

**Statistical Analysis of Temporal Evolution  
in Single-Neuron Firing Rates**

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# BACKGROUND

Keywords:

- neuron: cell that is the fundamental functional unit of nervous tissue. It can produce an electrical activity.
- firing: electrical discharge of a neuron.
- spike: firing

# MOTIVATION

The study is about the neuronal activity in the Supplementary Eye Field (SEF).

Our goals are

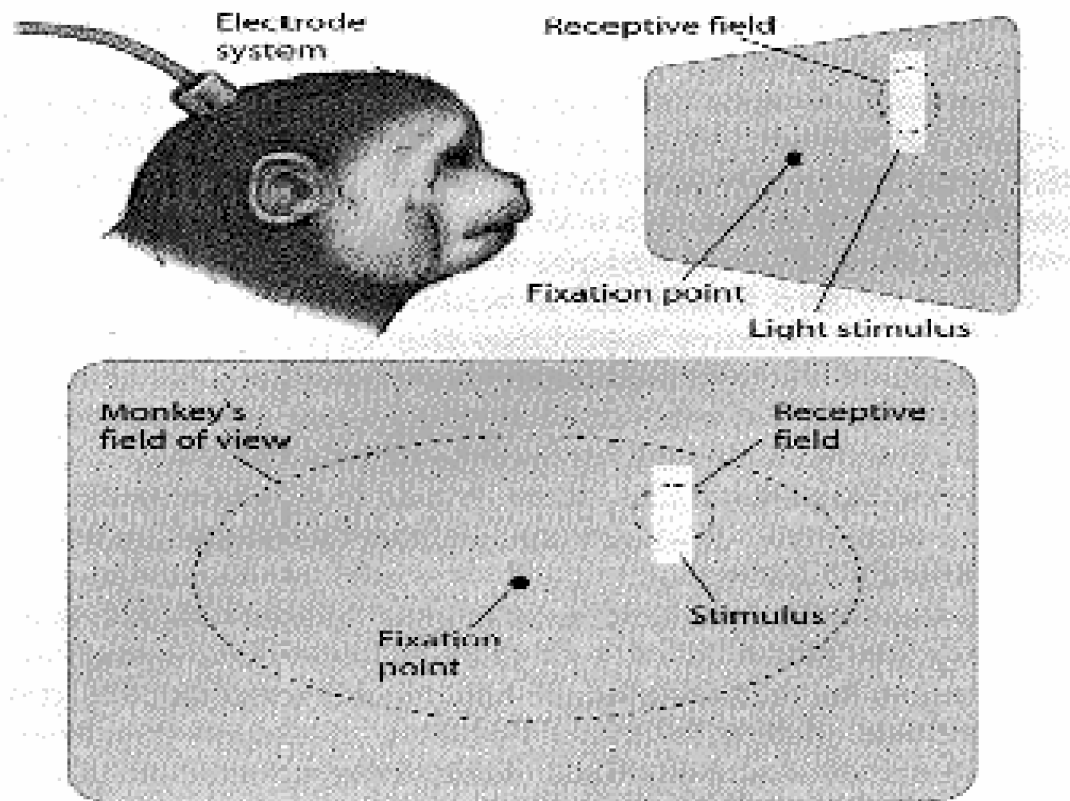
- to improve on traditional analyses
- to model the average firing rate of neurons as a function of time
- to make inferences about important characteristics of the average firing rate

# EXPERIMENT DESCRIPTION

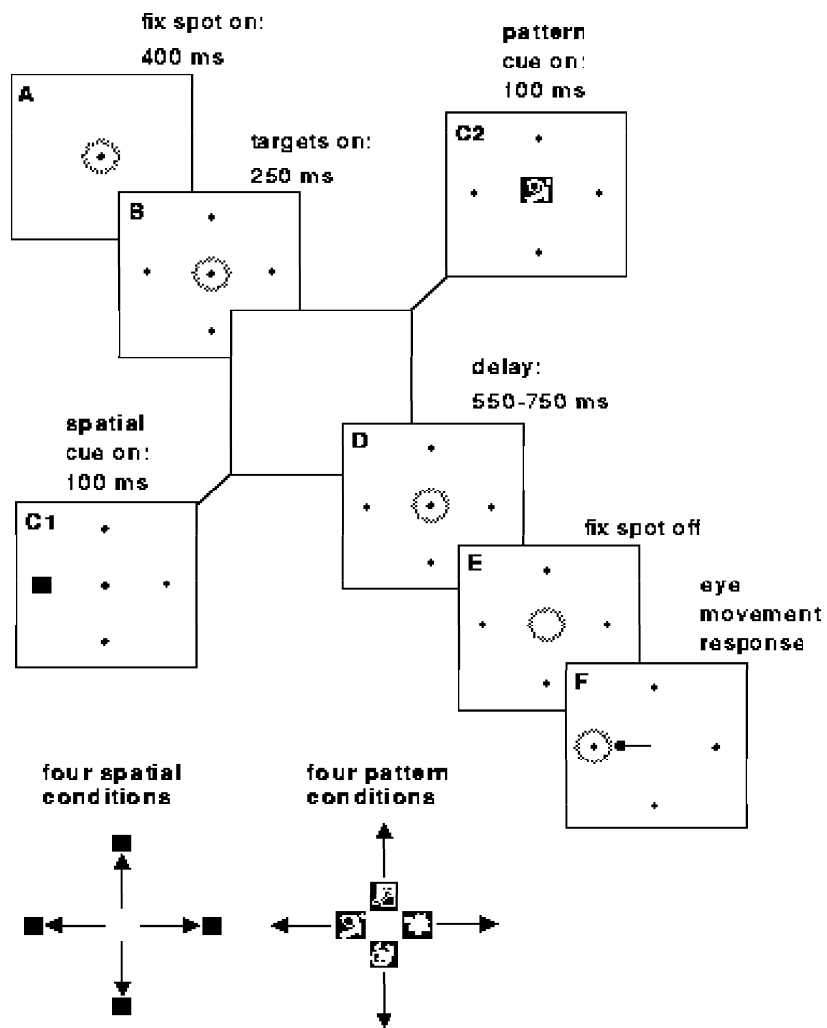
A trained monkey has to perform two kinds of tasks (spatial vs. pattern)

- firings recorded from a single neuron
- greater intensity (firing rate) corresponds to more activation

# EXPERIMENT DESCRIPTION



# EXPERIMENT DESCRIPTION



# DATA

The data from one experiment consist essentially of the codes of relevant events and of their corresponding times.

Events are:

experimental condition changes (example: appearance of the cue) or neuronal firings

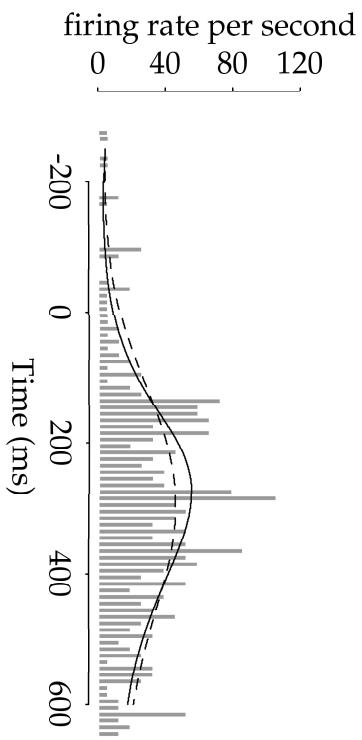
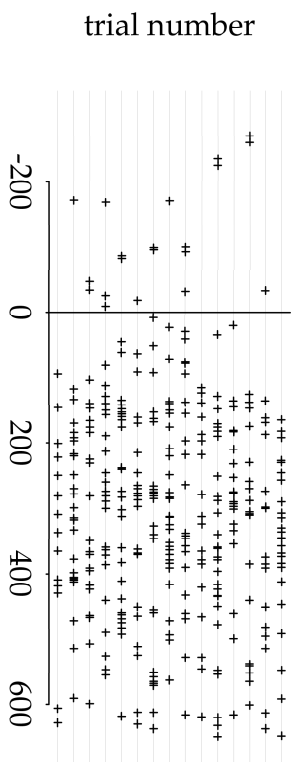
# DATA

- 84 neurons from the SEF
- 8 experimental conditions (4 spatial and 4 pattern)
- 11 to 42 trials with median 16

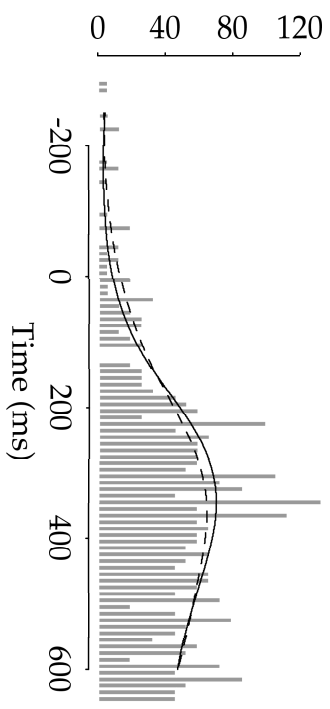
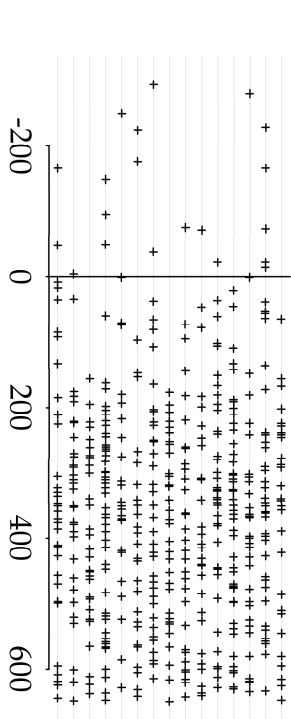
However each neuron has a *preferred direction* in which it fires most rapidly. We retained the data only in each neuron's preferred direction so

- 2 actual experimental conditions

# Spatial



# Pattern



## SUBSTANTIVE ISSUES

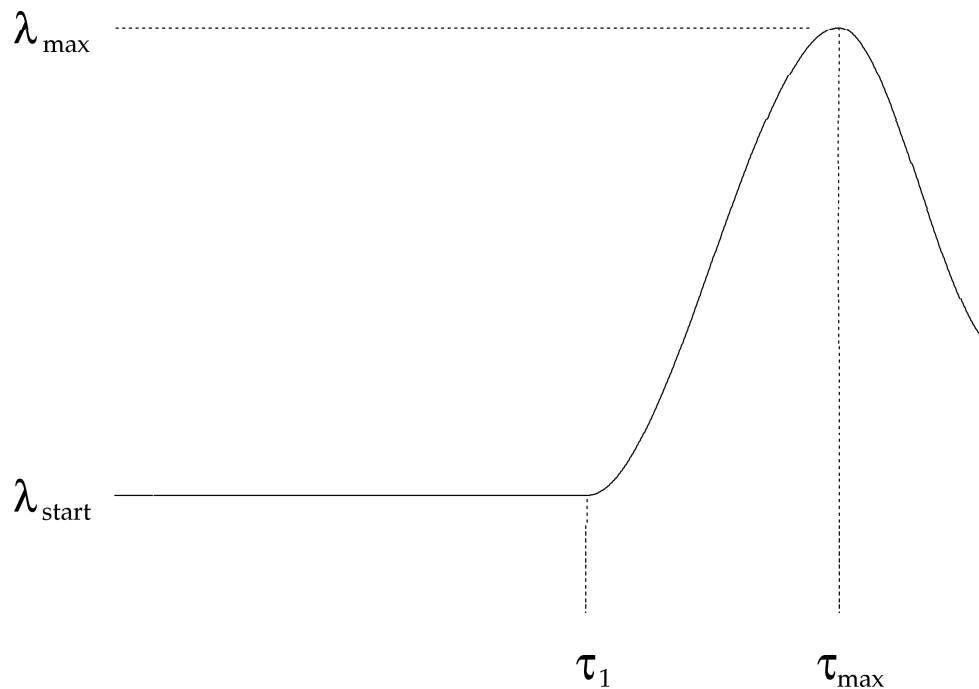
It is known that, following an endogenous cue (i.e. pattern cue) instead than an exogenous cue (i.e. spatial cue), attention is

- allocated more slowly
- lingers longer

We want to ascertain whether neural activity in the SEF follows a similar course.

# STATISTICAL ISSUES: INTENSITY FUNCTION $\lambda(t)$

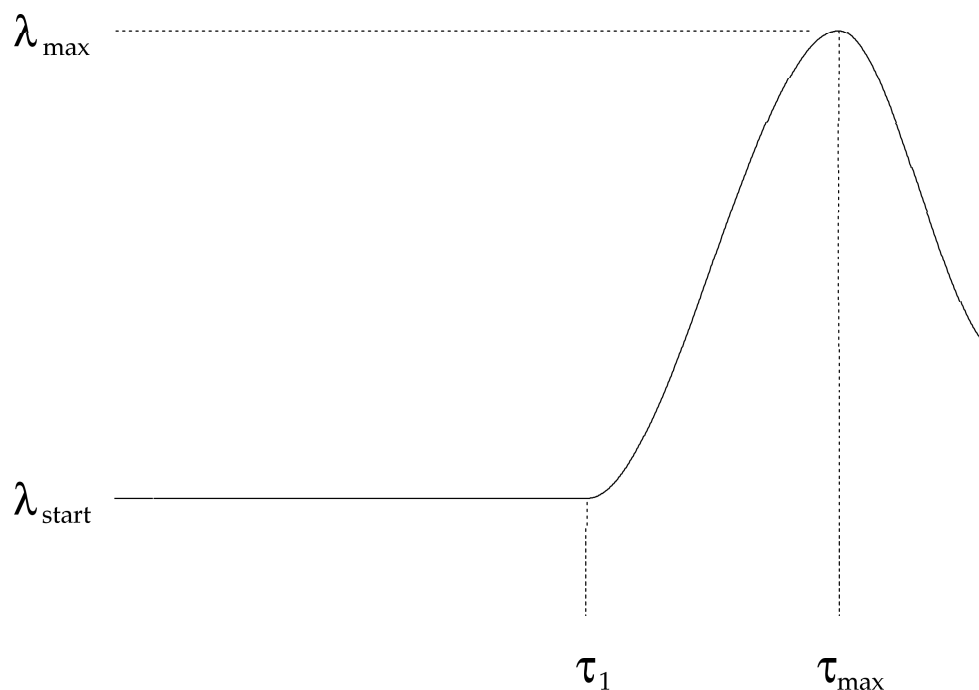
Model for the sequence of firings



# STATISTICAL ISSUES

The quantities of interest are

- the time at which the maximum firing rate occurs  $\tau_{max}$
- the maximal firing rate  $\lambda_{max}$
- the mean end firing rate  $\lambda_{end}$  (the firing rate averaged over the interval [500, 600]ms after the presentation of the cue)



# STATISTICAL ISSUES

We need to

- model the average firing rate of a neuron as a function of time
- check the fit
- examine the quantities of interest
- combine results (population analysis)

# INHOMOGENEOUS POISSON PROCESSES

Assumptions:

- $P(N_{t,t+h} = 1) = \lambda(t)h + o(h)$
- $P(N_{t,t+h} = 0) = 1 - \lambda(t)h + o(h) \quad \forall t, h$
- increments are independent

$\lambda(t)$  is the intensity function or instantaneous mean rate function:

$$\Pr(\text{one event in } (t, t + dt)) = \lambda(t) dt$$

# IMPORTANT PROPERTIES

Two important properties are

1. on the transformed time scale  $\tau(t) = \int_0^t \lambda(u)du$ , the series of events is a Poisson process of constant unit rate
2. when large numbers of trials are combined, the resulting set of pooled event times essentially follow an inhomogeneous Poisson process, due to general limit theory (*Daley and Vere-Jones, 1988*)

# POISSON MODELS: PARAMETRIC MODEL

For firings at times  $t_1, t_2, \dots, t_n$  in an interval  $(0, T]$ , the likelihood for a single trial is

$$L(\theta) = e^{-\int_0^T \lambda(u; \theta) du} \prod_{j=1}^n \lambda(t_j; \theta).$$

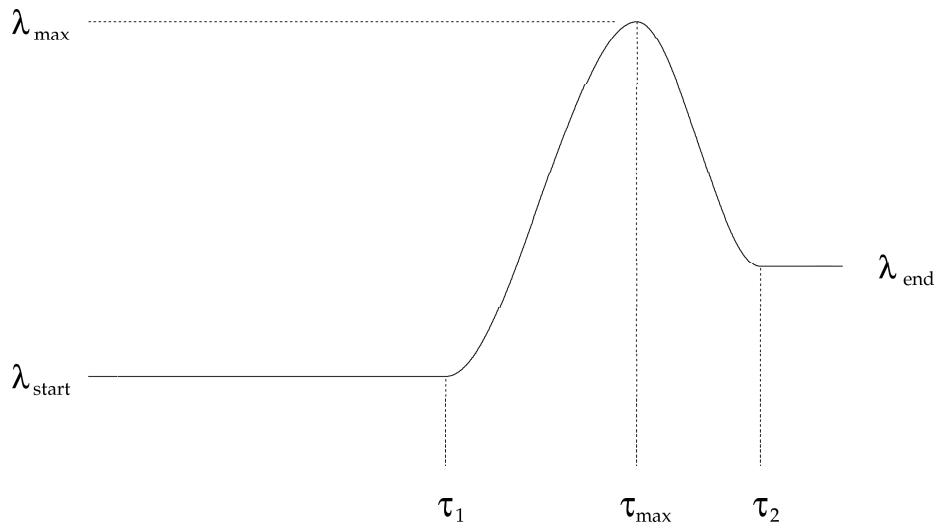
where  $\lambda(t; \theta)$  is the intensity function (mean firing rate) parametrized by the multidimensional parameter  $\theta$

The likelihood for a given experimental task is the product of the likelihoods for each of the trials recorded for that task:

$$L(\theta) = \prod_{i=1}^N \left\{ e^{-\int_0^{T_i} \lambda(u; \theta) du} \prod_{j=1}^{n_i} \lambda(t_{ij}; \theta) \right\}$$

# POISSON MODELS: PARAMETRIC MODEL

$\lambda(t; \theta)$  is a smooth hump-shaped function with constant initial and final parts:



# PARAMETRIC INTENSITY $\lambda(t)$

$\lambda(t)$  is a smooth hump-shaped function with constant initial and final parts.

Properties:

- piecewise polynomial
- continuous first derivative

$$\lambda(t) = \begin{cases} \lambda_{start}, & t \leq \tau_1 \\ \lambda_1(t) = a_3t^3 + a_2t^2 + a_1t + a_0, & \tau_1 < t \leq \tau_{max} \\ \lambda_2(t) = b_3t^3 + b_2t^2 + b_1t + b_0, & \tau_{max} < t \leq \tau_2 \\ \lambda_{end}, & t > \tau_2 \end{cases}$$

There are 7 equality constraints.

Free parameter(s):

$$\theta = (\lambda_{start}, \lambda_{end}, \lambda_{max}, \tau_1, \tau_{max}, \tau_2)$$

# POISSON MODELS: NONPARAMETRIC REGRESSION WITH SPLINES

- $\lambda(t)$  modeled using splines
- approximate Poisson likelihood by Poisson regression likelihood for binned data

$$L^*(\theta) = e^{-\delta N \sum_{k=1}^K \lambda(t_k^*)} \prod_{k=1}^K \lambda(t_k^*)^{y_k}.$$

where  $y_k$  is the number of spikes in the  $k$ -th bin of center  $t_k^*$

## POISSON MODELS: NONPARAMETRIC REGRESSION WITH SPLINES

Intensity has now a cubic spline form with flat initial part

$$\log \lambda(t) = \beta_0 + \beta_1(t - \xi_1)_+ + \beta_2(t - \xi_1)_+^2 + \beta_3(t - \xi_1)_+^3 + \beta_4(t - \xi_2)_+^3$$

where  $\xi_1 = -250$  ms and  $\xi_2 = 200$  ms are the knots.

Easy to fit via maximum likelihood

- create appropriate basis vectors
- use `glm` in S-PLUS

## KERNEL ESTIMATOR FOR $\lambda(t)$

We also want an estimate of  $\lambda(t)$  not relying on distributional assumptions

- nonparametrical estimate of  $\lambda(t)$
- smooth the histogram via a kernel estimator

$$\hat{\lambda}(t) = \frac{1}{Nh} \sum_{i=1}^M K\left(\frac{t - X_i}{h}\right)$$

where  $K()$  is the Gaussian kernel function and the bandwidth  $h$  is 100 ms

## MODEL CHECKING: POISSON ASSUMPTION

Under the Poisson assumption, by property (1) the sequence of firings on the transformed time scale  $\hat{\tau}(t) = \int_0^t \hat{\lambda}(u) du$  is a Poisson process of rate 1.

So

- transformed inter-firing times are  $\text{Exp}(1)$
- we can construct a Q-Q plot

## MODEL CHECKING: POISSON ASSUMPTION

Note that the by property (1) the rescaled inter-firing times

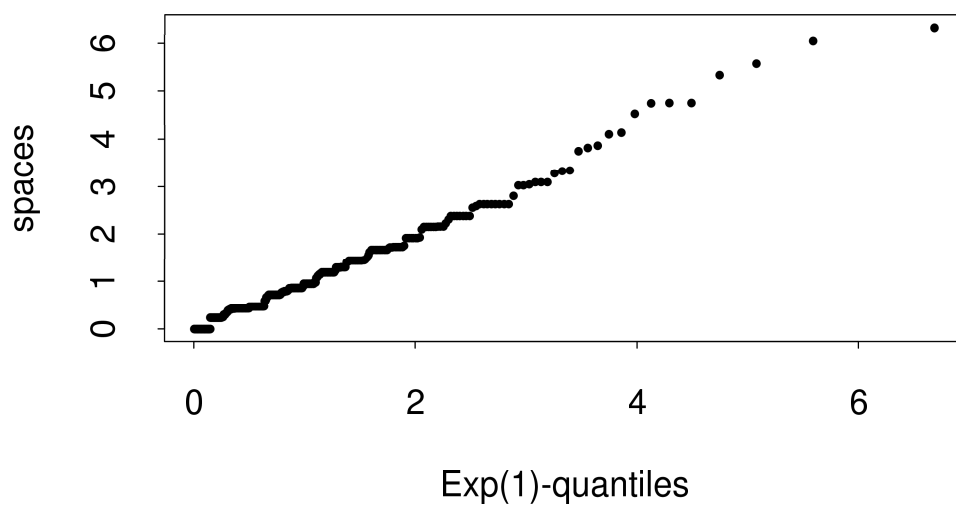
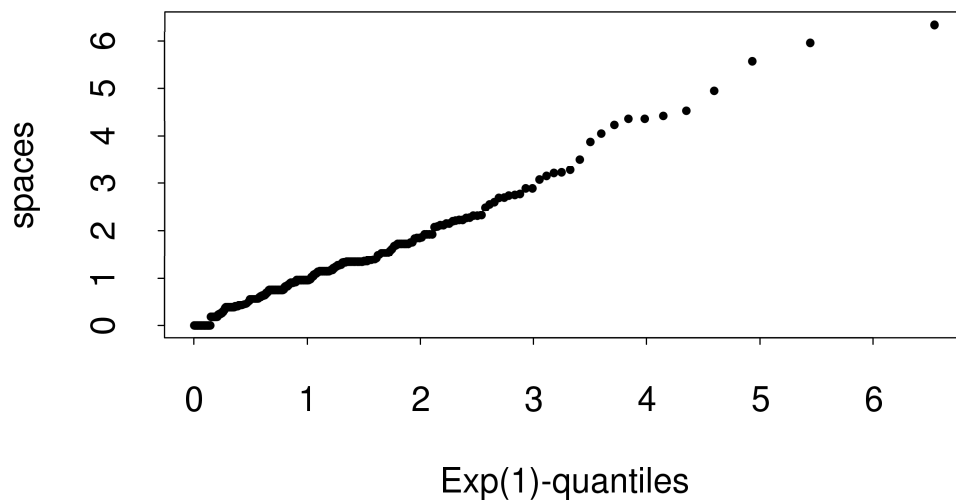
$$z_i = \int_{t_{i-1}}^{t_i} \lambda(t) dt$$

are independent and have an  $\text{Exp}(1)$  distribution if the  $t_i$ 's come from an inhomogeneous Poisson process of intensity  $\lambda(t)$ .

So, if  $\hat{\lambda}(t)$  is an estimate of  $\lambda(t)$ , we can construct a Q-Q plot for the  $\hat{z}_i$ , where

$$\hat{z}_i = \int_{t_{i-1}}^{t_i} \hat{\lambda}(t) dt$$

# Q-Q PLOTS (FOR A CHOSEN NEURON)



## FIT OF THE FIRING INTENSITY

- residual plots of  $\frac{O-E}{\sqrt{E}}$  ( $\sim N(0, 1)$  asympt.)

$O$  = observed number of firings (from histogram),

$E$  = expected number of firings from the MLE fit

- formal test of goodness of fit based on

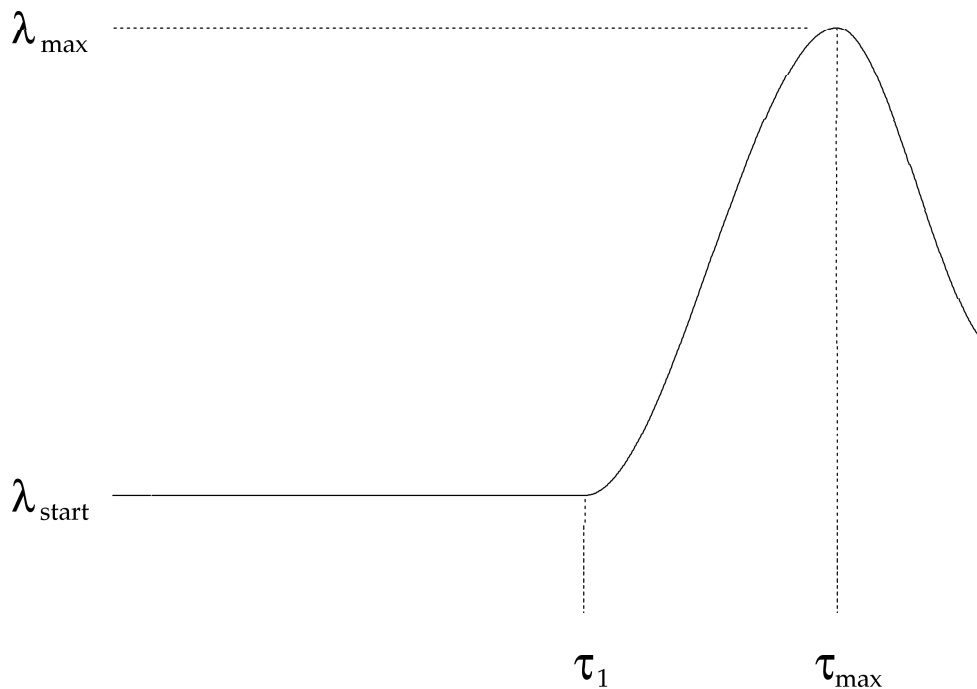
$$\left(\frac{O-E}{\sqrt{E}}\right)^2 \sim \chi_{n-p}^2$$

where  $n$  is the number of bins, and  $p$  the number of parameters

# INFERENCE: RELEVANT FEATURES

The interesting features are differences pattern-spatial

- difference of times of maximal firing rate:  $\tau_{max}^p - \tau_{max}^s$
- difference of maximal firing rates:  $\lambda_{max}^p - \lambda_{max}^s$
- difference of mean end firing rates:  $\lambda_{end}^p - \lambda_{end}^s$



# INFERENCE

Compare features of neuronal firing rate in the two tasks

- preferred direction

Two different kinds of analyses:

- **Single Neuron** analysis: single neurons as members of a population of neurons
- **Population** analysis: population means of the features

# INDIVIDUAL NEURON ANALISYS

We used three approaches

- functional comparison of two curves
- component tail areas
- bootstrap tests of significance

# FUNCTIONAL COMPARISON OF TWO CURVES

Test

$$H_0 : \lambda^s(t) = \lambda^p(t) \text{ for all } t$$

i.e.

$$H_0 : \beta^s = \beta^p$$

Under  $H_0$  the the multivariate  $T^2$  (Hotelling) statistic

$$T^2 = (\hat{\beta}^s - \hat{\beta}^p)'(\Sigma^s + \Sigma^p)^{-1}(\hat{\beta}^s - \hat{\beta}^p),$$

follows a  $\chi_k^2$  distribution, where  $k = \dim(\beta^p) = 5$ .

Note that

- MLE's are approximately normally distributed (large sample situation)
- this is a conservative test.

## COMPONENT TAIL AREAS

We want to test

$$\phi_j^p - \phi_j^s = 0 \text{ versus } \phi_j^p - \phi_j^s > 0, \quad j = 1, 2, 3$$

where

$$\phi^s = (\lambda_{max}^s, \tau_{max}^s, \lambda_{end}^s)$$

$$\phi^p = (\lambda_{max}^p, \tau_{max}^p, \lambda_{end}^p)$$

Asymptotically

$$\hat{\phi}^p - \hat{\phi}^s \sim N_3(\phi^p - \phi^s, \hat{\Sigma})$$

where  $\hat{\Sigma}$  is the variance-covariance matrix of  $\hat{\phi}^p - \hat{\phi}^s$ .

This yields tail areas that may be interpreted as either  $p$ -values or posterior probabilities.

# BOOTSTRAP TESTS OF SIGNIFICANCE

We also want to have inferences not depending on distributional assumptions. We use a nonparametric bootstrap approach to test

$H_0$ : The point processes for the pattern and spatial tasks are the same

Under this hypothesis

- combine all the trials (assumed to be i.i.d. replications) for the two tasks
- sample them at random with replacement
- assign the first  $n_1$  to the spatial task, where  $n_1$  is the original number of trials in the spatial task
- assign the remaining to the pattern task
- compute estimated features for each bootstrap sample
- compare bootstrap distributions of the differences with observed features to produce p-values

# POPULATION ANALYSIS

The 84 neurons of our data set

- constitute a sample from a larger population of neurons
- firing rates vary considerably among the neurons

We want to summarize population effect while quantifying variability

# POPULATION ANALYSIS

Posterior distribution of population features

- hierarchical model
- approximate posterior distribution based on normality of MLE's
- use Markov Chain Monte Carlo (MCMC) to obtain a sample from the posterior distribution of the parameters

# HIERARCHICAL MODEL

$\hat{\gamma}_i = \hat{\phi}_{(i)}^p - \hat{\phi}_{(i)}^s$  the observed vector of mle's for neuron  $i$

$\hat{\Sigma}_i$  the variance matrix of  $\hat{\gamma}_i$  based on observed information.

We assume

$$\hat{\gamma}_i \sim N_3(\gamma_i, \hat{\Sigma}_i)$$

$$\gamma_i \sim N_3(\mu, D)$$

$$\mu \sim N_3(0, \Omega)$$

$$D^{-1} \sim \text{Wishart}(R)$$

where the diagonal elements of  $\Omega$  are very large so to give an almost flat hyperprior.

# RESULTS: SINGLE NEURON

Hotelling's T test

- clear evidence of different firing intensities in the two tasks for many neurons (75% of neurons significant at  $p = 0.05$ , 66% at  $p = 0.01$ , and 57% at  $p = 0.001$ )

# RESULTS: SINGLE NEURON

At 5 % significance (entries are percentages)

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	$\tau_{max}^p - \tau_{max}^s$	$\lambda_{max}^p - \lambda_{max}^s$	$\lambda_{end}^p - \lambda_{end}^s$
	> 0 / < 0	> 0 / < 0	> 0 / < 0
Spline	48.8 / 3.6	25 / 29.8	52.4 / 10.7
Bootstrap	48.8 / 7.1	11.9 / 21.4	39.3 / 6.0

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At 1 % significance (entries are percentages)

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	$\tau_{max}^p - \tau_{max}^s$	$\lambda_{max}^p - \lambda_{max}^s$	$\lambda_{end}^p - \lambda_{end}^s$
	> 0 / < 0	> 0 / < 0	> 0 / < 0
Spline	40.5 / 2.4	19 / 21.4	44.0 / 6.0
Bootstrap	23.8 / 2.4	4.8 / 13.1	29.8 / 1.2

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# RESULTS: POPULATION

Population mean  $\mu$

	$\tau_{max}^p - \tau_{max}^s$ (ms)	$\lambda_{max}^p - \lambda_{max}^s$ (s <sup>-1</sup> )	$\lambda_{end}^p - \lambda_{end}^s$ (s <sup>-1</sup> )
posterior mean	137.1	-1.15	9.67
posterior SD	17.7	2.06	1.59

Population standard deviations  $\sqrt{D_{ii}}$

	$\tau_{max}^p - \tau_{max}^s$ (ms)	$\lambda_{max}^p - \lambda_{max}^s$ (s <sup>-1</sup> )	$\lambda_{end}^p - \lambda_{end}^s$ (s <sup>-1</sup> )
posterior mean	140.1	18.31	14.08

## RESULTS: POPULATION

- population mean delay to maximum firing intensity is  $137 \pm 17$  ms with population standard deviation 140 ms
- population mean difference in end firing rate is  $9.7 \pm 1.6$  spikes per second with standard deviation 14 spikes per second

# CONCLUSIONS

Two aspects of neuronal activity are influenced by the nature of the cue

- activity reflecting the direction of impending response develop more rapidly following spatial than following pattern cues
- final activity tends to be higher following pattern than following spatial cues