



The role of cellular memory in the function of stellate cells in the rat entorhinal cortex

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Introduction

When depolarized, cells in the perirhinal (Bilkey and Heinemann, 1999) and entorhinal cortices (Alonso and Llinás, 1989) exhibit clustered spikes, loosely phase-locked to a subthreshold voltage oscillation in the theta frequency range.

Field voltage oscillations at the same frequencies are often observed in these areas during freely moving behavior (Bland, 1986), indicating synchronized neuronal activity and, very likely, rhythmic synaptic input to these neurons.

As we demonstrate with a statistical model of spike production, clustered spiking represents a short term memory of the cell for its own recent activity. We wondered whether this memory persisted in the presence of a periodic stimulus and whether it might have functional consequences for the processing of simple patterns of synaptic input.

Methods

Recordings

Recordings were made with patch clamp electrodes in 300 μm horizontal hippocampal slices taken from Long Evans rats aged 20-26 days. Recording fluids were 125 mM NaCl, 2.5 mM KCl, 1 mM MgCl_2 , 25 mM NaHCO_3 , 1.25 mM NaH_2PO_4 , 25 mM glucose, 4 mM kynurenic acid, 10 μM bicuculline. Current stimuli were delivered from Matlab via the Ax-clamp 700A amplifier.

Markov model

Oscillations were identified in the cell voltage, after bandpass filtering (constant current stimuli) or according to the phase of the input (sinusoidal stimuli). Each cycle was coded as a 1 or 0 according to the occurrence or absence of a spike.

Markov models to fifth order were generated from response codes by sampling the number of times a 1 followed each possible sequence of 2^5 five-bin sequences in a long stretch of the response (at least 3 mins).

Results

1. Entorhinal stellate cells have memory.

Figure 1.1. Under constant current, stellate cells of the entorhinal cortex exhibit a voltage oscillation and clustered spiking (above). We coded the cell's output as a binary string according to whether the cell did (1) or did not (0) spike on consecutive cycles (below). Current is 210 pA. Spikes are cut off.



110 0 1111000 0 110 0 1 110001100 0 0 1 1110 0 0 110 0 0

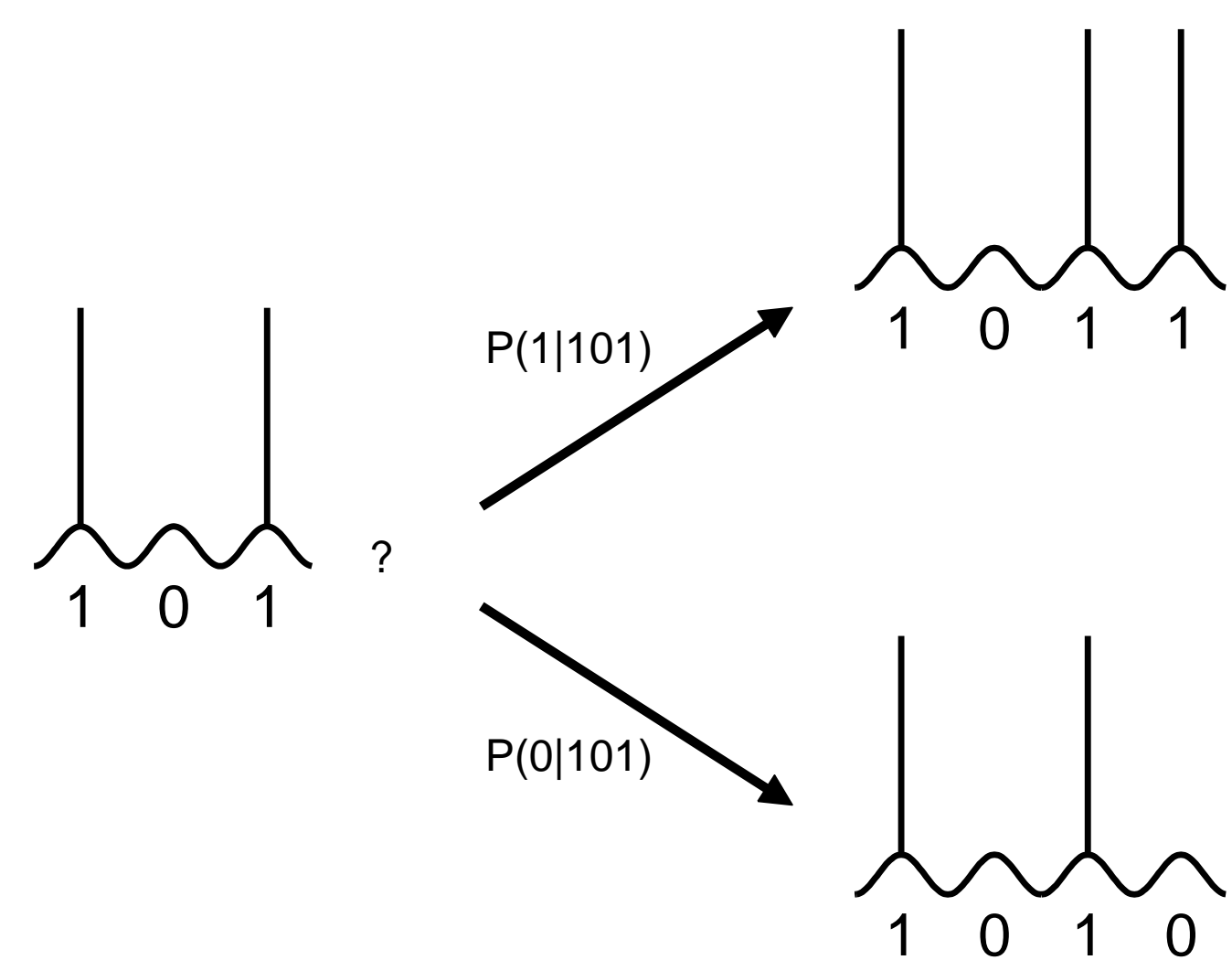


Figure 1.2. We formed a statistical (Markov) model of spike patterning from this code by sampling the probabilities of a 1 (a spike) following different short binary sequences (recent activity). For example, for a third order model, one would sample these probabilities for the eight possible spike histories, {000, 001, 010, 011, 100, 101, 110, 111}.

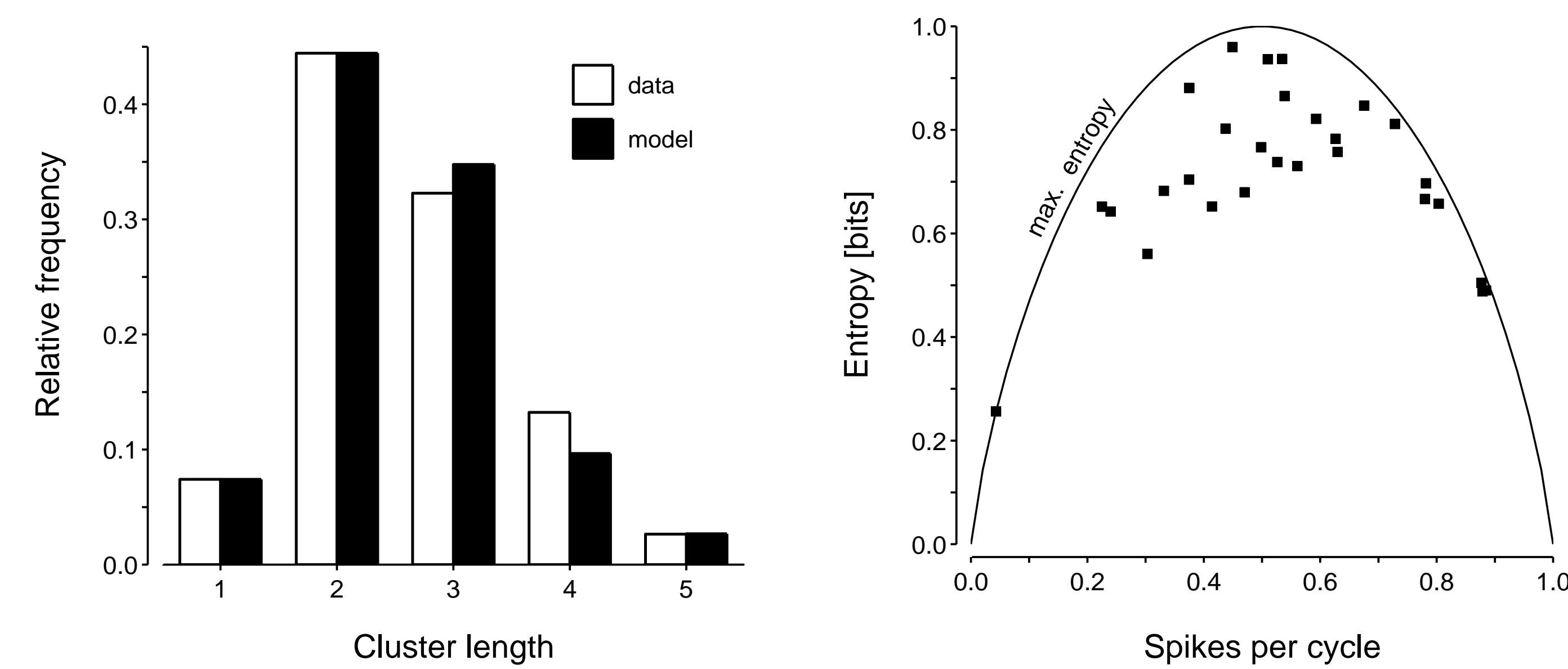


Figure 1.3. The power of the model is reflected in its ability to make predictions of spike train patterning such as the distribution of cluster lengths (the number of spikes in a cluster).

Figure 1.4. The cell's entropy rate, calculated from the model, is always less than that expected for a memoryless binary source (solid line), reflecting the influence of the past on spike production. Points calculated for six cells under several background currents per cell.

2. Entorhinal stellate cells can follow a simple patterned input.

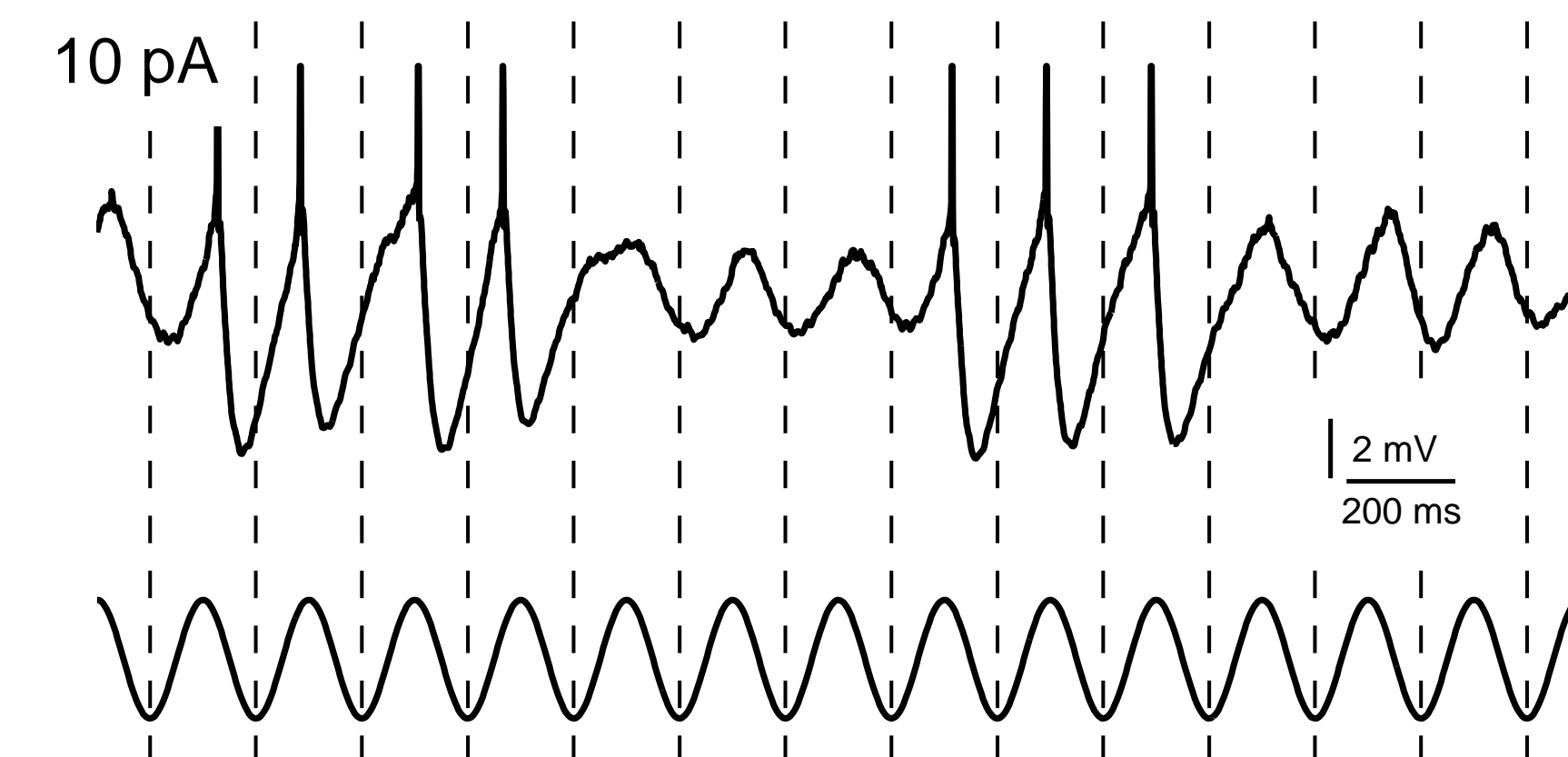


Figure 2.1. Entorhinal stellate cells can be easily entrained by sinusoidal current and still exhibit spike clustering. Above, response to a stimulus of 10 pA peak-to-peak amplitude. Below, stimulus.

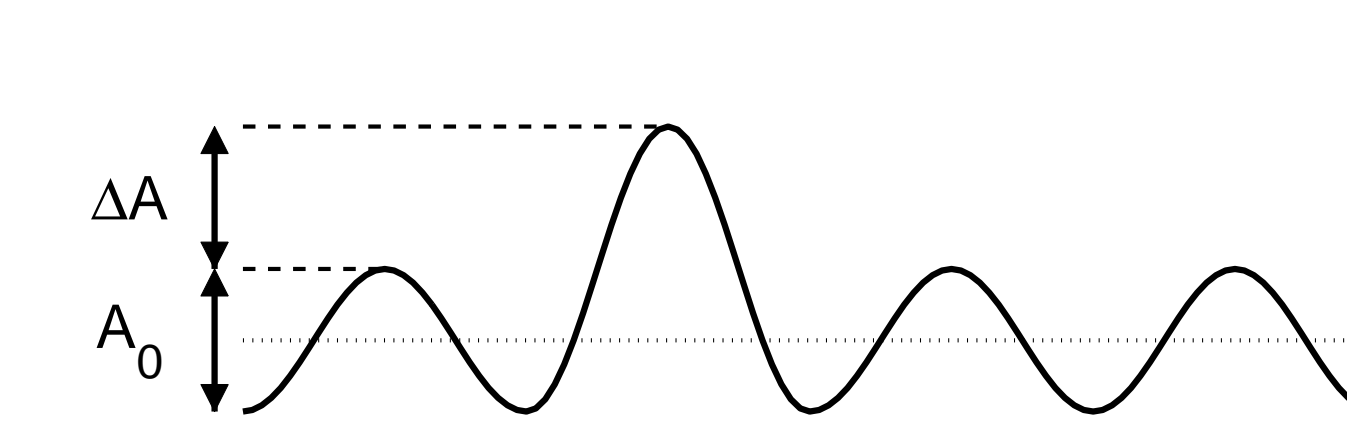
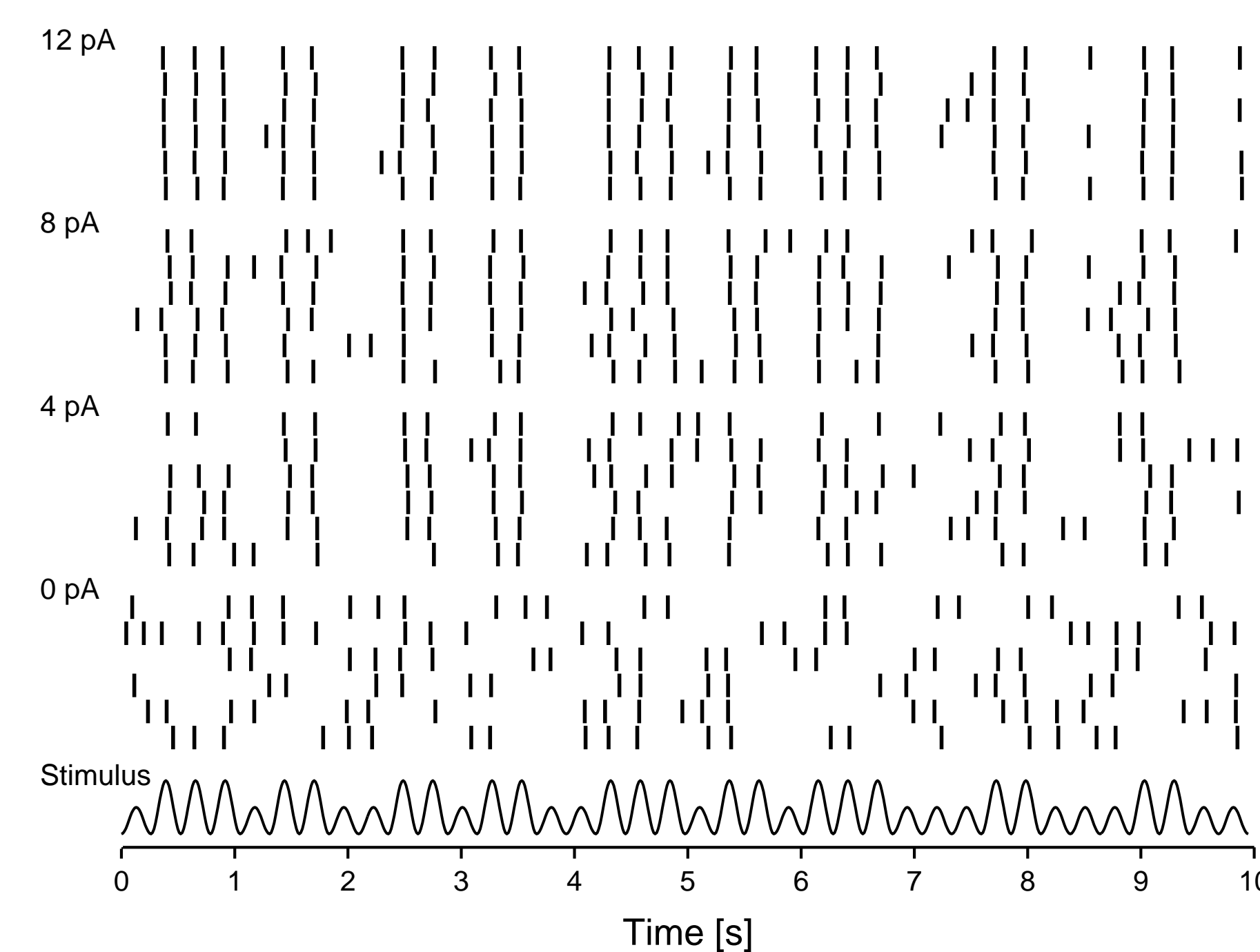


Figure 2.2. We delivered modulated sinusoidal current stimuli in which the peak-to-peak amplitude of a given cycle is either A_0 or $A_0 + \Delta A$. The sequence of high and low amplitudes was generated from the statistical model of spike patterning elicited by a non-modulated sinusoid.

Figure 2.3. As stimulus amplitude, ΔA , is increased, the reliability of a cell's response increases, indicating that the cell is comfortable responding to natural stimulus sequences. Bottom, stimulus excerpt. Above, raster plot of spike times in response to six repeats of the stimulus at different amplitudes, ΔA . $A_0 = 8$ pA.



3. Entorhinal stellate cells are more reliable to 'natural' input sequences.

We code the binary sinusoid stimulus as a binary string, 1 for a high amplitude, 0 for a low. The response is similarly coded, 1 for a spike, 0 for none.

We define two measures of the response of a stellate cell to a binary sinusoidal input (Box 1):

- Fidelity: How much the response code resembles the stimulus code.
- Reliability: How much the coded responses to a repeated stimulus resemble each other.

We calculated these measures for a stellate cell responding to binary sinusoidal stimuli with two different types of patterning, one generated from the statistical model of responses to a non-modulated sinusoid, the other with no dependency between cycles.

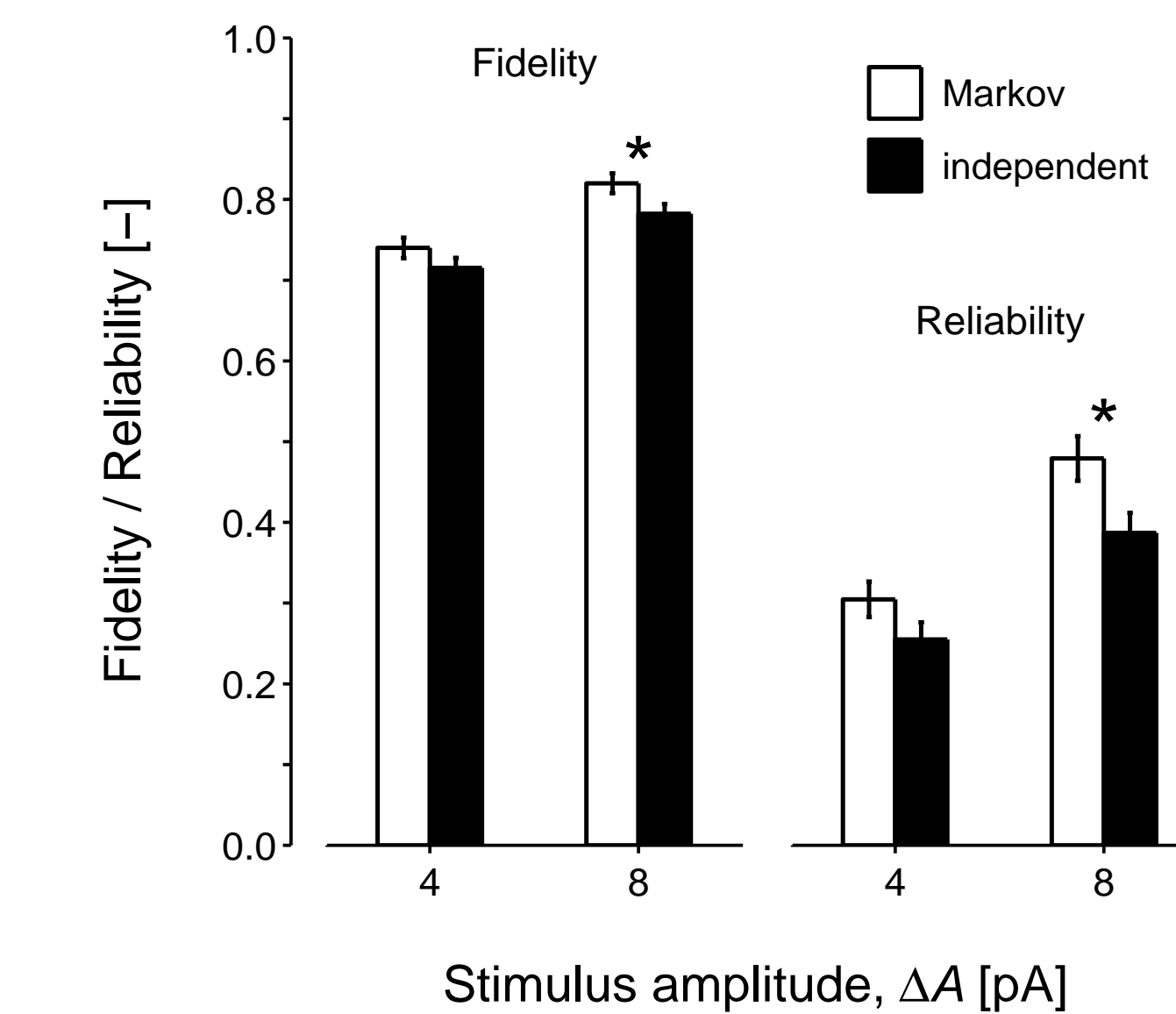


Figure 3.1. In this cell, measures of fidelity and reliability are higher for naturally patterned (Markov) stimuli than for independent sequences, especially at a stimulus amplitude, ΔA , of 8 pA. Bars indicate S.E.M., calculated across all cycles in the stimulus. * indicates a significant difference at the 5% level (two-tailed t -test). $A_0 = 8$ pA. Cycles per stimulus, 115. Repeats per stimulus, 20.

Conclusion

Stellate cells seem adapted to respond to periodic inputs and this type of input is consistent with what is known about population activity in the entorhinal cortex.

We have used perhaps the simplest possible patterned input, a modulated sinusoid taking one of just two values on each cycle.

Stellate cells can comfortably represent such inputs in the pattern of their outputs. However, we found that a stellate cell responded more reliably to sequences with particular statistical structures.

This stellate cell achieved higher reliability in response to 'natural' sequences by representing them more faithfully than it represented less predictable sequences. One can say that the cell was performing a rudimentary matched filtering, although further recordings are required to generalize this statement.

Box 1. Fidelity, F , and reliability, R .

$$F = 1 - \frac{1}{M} \sum_{m=1}^M \frac{1}{K} \sum_{k=1}^K |y_{mk} - x_m| \quad (1)$$

where m indexes the M oscillation cycles, k indexes the K stimulus repeats, x is the coded input and y is the coded output.

$$R = 1 - \frac{1}{M} \sum_{m=1}^M \frac{2}{K} \sum_{k=1}^K |y_{mk} - \bar{y}_m| \quad (2)$$

where

$$\bar{y}_m = \frac{1}{K} \sum_{k=1}^K y_{mk} \quad (3)$$

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References

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- BILKEY DK AND HEINEMANN U (1999). Intrinsic theta-frequency membrane potential oscillations in layer III/V perirhinal cortex neurons of the rat. *Hippocampus* 9: 510-518.
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