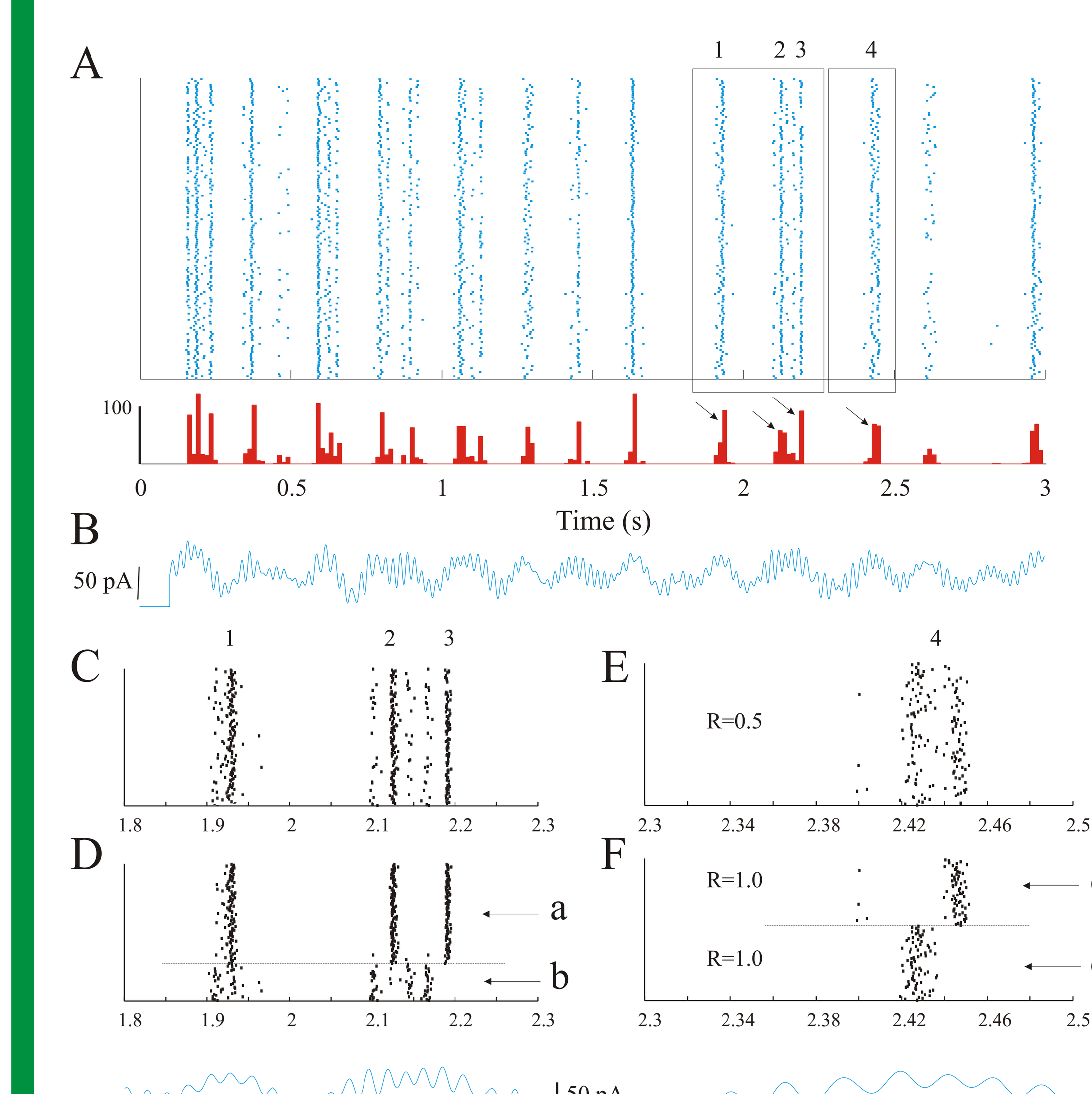
$$O_f(U,V) = \sum_{i=1}^{N} \sum_{j=1}^{K} u_{ij}^f \left\| V_i - C_j \right\|^2$$



3.2 Tests on a surrogate dataset



3.3 Responses to multiple frequencies in vitro



Evidence for spike patterns in vitro.
A: A layer V prefrontal pyramidal cell was repeatedly injected with the same current waveform (**B**) consisting in the mixture of two broadband stimuli 5 Hz (+-3, 75%) and 40 Hz (+-10, 25%). 150 trials are shown, each tick marks the occurrence of an action potential. The histogram is presented below the rastergram. Labels 1-4 are sample times when histogram peaks are clearly detected (arrows). Panels **C** and **E** show an expanded view of two sample sections depicted by the left and right boxes in A, respectively. Panels **D** and **F** show the reordering of the trials in C and E, using the fuzzy K-mean clustering algorithm. The algorithm was run separately on C and E. The clustering algorithm reveals the presence of temporal structure within trials. In the two cases, the trials can be separated in two groups that show distinct firing patterns (arrows, labels a-d). These patterns were not apparent from the raw rastergrams (C and E). The stimulus is reproduced under each rastergram.

Conclusions

- We introduce a newcorrelation-based measure of spike timing reliability. The measure degrades smoothly with jitter, and extra and missing spikes and relies on only one parameter.
- Model neurons are more reliable at a frequency that corresponds to their DC firing rate (Hunter et. al. 1998). Their frequency preference can be modulated by modulating intrinsic membrane currents.
- Neurons in vitro respond to mixture of frequencies by generating several discrete spike patterns (attractors). Reliability depends on the attractor structure of the response.
- Clustering algorithms with pairwise correlation-based similarity measures between individual spike trains can identify the different attractors, which may not be visible in the PSTH.

References

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Acknowledgments

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