Statistical method for detection of firing rate changes in spontaneously active neurons

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Abstract

We present a simple statistical method for detection and identification of firing rate changes in spontaneously active neurons. Spontaneously active neurons (such as olfactory neurons) can be, in response to stimulation, either excited or suppressed and thus increase or decrease the spike firing rate. The described method is based on the detection of changes in slope of cumulative spike time distribution and efficiently detects excitations and suppressions. Using the simulated spike trains we examined the methods power in relation to response strength and duration.

Keywords: Spike train analysis; Cumulative distribution function; Firing rate; Spontaneous activity; Olfaction

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1. Introduction

Single olfactory receptor cell responds to chemical stimulation with either decreased (suppression) or increased (excitation) action potential firing rates. Most olfactory receptor cells respond to several different chemical stimuli. To understand the quantitative properties of the olfactory code composed of receptor cell activities, one needs to know the activity of a large number of olfactory receptor neurons. Detection of either excited or inhibited responses of the follower mitral cells is also very important in understanding nerve code of olfactory stimuli in the second layer of the olfactory network. Although there are many recent contributions to improve the spike train activity response detection [1, 4], the peri-stimulus histogram (PSTH) is the most common method for description and detection of firing rate changes.

Here we first present the method, based on the changes of spike times cumulative distribution slopes, for rapid and reliable detection of neuron's firing rate changes. Next we describe the simulated spike trains used to asses method's power. Then we show some results from studies of olfactory neurons responses.

2. Method description

A spike train, shown as a raster plot on Fig. 1., can be considered as a sequence of discrete spike events (or simply events) with occurring times $\{t_i\}$, $i = 1, 2, \ldots, n$. Cumulative distribution function (cdf) at time t_i is defined as a number of events prior and up to t_i or rank(t_i) = i and is strictly increasing step function changing at times t_i in unit steps (Fig. 1.). The slope of cumulative distribution changes with density of events

and is equal to density of events (per unit time) or firing rate. For each reference event t_i an *neighborhood* ($W_{i,j}$) is defined as interval (t_{i-j-1} , t_{i+j}] that contains $J = 2j+1$ events and has duration $T_i = t_{i+j} - t_{i-j-1}$. Local linear regression, based on events in neighborhoods $W_{i,j}$ may be used to estimate the cdf slope. At any spike time t_i the regression line slope b_i estimates the density of events at reference time t_i (Fig. 1.).

The distribution of firing rates (slopes b_i) of spontaneous activity prior to stimulus application serves as the basis for comparing activity during stimulus application with basal spontaneous activity. Quantile values Q_α and $Q_{1-\alpha}$ (for example, percentiles C_5 and C_{95}), can be used to predict expected slopes during spontaneous activity. Consider the case where stimulus is applied and one expects the response within a reasonably short time interval after stimulus application. On the basis of control limits Q_α and $Q_{1-\alpha}$, three possible decisions can then be made:

a) if firing rates during expected response time are higher than $Q_{1-\alpha}$ the activity is identified as 'excitation' (E),

b) if firing rates are lower than Q_α the activity is identified as 'suppression' (S), and

c) if firing rates are between the control limits the activity cannot be distinguished from the spontaneous (basal) activity ('no response', N).

The first two decision rules can incorrectly identify a response when none has occurred (Type I error). The last decision rule can possibly fail to detect a response when one has occurred (Type II error). Using the simulated spike trains and control limits for selected Type I error rate α, the power was calculated as the percentage of correctly identified responses in predefined time window.

3. Rate functions used in computer simulation

To asses method's power we employed computer intensive analyses of simulated spike trains based on rate functions [3]

$$\rho_{b,A,w}(t) = b + A\beta_{\tau_1,\tau_2}(t - t_0)$$

where b is baseline spontaneous activity firing rate, A measures the response strength as a maximal change of firing rate during response and t_0 denotes the time of response onset. Normalized response function β_{τ_1,τ_2} is defined as

$$\beta_{\tau_1,\tau_2}(t) = \begin{cases} \beta_0(e^{-\frac{t}{\tau_1}} - e^{-\frac{t}{\tau_2}}) & t \geq 0 \\ 0 & t < 0 \end{cases},$$

where $\tau_1 > \tau_2 > 0$ are fall and raise time constants and $\beta_0 = (\tau_1 / \tau_2)^{(\tau_1+\tau_2)/(\tau_1-\tau_2)}$ is the normalizing parameter. Function $\beta_{\tau_1,\tau_2}(t)$ is normalized to have a unit maximum value between 0 and its standard width given by $w = \sqrt{\tau_1^2 + \tau_2^2}$. The family of rate functions $\rho_{b,A,w}$ can be used to simulate excitations (A>0), suppressions (A<0) as well as no change from basal firing rate b (A=0). The temporal extend of response can be described with w and response relative strength by A/b. Sets of N=100 simulated spike trains for different combinations of parameters b, A, and w were analyzed. Detected change in firing rate was identified as response if found in time window w after simulated stimulus application. As additional test of correct response determination the response onset time t_0 was estimated.

4. Simulation results

The results of power determination for different combinations of basal spontaneous activity b and response strength A are shown in Fig 2. The power increases with increasing absolute response intensity A (signal), but decreases with increasing basal spontaneous activity b (noise) (Fig 2). The power basically depends on relative intensity of response A/b and increases with absolute relative intensity (signal-to-noise ratio). In the simulations empirical Type I error rate was about 0.06, close to used $\alpha=0.05$ (Fig 2.). The power of response detection shows similar pattern for response duration w and increases with increasing response duration w for both, excitations and suppressions. Estimated response onset times were close to simulated response onset times t_0.

5. Application to experimental data

Fig. 3 and 4 show the results of analysis of experimental data. Data were recorded extracelulary from mitral cells in olfactory bulb of goldfish (*Carassius auratus*) briefly exposed to pheromone mixtures [2]. Brief excitation is detected and shown on Fig. 3. while mixed response (suppression followed by an excitation) is shown on Fig. 4.

6. Conclusion

Described method is simple yet efficient way for detection of firing rate changes in spontaneously active neurons. Compared to usually used peri-stimulus histograms (PSTH), it avoids problems with binning of data. In comparison to PSTH analysis, which

is an average over many trials, described method detects changes in spontaneous activity in one realization of the stimulus. It is able to detect both types of responses, excitation and suppression. Its power mostly depends on the relative intensity of response and response duration. The pre-stimulus recording, on which the control limits are based, should contain sufficient number of spikes which means that pre-stimulus recordings should be longer for neurons with low spontaneous firing rate. For application of described method, the division of the recording to the part of spontaneous activity (before start of stimulus application) and part of potentially disturbed activity (after start of stimulus application) is essential, though exact stimulus onset at the receptor site is not needed. In such situations, the method is able not only to determine the response type but also to estimate the response onset (Figs 3. and 4.).

The method was successfully used in analysis of responses of olfactory receptor neurons in fishes [2, 5, 6]. The method is implemented in S-PLUS, and is suitable for rapid analysis of batches of recordings.

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References

[1] Z. Chi, P.L. Rauske, D. Margoliash, Pattern filtering for detection of neural activity, with examples from HVc activity During sleep in zebra finches Neural Computation 15 (2003) 2307-2337.

[2] L. Hanson, Ph. D. Thesis, Department of Fisheries, Wildlife and Conservation Biology, University of Minnesota, (2001).

[3] M. Nawrot, A. Aertsen, S. Rotter, Single-trial estimation of neuronal firing rates: From single-neuron spike trains to population activity. J Neurosci Methods, 94 (1999) 81-92.

[4] R. Ratnam, J. B. M. Goense, and M.E. Nelson, Change-point detection in neuronal spike train activity. Neurocomputing 52-54 (2003) 849-955.

[5] P.W. Sorensen, Biological responsiveness to pheromones provides fundamental and unique insight into olfactory function, Chemical Senses 21 (1996) 245-256.

[6] T. Valentincic, J. Metelko, D. Ota, V. Pirc, A. Blejec, Olfactory discrimination of amino acids in brown bullhead catfish, Chemical Senses 25 (2000): 21-29.

Andrej Blejec (born 1953) studied mathematics at University of Ljubljana, Slovenia, and got Ph.D. at the same university. He is an assistant professor of Statistics and Computer science at the University of Ljubljana, Department of Biology. Currently he works as a statistician at the National Institute of Biology in Ljubljana. Analysis of neurophysiologic data is a part of his work as statistical consultant for research in biology.

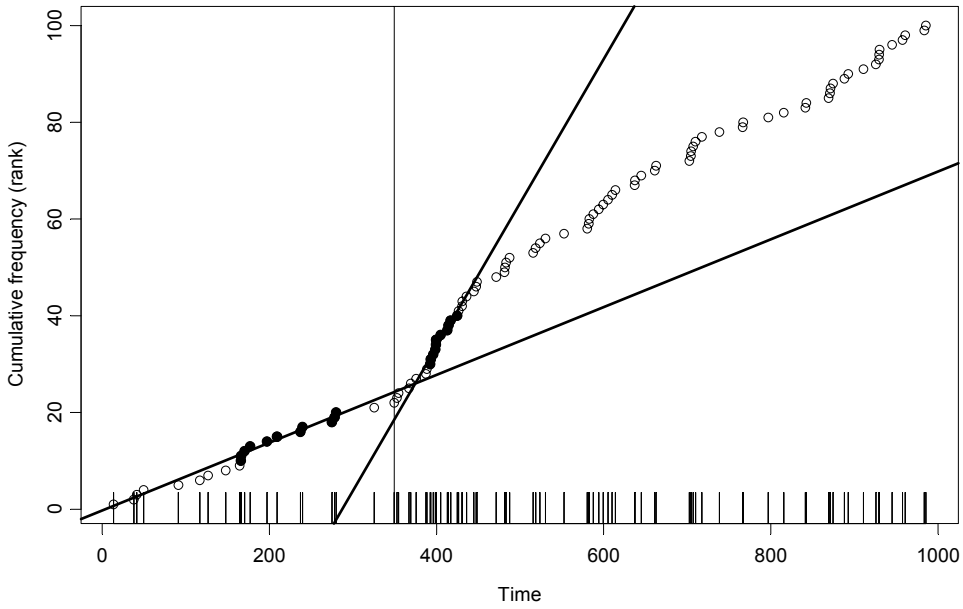

Fig. 1. Cumulative distribution (○) of excitation (simulated data) after stimulus application at time 350 (vertical line). Local linear regression lines (slanted lines), based on neighborhood data (●), showing the slope at first spike times after 200 and 400.

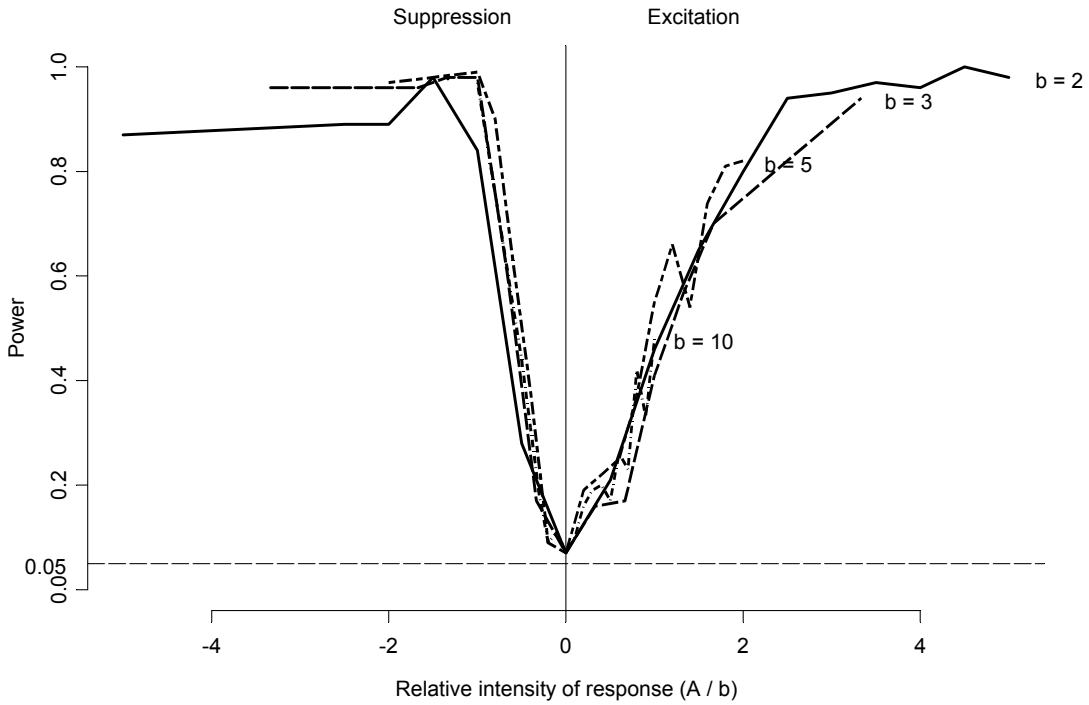

Fig. 2. Power versus relative intensity of response *A/b* for various basal firing rates *b* = 2 (—), 3 (– –), 5 (– - –), and 10 (– · –) and α=0.05 (horizontal dashed line).

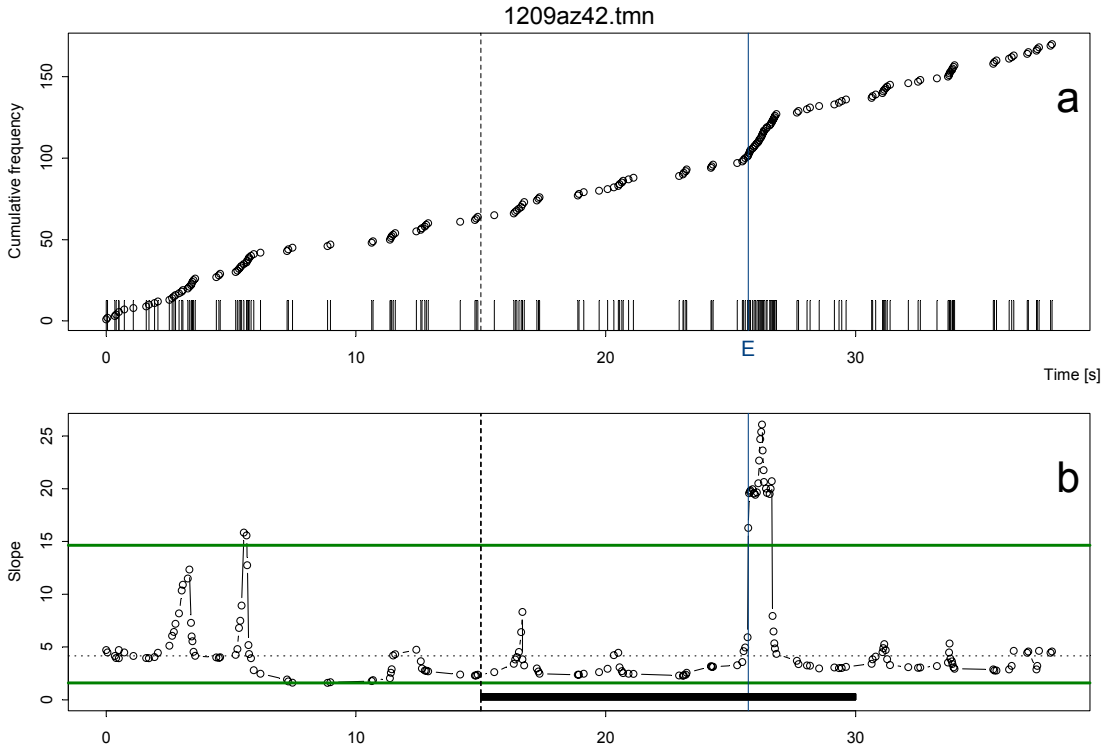

Fig. 3. Analysis of extracelular recording from mitral cell in olfactory bulb of goldfish (Carassius auratus), briefly exposed to pheromone mixtures. Excitation (E) was detected during the expected response time interval (horizontal bar in panel b), 7.393s after stimulus application. Cumulative distribution (a) and estimated slopes (b) with control limits (horizontal lines), median slope (dotted horizontal line), time of expected response (horizontal bar), time of stimulus application (dashed vertical line), and response detection time (vertical line, E).

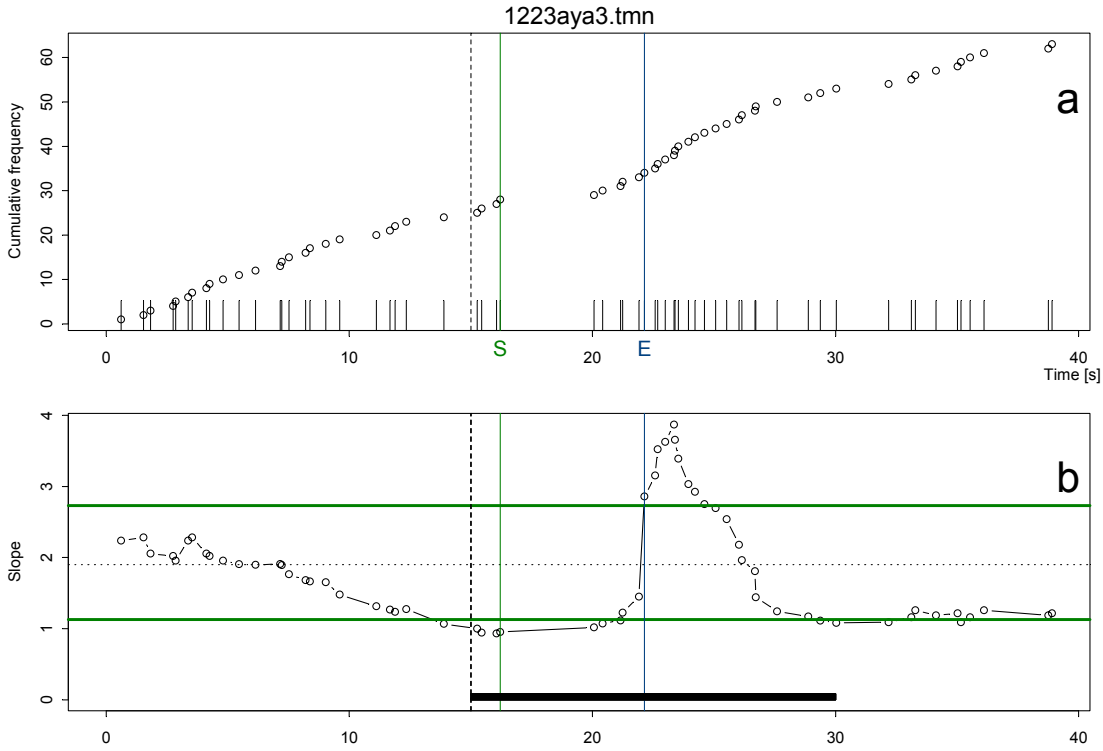

Fig. 4. Analysis of extracelular recording from mitral cell in olfactory bulb of goldfish (Carassius auratus) briefly exposed to pheromone mixtures. Suppression (S, 0.082s after stimulus application) and excitation (E, 6.545s after stimulus application) were detected during the expected response time interval (horizontal bar in panel b). Cumulative distribution (a) and estimated slopes (b) with control limits (horizontal lines), median slope (dotted horizontal line), time of expected response (horizontal bar), time of stimulus application (dashed vertical line), and response detection times (vertical lines; S, E).