From Neurophysiological Data to Statistical Models and Software Development

Christophe Pouzat

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Outline

A brief introduction to a biological problem

Neurophysiologists are trying to record many neurons at once because:

- They can collect more data per experiment.
- They have reasons to think that neuronal information processing might involve synchronization among neurons, an hypothesis dubbed binding by synchronization in the field.

What is binding?

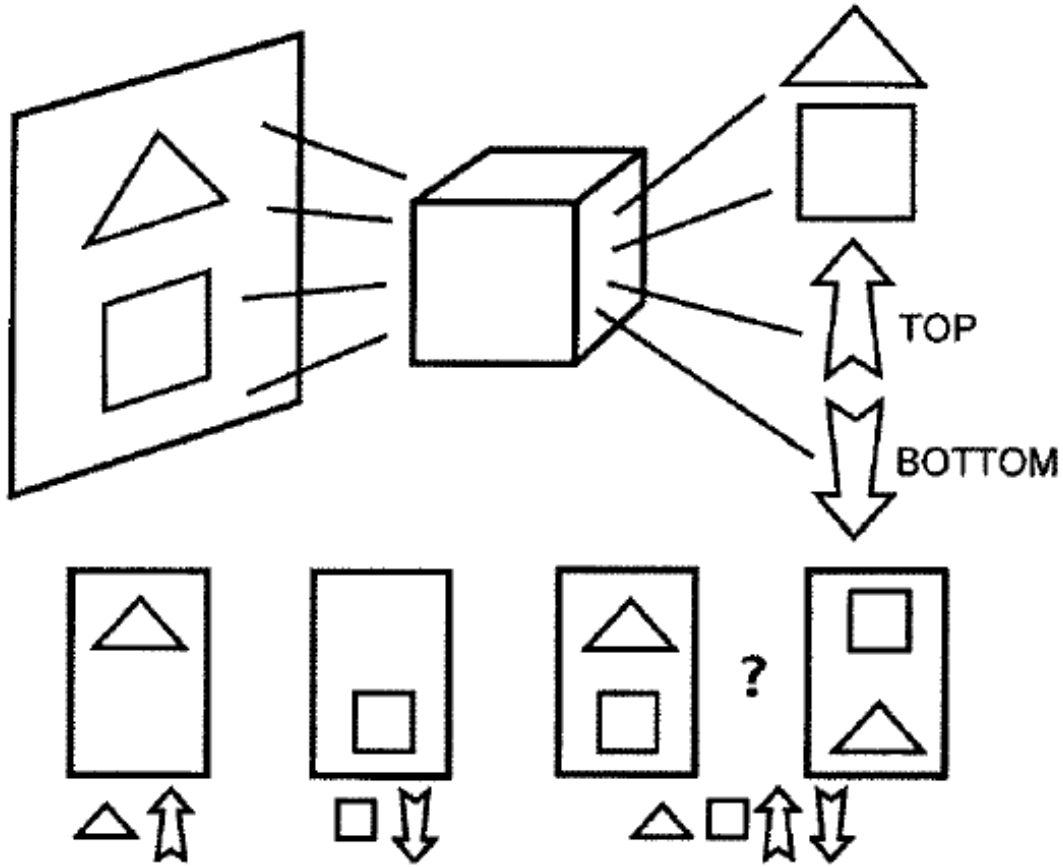


Figure 1. Rosenblatt's Example

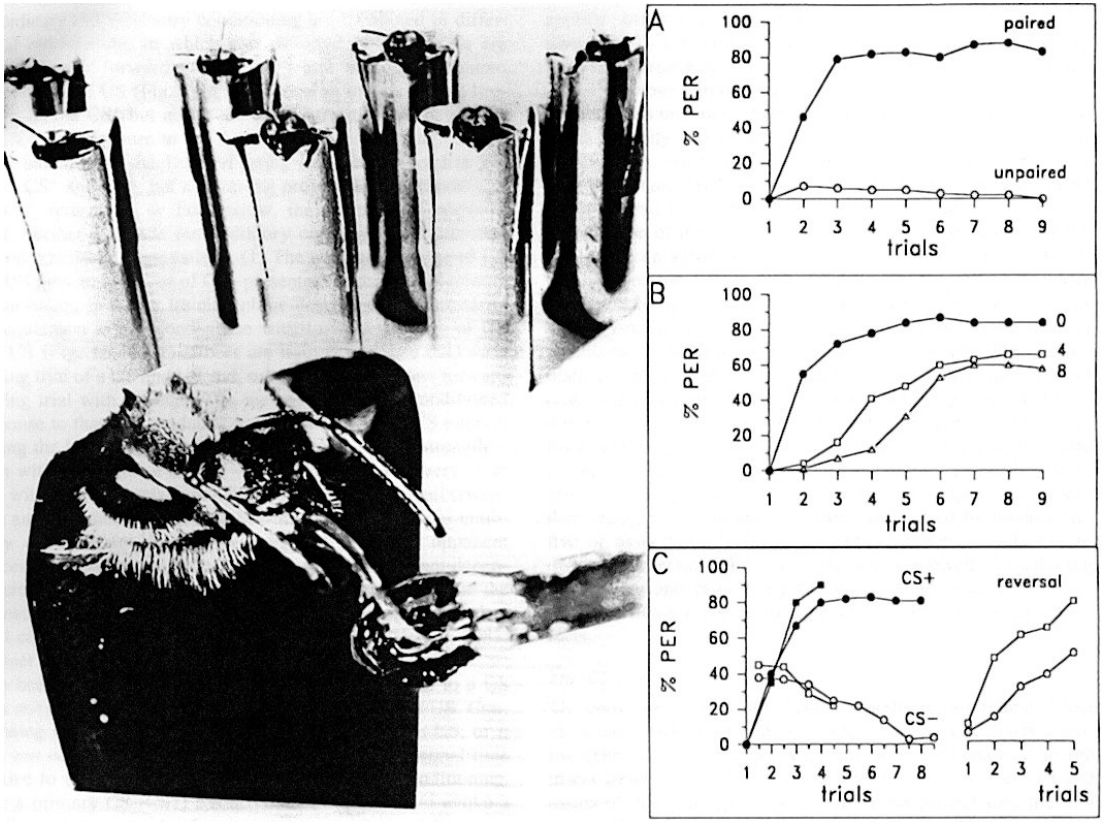
A toy example of a 4 neurons system. One neuron detects triangles, one detects squares, an other one responds to objects in the upper visual field, while the last one detects objects in the lower visual field.

The classical example shown in binding talks

Experimental problems of binding studies

- We must be sure that the animal recognizes the complex stimulus. The animal must therefore be conditioned.
- Working with vertebrates implies then the use of cats or monkeys.
- We then end up looking for synchronized neurons in networks made of 10^7 cells after spending months conditioning the animal... It is a bit like looking for a needle in a hay stack.
- *In vivo* recordings in vertebrates are moreover unstable: the heart must beat which expands the arteries. The tissue is therefore necessarily moving around the recording electrodes.

An alternative approach: proboscis extension and olfactory conditioning in insects



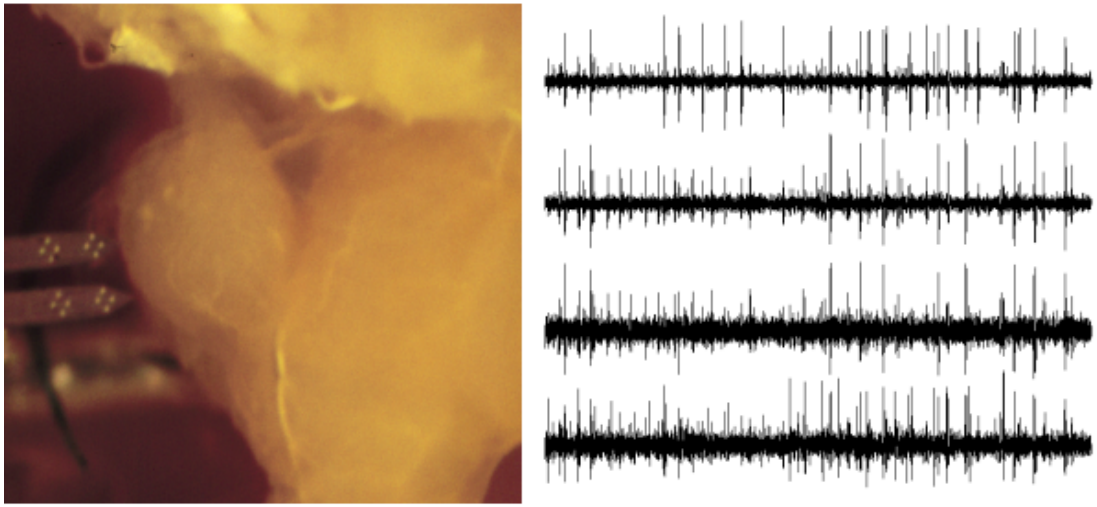
Learning curves obtained from honey bees, *Apis mellifera*, by Hammer and Menzel (1995). Other insects like, most importantly for us, cockroaches, *Periplaneta americana*, can also be conditioned (Watanabe et al, 2003; Watanabe and Mizunami, 2006).

What are we trying to do?

- An elegant series of experiments by Hammer and Menzel (1998) suggests that part of the conditioning induced neuronal modifications occur in the first olfactory relay of the insect: the antennal lobe.
- The (simple) idea is then to record neuronal responses in the antennal lobe to mixtures of pure compounds like citral and octanol in two groups of insects: one conditioned to recognize the mixture, the other one not.
- To demonstrate synchronization in one group and not in the other we must record several neurons at once for a long time.

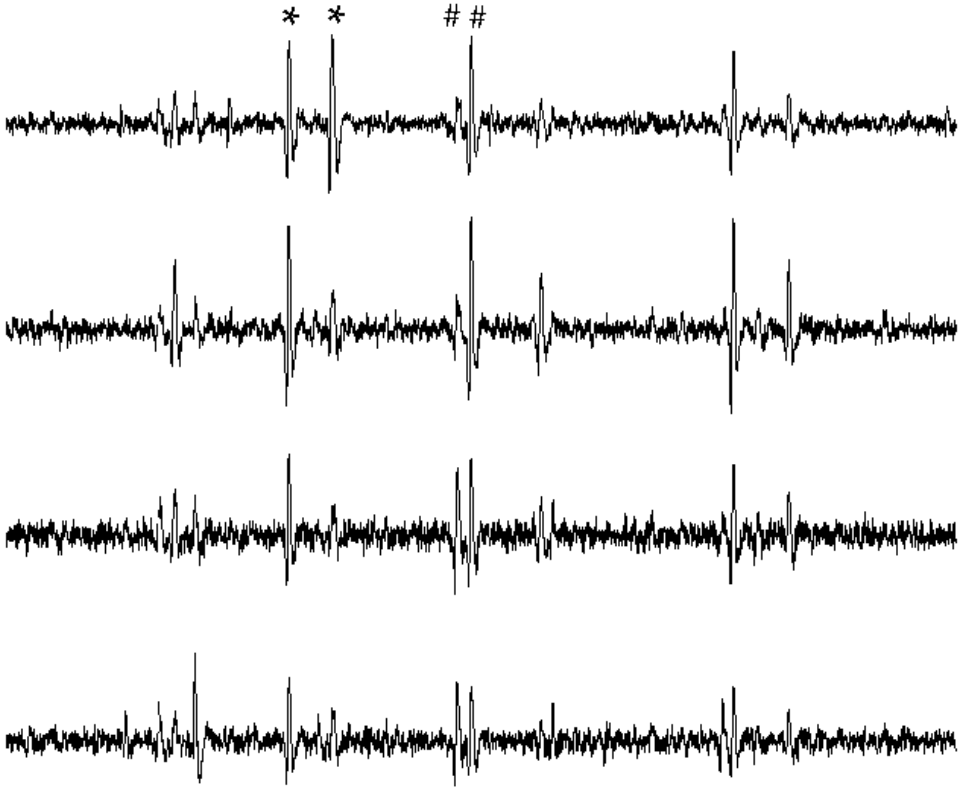
Multi-electrodes *in vivo* recordings in insects

"From the outside" the neuronal activity appears as brief electrical impulses: the action potentials or spikes.



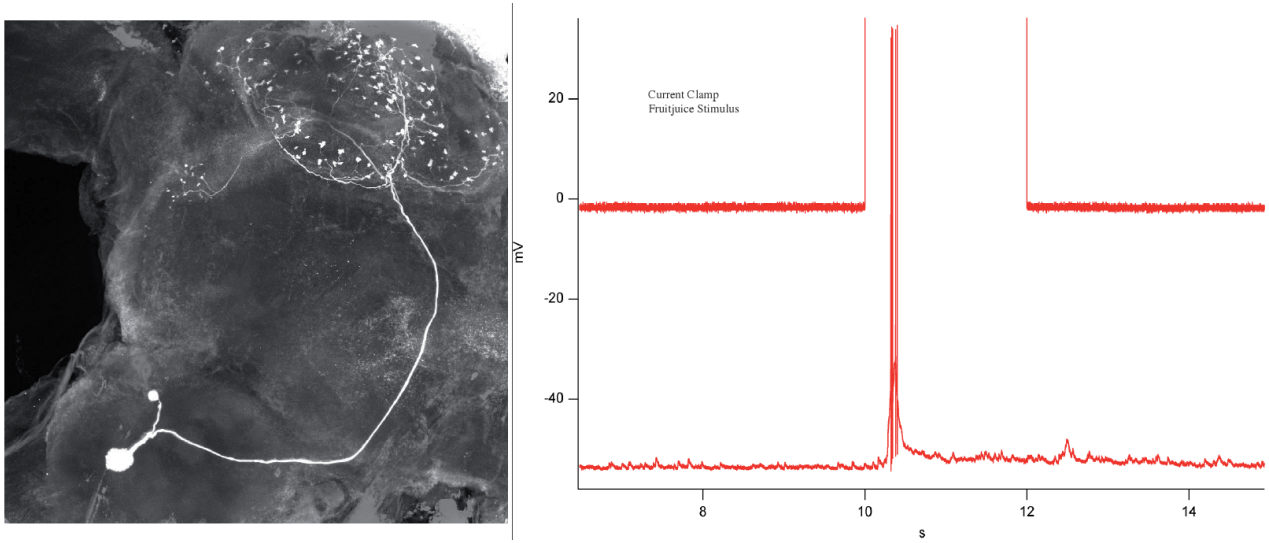
Left, the brain and the recording probe with 16 electrodes (bright spots). Width of one probe shank: 80 μm. Right, 1 sec of raw data from 4 electrodes. The local extrema are the action potentials. The insect shown on the figure is a locust, *Schistocerca americana*. The figure would look almost the same if another insect, like a cockroach, *Periplaneta americana*, had been used instead (Chaffiol, 2007).

Why are tetrodes used?



The last 200 ms of the previous figure. With the upper recording site only it would be difficult to properly classify the two first large spikes (**). With the lower site only it would be difficult to properly classify the two spikes labeled by ##.

Other experimental techniques can also be used



A single neuron patch-clamp recording coupled to calcium imaging. Data from Moritz Paehler and Peter Kloppenburg (Cologne University). The above recording was performed in a preparation where the whole brain with the antennae attached was removed from the animal, a cockroach, *Periplaneta americana*, and placed in a "patch-clamp" recording chamber. See Husch et al (2009) for details.

What do we want?

- Find the number of neurons contributing to the data.
- Find the value of a set of parameters characterizing the signal generated by each neuron (*e.g.*, the spike waveform of each neuron on each recording site).
- Acknowledging the classification ambiguity which can arise from waveform similarity and/or signal corruption due to noise, the probability for each neuron to have generated each event (spike) in the data set.
- A method as automatic as possible.
- A method based on an explicit probabilistic model for data generation.

Software issues

Spike sorting like any data analysis problem can be made tremendously easier by a "proper" software choice. I work a lot with `R` because:

- `R` is an open-source software running on basically any computer / OS combination available.
- It is actively maintained.
- It is an elegant programming language derived from `Lisp`.
- It makes trivial parallelization really trivial.
- It is easy to interface with `fortran`, `C` or `C++` libraries.

A similar problem (1)

- Think of a room with many people seating and talking to each other using a language we do not know.
- Assume that microphones were placed in the room and that their recordings are given to us.
- Our task is to isolate the discourse of each person.

A similar problem (2)

To fulfill our task we could make use of the following features:

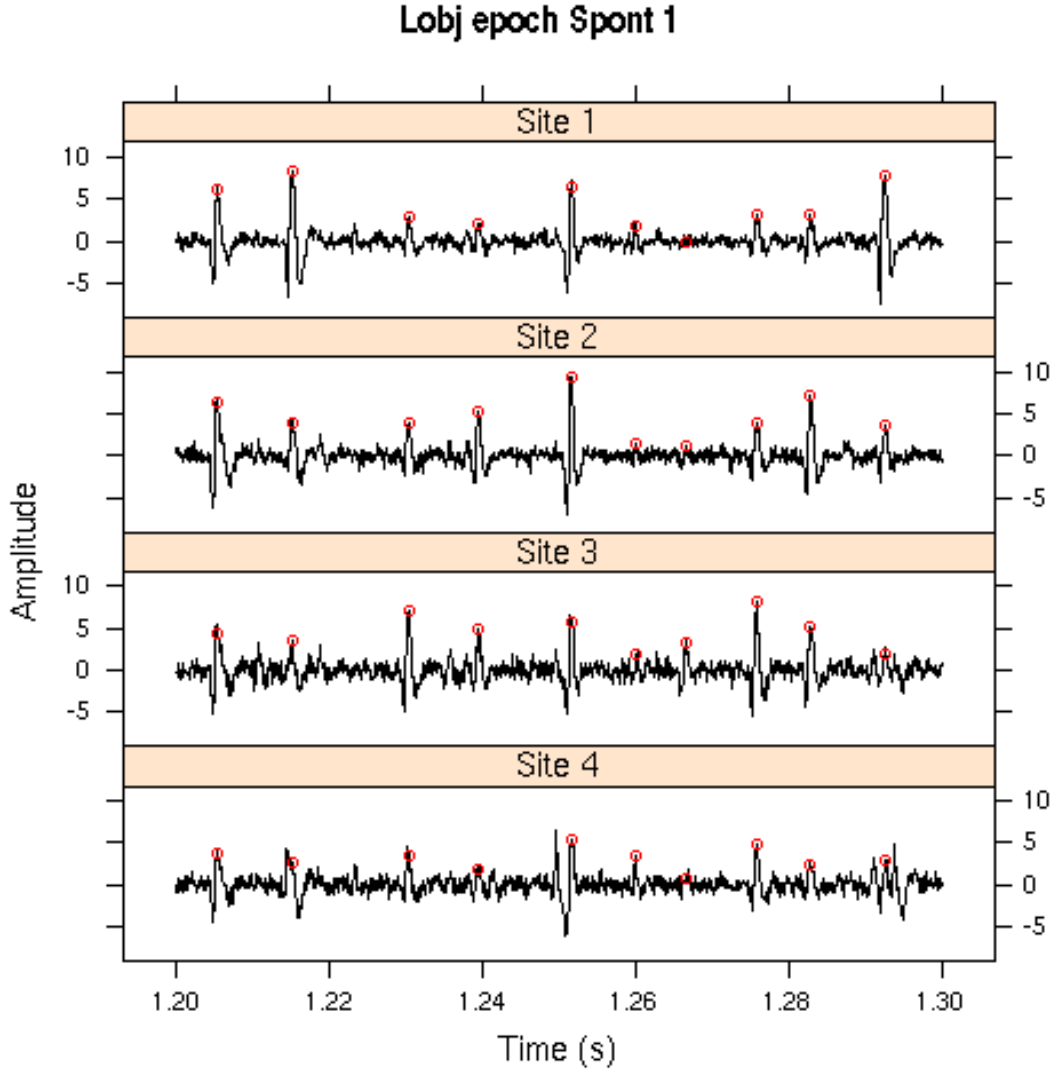
- Some people have a low pitch voice while other have a high pitch one.
- Some people speak loudly while other do not.
- One person can be close to one microphone and far from another such that its talk is simultaneously recorded by the two with different amplitudes.
- Some people speak all the time while other just utter a comment here and there, that is, the discourse statistics changes from person to person.

Spike Sorting as a Set of Standard Statistical Problems

With "nice" (but not so rare) data, efficient spike sorting requires:

1. Events detection followed by events space dimension reduction.
2. A clustering stage. This can be partially or fully automatized depending on the data.
3. Events classification.

Detection illustration

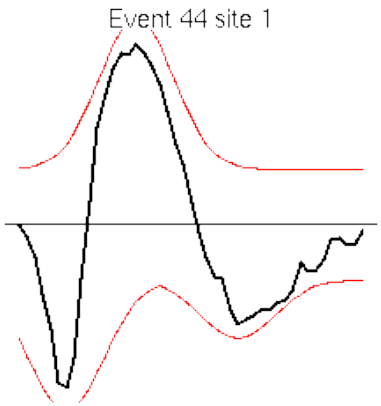


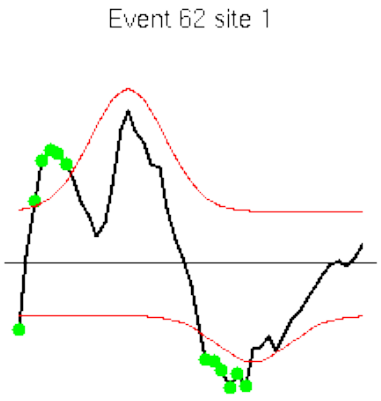
Once spikes have been detected as local extrema whose absolute value exceeds a threshold, windows are "cut" around the spike extremum occurrence time on the raw data *on each recording site*.

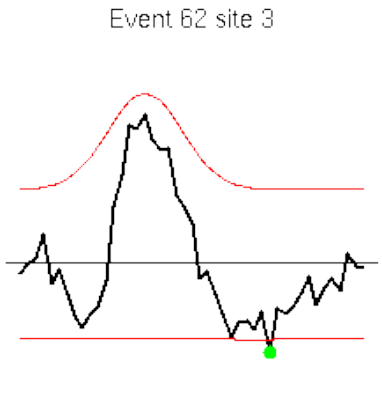
"Clean" events

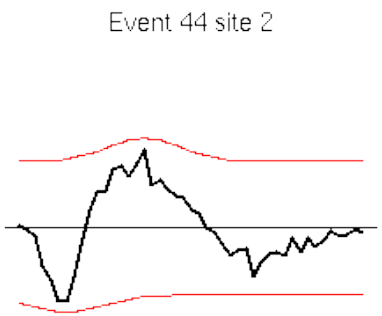
- When many neurons are active in the data set superposed events are likely to occur.
- Such events are due to the firing of 2 different neurons within one of our event defining window.
- Ideally we would like to identify and classify superposed events as such.
- We proceed in 3 steps:
  - A "clean" sample made of non-superposed events is first define.
  - A model of clean events is estimated on this sample.
  - The initial sample is classified and superpositions are identified.

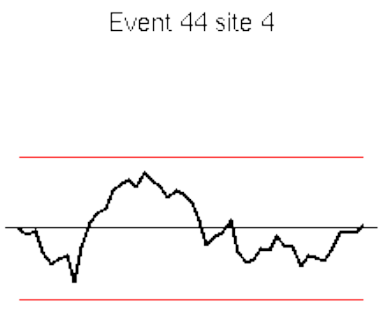
Clean events selection illustration

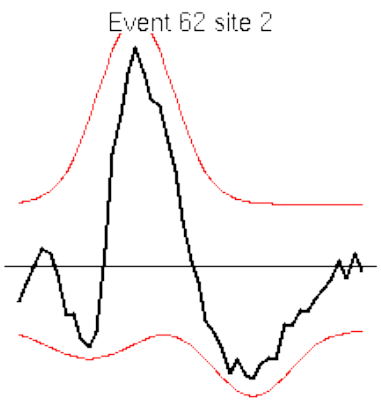


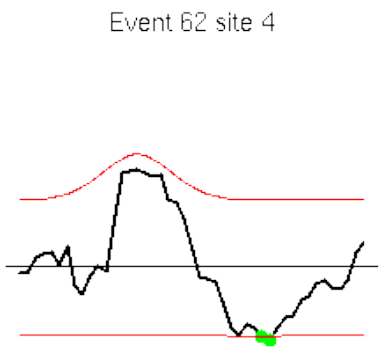








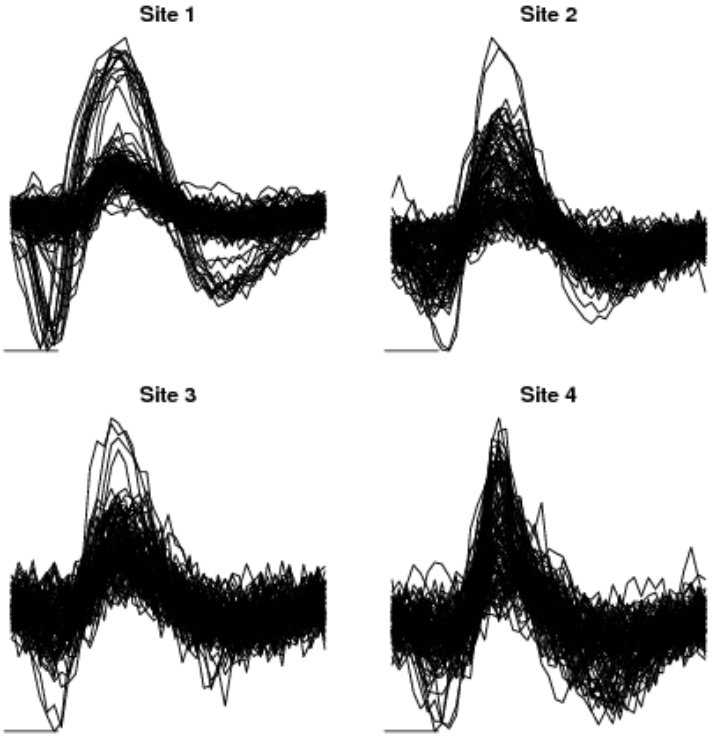


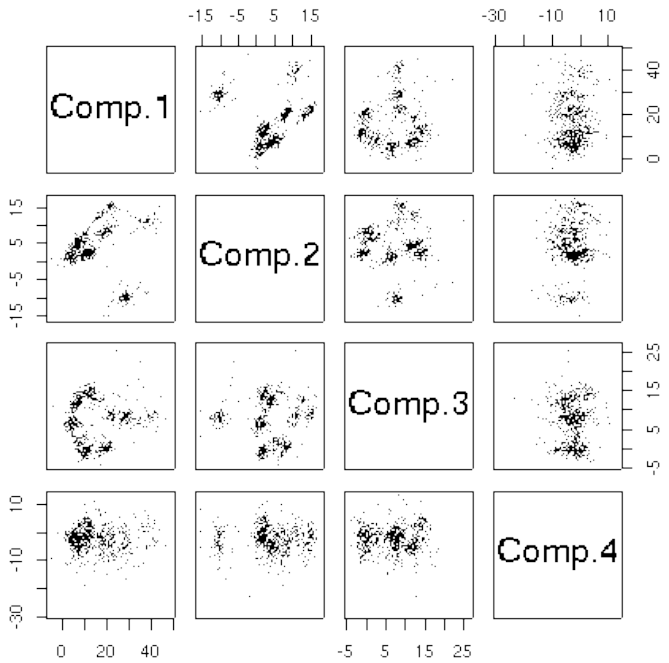


Dimension reduction (1)

- The events making the sample you have seen are defined on 3 ms long windows with data sampled at 15 kHz.
- This implies that $4 \times 15 \times 10^3 \times 3 \times 10^{-3} = 180$ voltage measurements are used to describe our events.
- In other words our sample space is $\mathbb{R}^{180}$.
- Since it is hard to visualize objects and dangerous to estimate probability densities in such a space, we usually reduce the dimension of our sample space.
- We usually use a principal component analysis to this end. We keep components until the projection of the data on the plane defined by the last two appears featureless.

Dimension reduction (2)





Left, 100 spikes (scale bar: 0.5 ms). Right, 1000 spikes projected on the subspace defined by the first 4 principal components.

High-dimensional data visualization

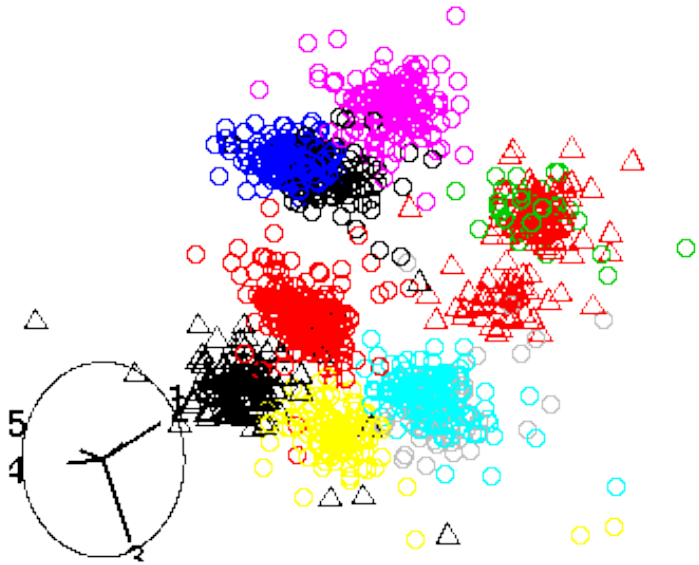
Before using clustering software on our data, looking at them with a dynamic visualization software can be enlightening.

- `GGobi` is an open-source software also running on Linux, Windows, Mac OS.
- It is actively maintained by Debby Swaine, Di Cook, Duncan Temple Lang and Andreas Buja.

Semi-automatic and automatic clustering

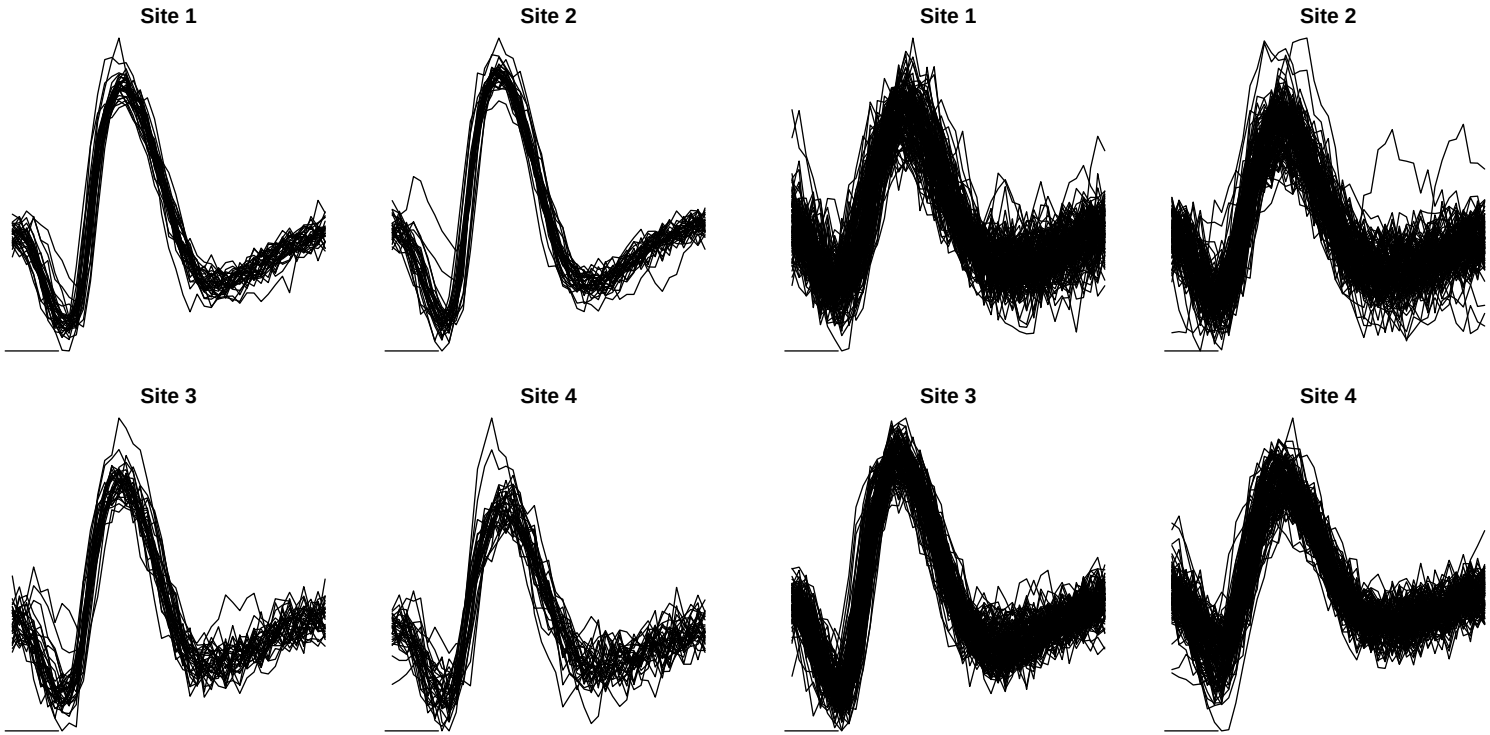
- We perform semi-automatic clustering with `k-means` or `bagged clustering`.
- With these methods the user has to decide what is the "correct" number of clusters.
- Automatic clustering is performed by fitting a Gaussian mixture model to the data using `mclust` or `MixMod`.
- These two software provide criteria like the `BIC` (Bayesian Information Criterion) or the `AIC` (An Information Criterion, introduced by Akaike) to select the number of clusters.
- In practice the `BIC` works best but gives only an indication.

An example of clustering result

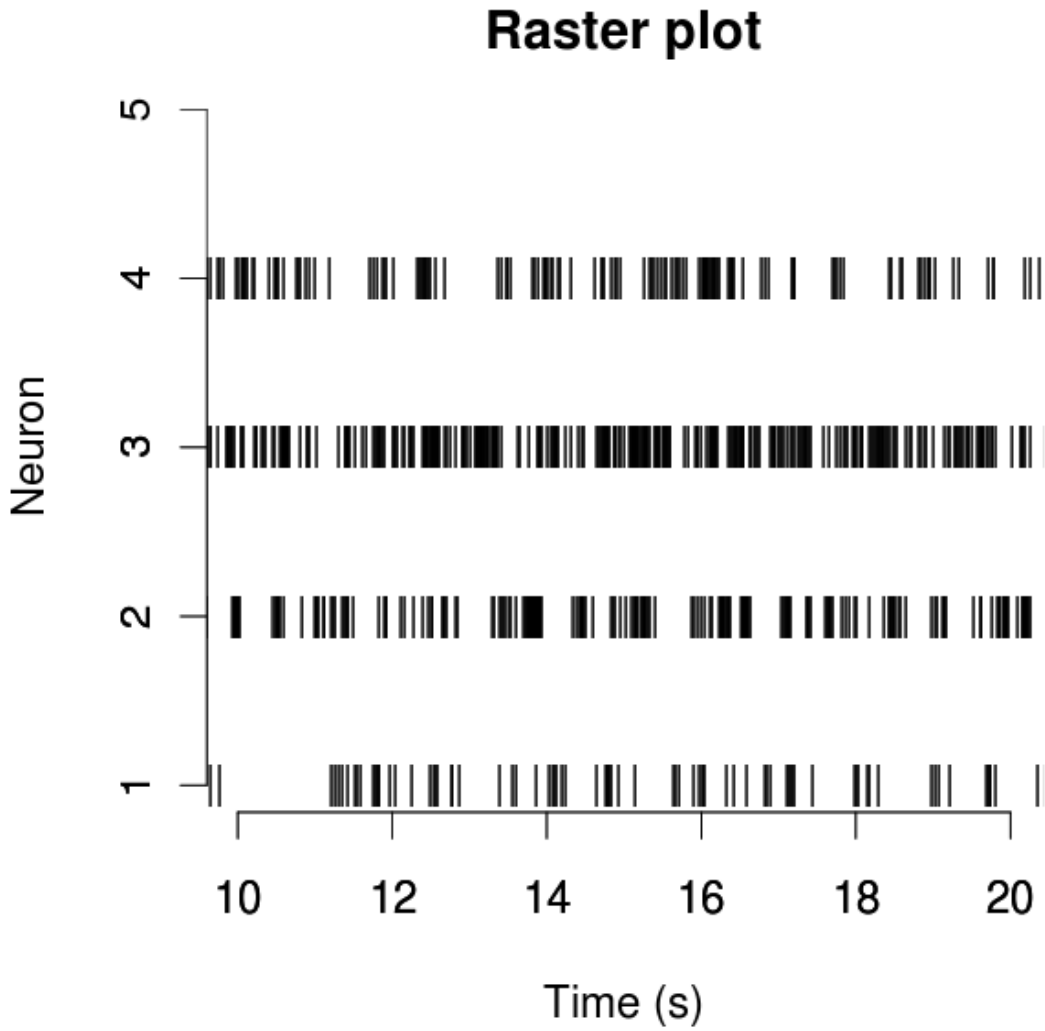


This clustering was performed with `MixMod` using a from 8 to 15 clusters. The `BIC` was minimized with 10 clusters. At that stage we identify neurons with clusters.

The action potentials of neuron 3 (left) and 10 (right)



Spike trains

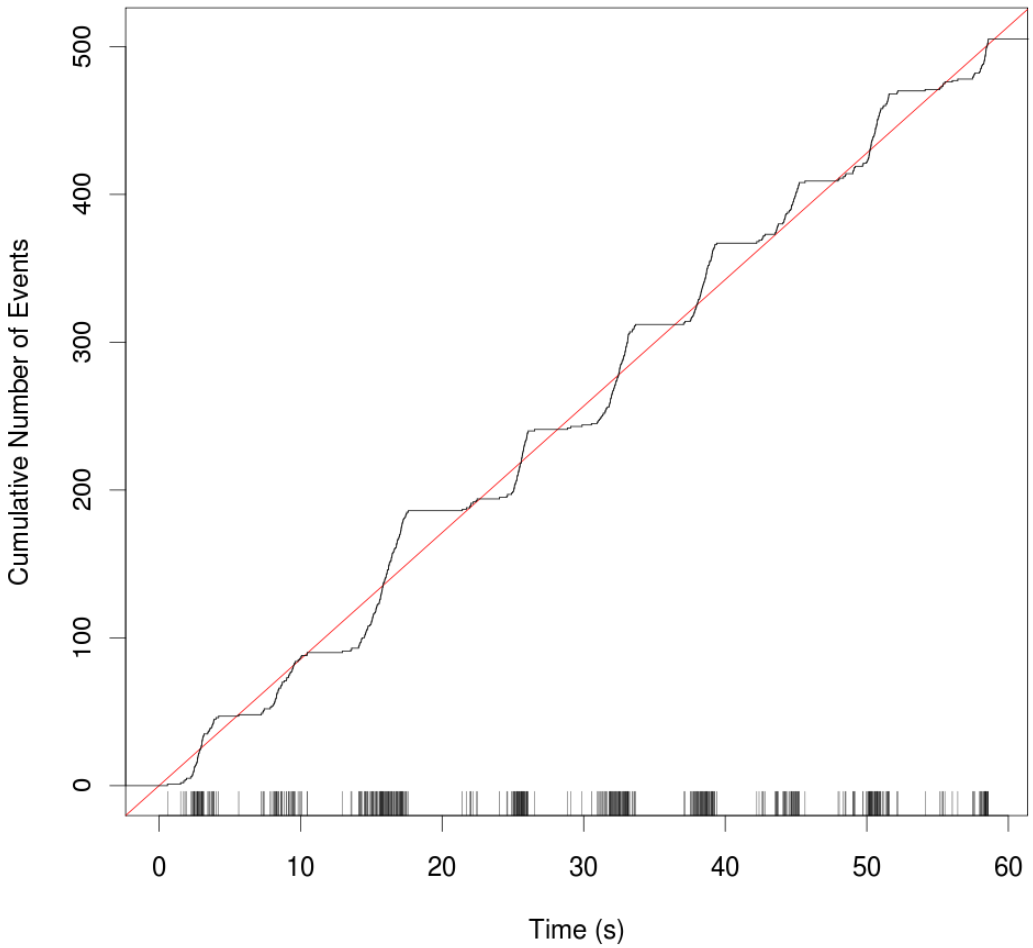


Once a satisfying spike sorting has been obtained, fun can continue with the analysis of the "bar codes" made by the spike trains of individual neurons.

Studying spike trains *per se*

- A central working hypothesis of systems neuroscience is that action potential or spike occurrence times, as opposed to spike waveforms, are the sole information carrier between brain regions (Adrian and Zotterman, 1926).
- This hypothesis legitimates and leads to the study of spike trains *per se*.
- It also encourages the development of models whose goal is to predict the probability of occurrence of a spike at a given time, without necessarily considering the biophysical spike generation mechanisms.

Spike trains are not Poisson processes



The "raw data" of one bursty neuron of the cockroach antennal lobe. 1 minute of spontaneous activity.

Homogenous Poisson Process

A homogenous Poisson process (HPP) has the following properties:

1. The process is homogenous (or stationary), that is, the probability of observing n events in $(t, t + \Delta t)$ depends only on Δt and not on t. If N is the random variable describing the number of events observed during Δt, we have:

$$\text{Prob}\{N = n\} = p_n(\Delta t)\,.$$

2. The process is orderly, that is:

$$\lim_{\Delta t \to 0} \frac{\text{Prob}\{N > 1\}}{\text{Prob}\{N = 1\}} = 0\,.$$

   There is at most one event at a time.

3. The process is without memory, that is, if T_i is the random variable corresponding to the interval between events i and $i + 1$ then:

$$\text{Prob}\{T_i > t + s \mid T_i > s\} = \text{Prob}\{T_i > t\}, \quad \forall i\,.$$

HPP properties

We can show (Pelat, 1996) that a HPP has the following properties:

- There exists a $\nu > 0$ such that:

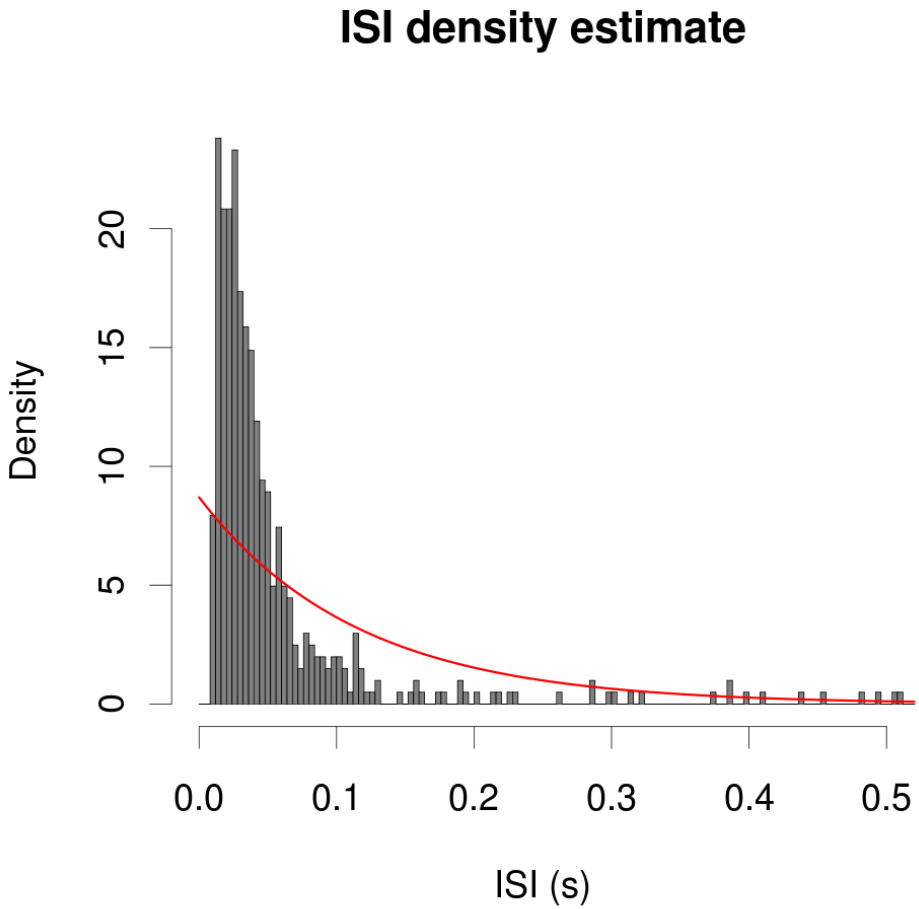
$$p(T_i = t) = \nu \exp(-\nu t), \quad t \geq 0\,,$$

  where $p(T_i = t)$ stands for the probability density function (pdf) of T_i.

- The number n of events observed in an interval $(t, t + \Delta t)$ is the realization of a Poisson distribution of parameter $\nu \Delta t$:

$$\mathrm{Prob}\{N = n \text{ in } (t, t + \Delta t)\} = \frac{(\nu \Delta t)^n}{n!} \exp(-\nu \Delta t)\,.$$

Spike trains are not Poisson processes (again)



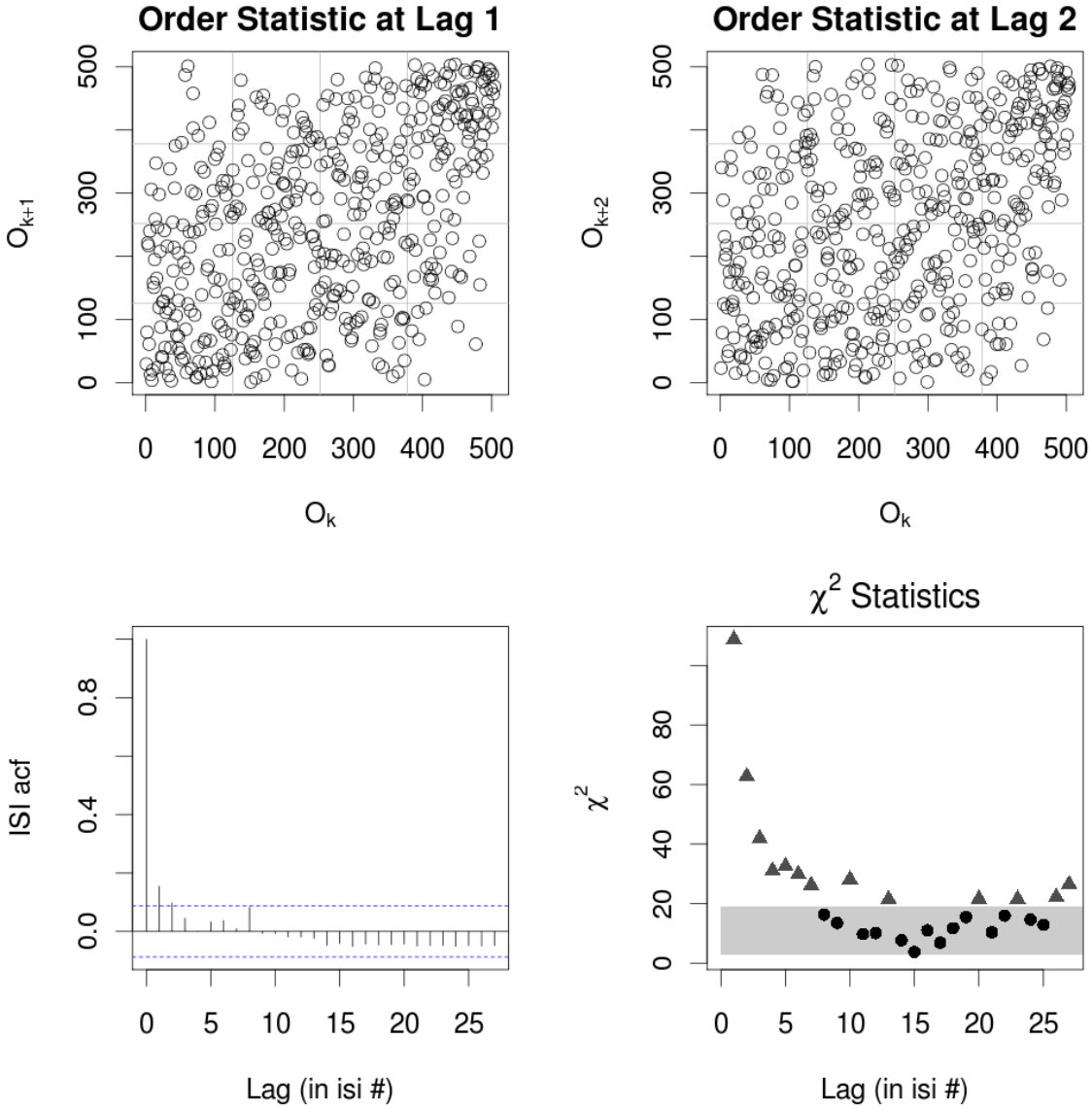
Density estimate (gray) and Poisson process fit (red) for the inter spike intervals (ISIs) of the previous train. The largest ISI was 3.8 s.

Renewal Processes

When a Poisson process does not apply, the next "simplest" process we can consider is the renewal process (Perkel et al, 1967) which can be defined as:

- The ISIs of a renewal process are identically and independently distributed (IID).
- This type of process is used to describe occurrence times of failures in "machines" like light bulbs, hard drives, etc.

Spike trains are rarely renewal processes



Some "renewal tests" applied to the previous data. See Pouzat and Chaffiol (2009) for details.

A counting process formalism (1)

Probabilists and Statisticians working on series of events whose only (or most prominent) feature is there occurrence time (car accidents, earthquakes) use a formalism based on the following three quantities (Brillinger, 1988).

- Counting Process: For points $\{t_j\}$ randomly scattered along a line, the counting process $N(t)$ gives the number of points observed in the interval $(0, t]$:

$$N(t) = \sharp\{t_j \text{ with } 0 < t_j \leq t\},$$

where $\sharp$ stands for the cardinality (number of elements) of a set.

A counting process formalism (2)

- History / Filtration: The history, $\mathcal{H}_t$, consists of the variates determined up to and including time t that are necessary to describe the evolution of the counting process.
- Conditional Intensity: For the process N and history $\mathcal{H}_t$, the conditional intensity at time t is defined as:

$$\lambda(t \mid \mathcal{H}_t) = \lim_{h \downarrow 0} \frac{\text{Prob}\{\text{event } \in (t, t+h] \mid \mathcal{H}_t\}}{h},$$

for small h one has the interpretation:

$$\text{Prob}\{\text{event } \in (t, t+h] \mid \mathcal{H}_t\} \approx \lambda(t \mid \mathcal{H}_t)\, h\,.$$

Meaning of "spike train analysis" in this talk

In this talk "spike train analysis" can be narrowly identified with conditional intensity estimation:

$$\text{spike train analysis} \equiv \text{get } \hat{\lambda}(t \mid \mathcal{H}_t)\,,$$

where $\hat{\lambda}$ stands for an estimate of λ.

Goodness of fit tests for counting processes

- All goodness of fit tests derive from a mapping or a "time transformation" of the observed process realization.
- Namely one introduces the integrated conditional intensity:

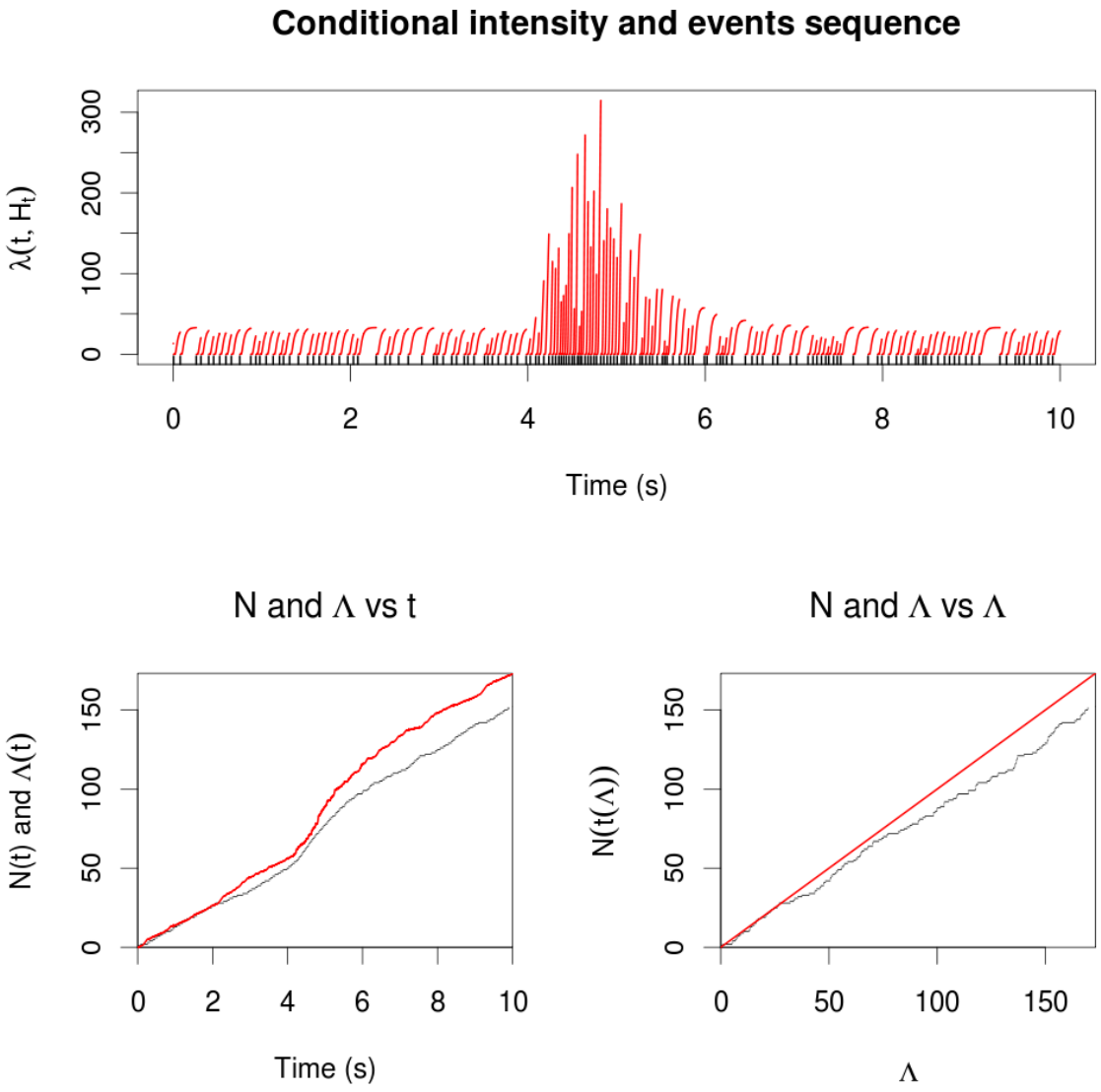
$$\Lambda(t) = \int_0^t \lambda(u \mid \mathcal{H}_u)\, du\,.$$

- If Λ is correct it is not hard to show (Brown et al, 2002) that the process defined by:

$$\{t_1, \ldots, t_n\} \mapsto \{\Lambda(t_1), \ldots, \Lambda(t_n)\}\,,$$

is a Poisson process with rate 1.

Time transformation illustrated



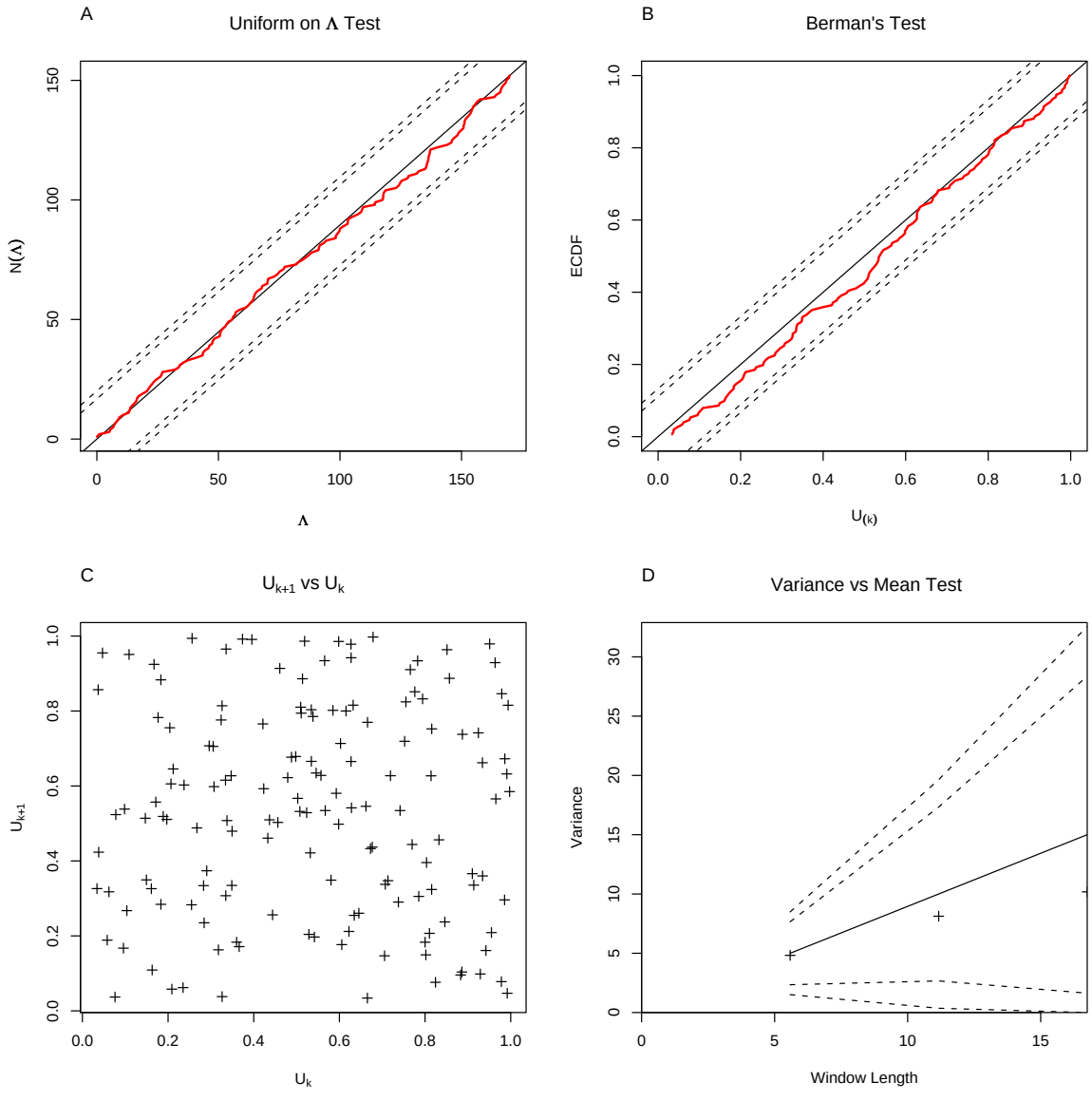
An illustration with simulated data. See Pouzat and Chaffiol (2009b) for details.

Ogata's tests (1)

Yosihiko Ogata (1988) introduced several procedures testing the time transformed event sequence against the uniform Poisson hypothesis. The first test is based on the following property:

- If a homogeneous Poisson process with rate 1 is observed until its /n/th event, then the event times, $\{\Lambda(t_i)\}_{i=1}^{n}$, have a uniform distribution on $(0, \Lambda(t_n))$ (Barnard, 1953; Cox and Lewis, 1966). This uniformity can be tested with a Kolmogorov test.

First test displayed on the upper left



Ogata's tests on the simulated data.

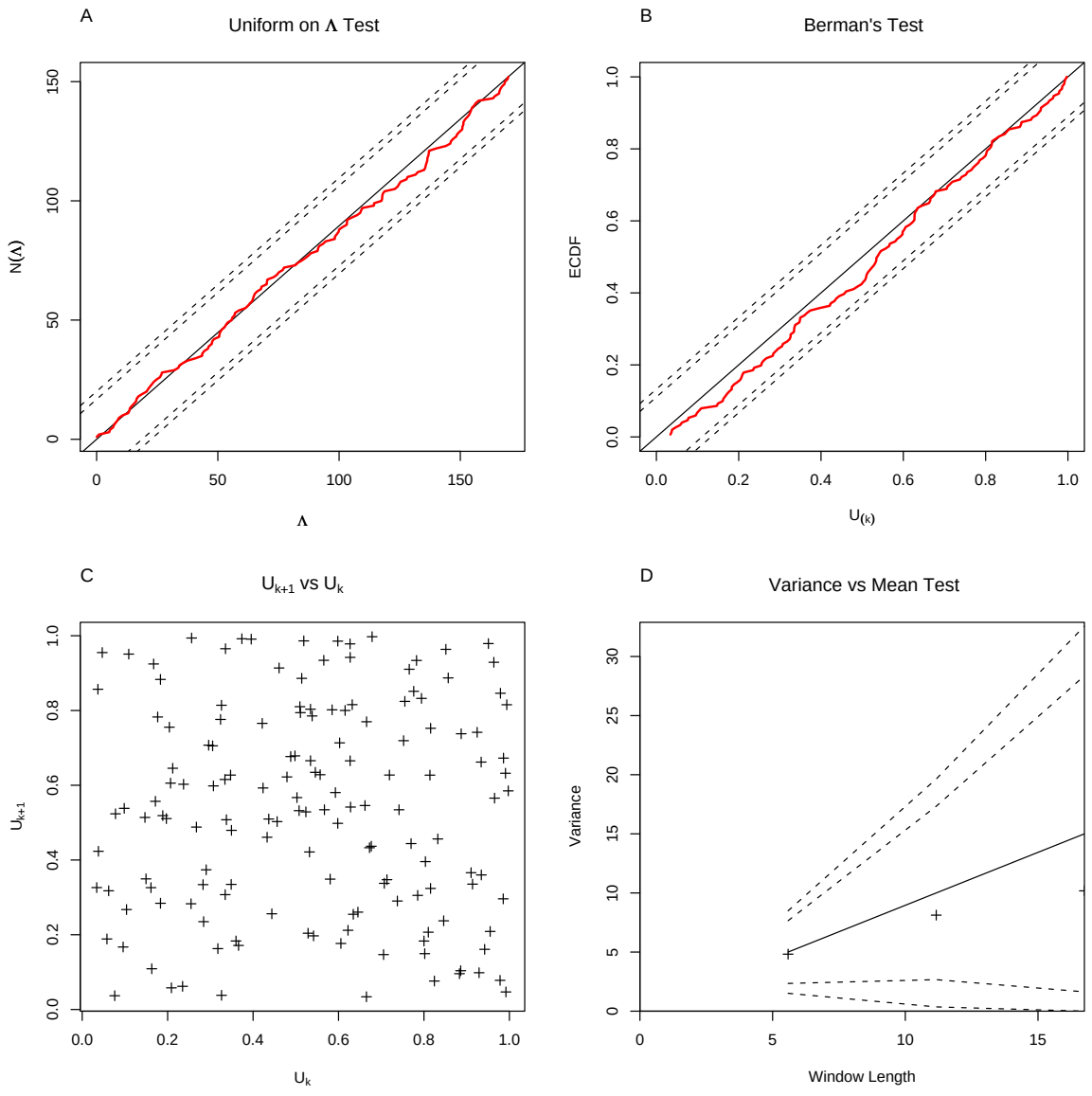
Ogata's tests (2)

The u_k defined, for $k > 1$, by:

$$u_k = 1 - \exp\left(-\left(\Lambda(t_k) - \Lambda(t_{k-1})\right)\right) ,$$

should be IID with a uniform distribution on $(0, 1)$. The empirical cumulative distribution function (ECDF) of the sorted $\{u_k\}$ can be compared to the ECDF of the null hypothesis with a Kolmogorov test. This test is attributed to Berman in Ogata (1988) and is the test proposed and used by Brown et al (2002).

Second test displayed on the upper right



Ogata's tests (3)

A plot of u_{k+1} vs u_k exhibiting a pattern would be inconsistent with the homogeneous Poisson process hypothesis. A shortcoming of this test is that it is only graphical and that it requires a fair number of events to be meaningful.

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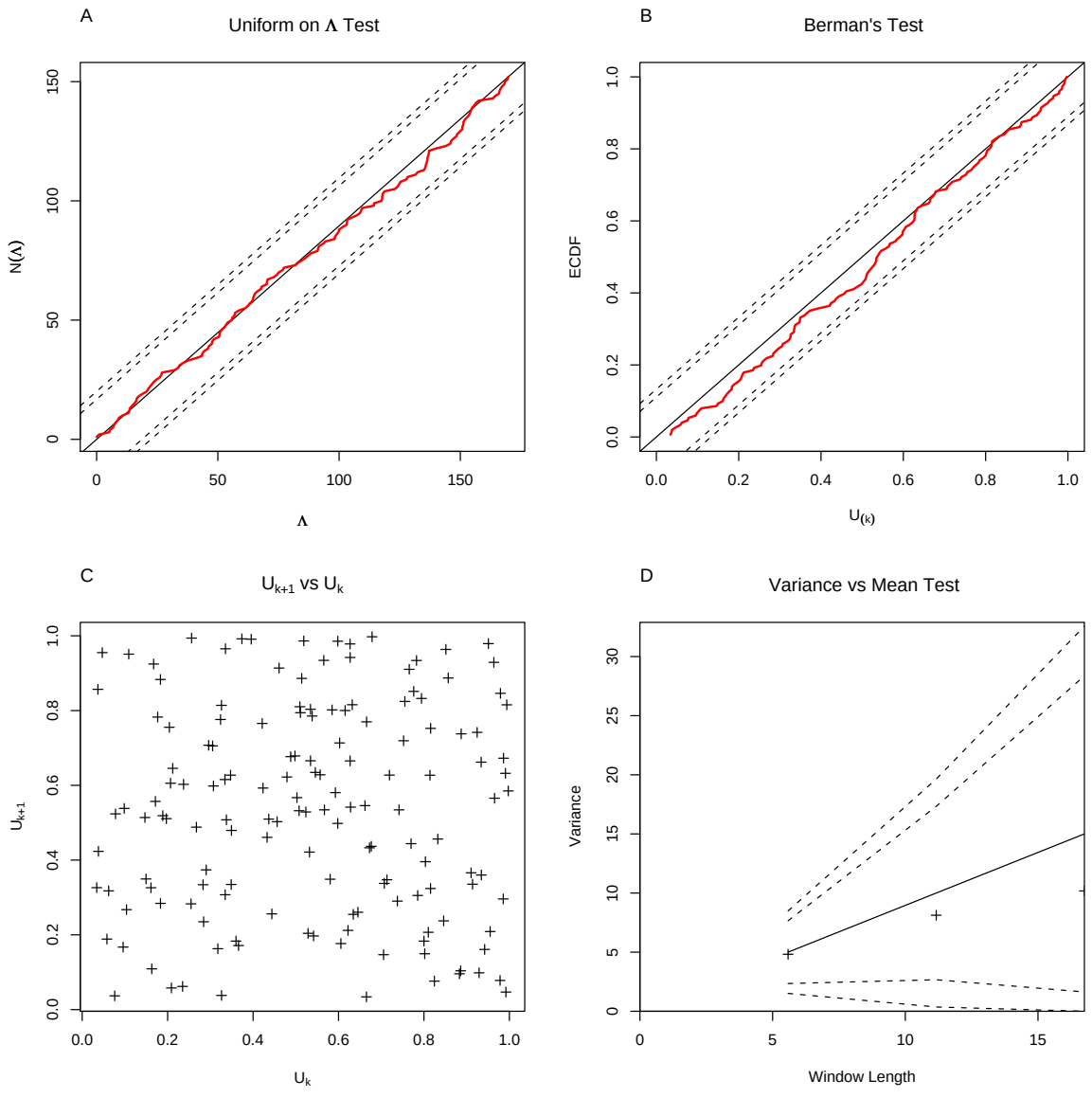
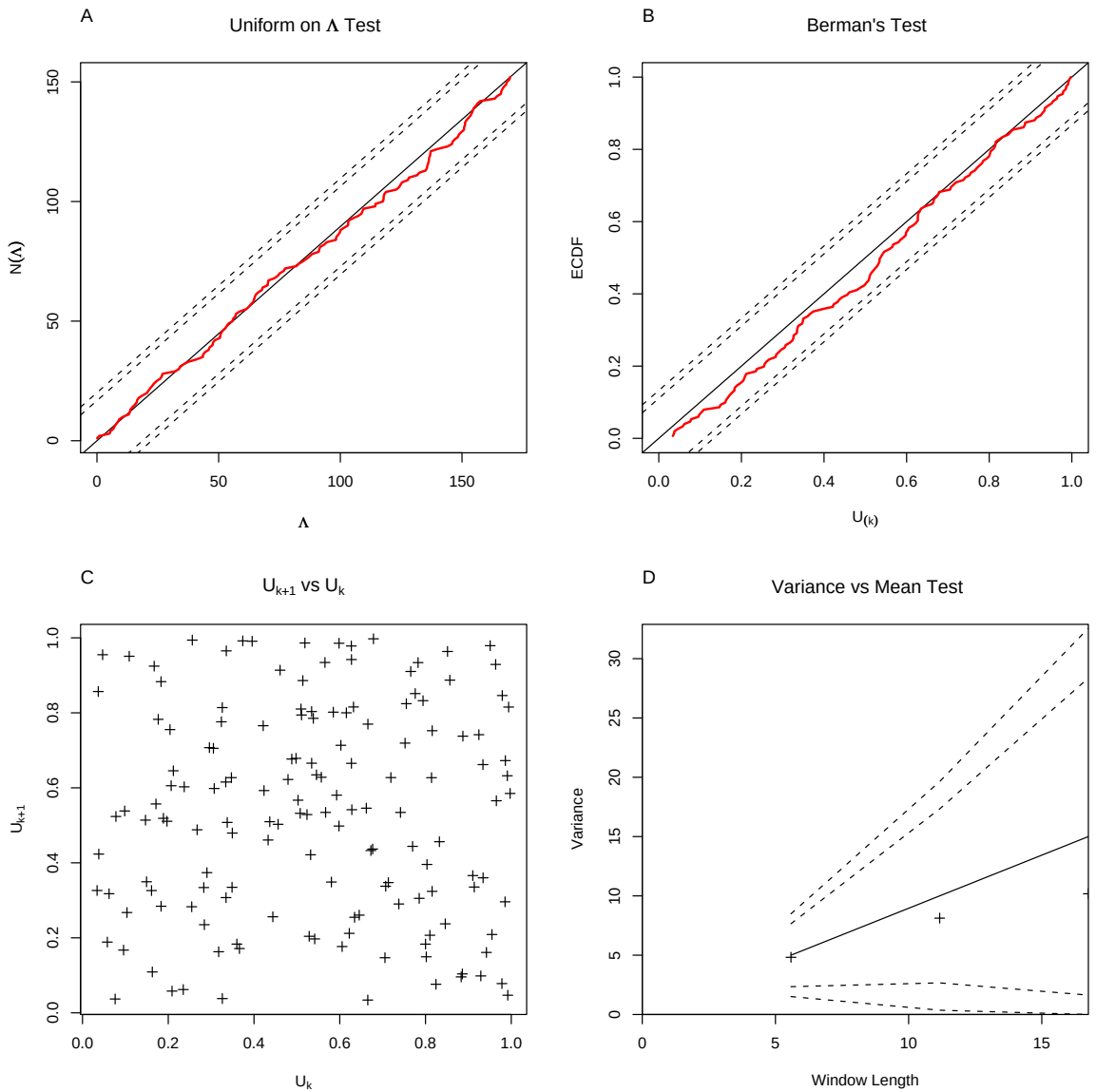


Ogata's tests (4)

The last test is obtained by splitting the transformed time axis into K_w non-overlapping windows of the same size w, counting the number of events in each window and getting a mean count N_w and a variance V_w computed over the K_w windows. Using a set of increasing window sizes: $\{w_1, \ldots, w_L\}$ a graph of V_w as a function of N_w is build. If the Poisson process with rate 1 hypothesis is correct the result should fall on a straight line going through the origin with a unit slope. Pointwise confidence intervals can be obtained using the normal approximation of a Poisson distribution.

Second test displayed on the lower right



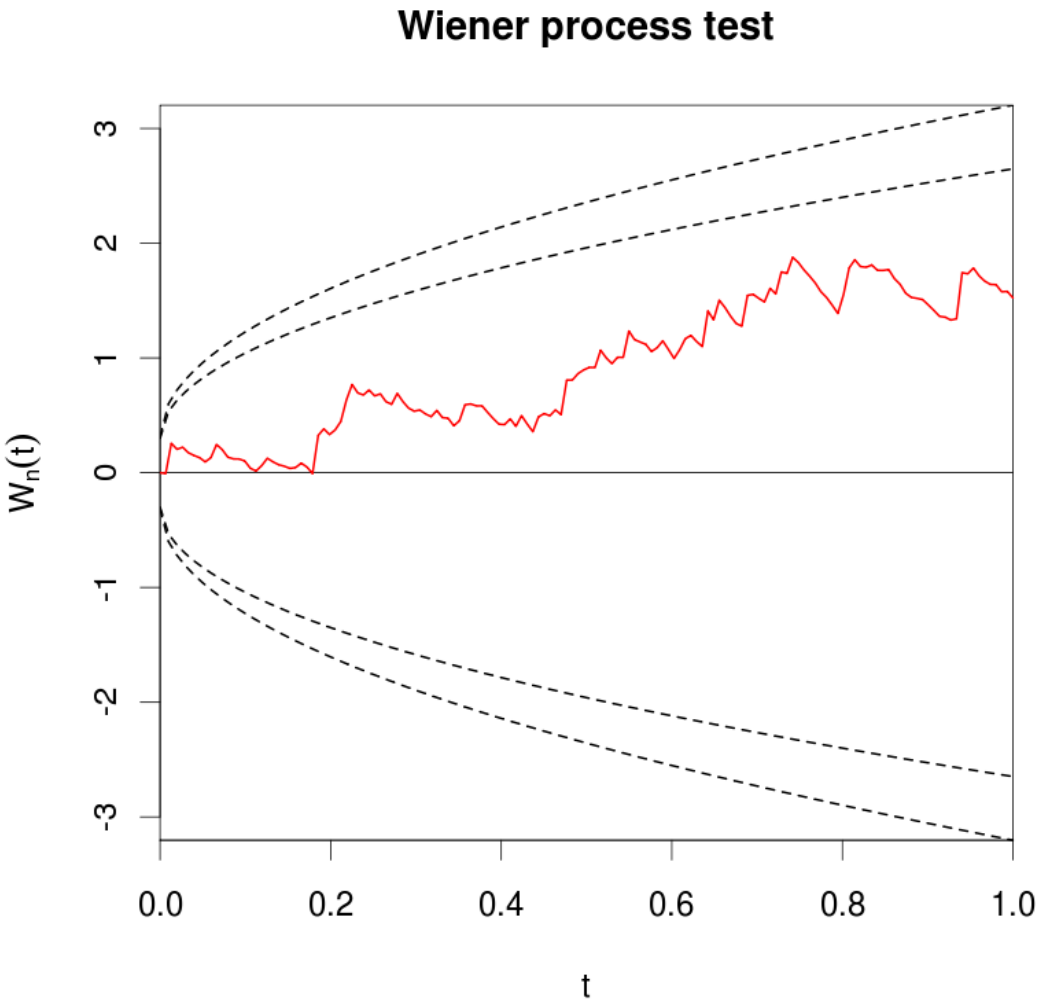
A new test based on Donsker's theorem

- We propose an additional test built as follows:

$$\begin{aligned} X_j &= \Lambda(t_{j+1}) - \Lambda(t_j) - 1\,, \\ S_m &= \sum_{j=1}^{m} X_j\,, \\ W_n(t) &= S_{\lfloor nt \rfloor}/\sqrt{n}\,. \end{aligned}$$

- Donsker's theorem (Billingsley, 1999; Durrett, 2009) implies that if Λ is correct then W_n converges weakly to a standard Wiener process.
- We therefore test if the observed W_n is within the tight confidence bands obtained by Kendall et al (2007) for standard Wiener processes.

Illustration of the proposed test



The proposed test applied to the simulated data. The boundaries have the form: $f(x; a, b) = a + b\sqrt{x}$.

Where Are We?

- We are now in the fairly unusual situation (from the neuroscientist's viewpoint) of knowing how to show that the model we entertain is wrong without having an explicit expression for this model...
- We now need a way to find candidates for the CI: $\lambda(t \mid \mathcal{H}_t)$.

What Do We "Put" in $\mathcal{H}_t$?

- It is common to summarize the stationary discharge of a neuron by its inter-spike interval (ISI) histogram.
- If the latter histogram is not a pure decreasing mono-exponential, that implies that $\lambda(t \mid \mathcal{H}_t)$ will at least depend on the elapsed time since the last spike: $t - t_l$.
- For the real data we saw previously we also expect at least a dependence on the length of the previous inter spike interval, isi_1. We would then have:

$$\lambda(t \mid \mathcal{H}_t) = \lambda(t - t_l, isi_1)\,,$$

that is, a Wold process.

What About The Functional Form?

- We haven't even started yet and we are already considering a function of at least 2 variables: $t - t_l, isi_1$. What about its functional form?
- Following Brillinger (1988) we discretize our time axis into bins of size h small enough to have at most 1 spike per bin.
- We are therefore lead to a binomial regression problem.
- For analytical and computational convenience we are going to use the logistic transform:

$$\log\left(\frac{\lambda(t - t_l, isi_1)\, h}{1 - \lambda(t - t_l, isi_1)\, h}\right) = \eta(t - t_l, isi_1)\,.$$

The Discretized Data

	event	time	neuron	lN.1	i1
14604	0	58.412	1	0.012	0.016
14605	1	58.416	1	0.016	0.016
14606	0	58.420	1	0.004	0.016
14607	1	58.424	1	0.008	0.016
14608	0	58.428	1	0.004	0.008
14609	0	58.432	1	0.008	0.008
14610	1	58.436	1	0.012	0.008
14611	0	58.440	1	0.004	0.012

`event` is the discretized spike train, `time` is the bin center time, `neuron` is the neuron to whom the spikes in `event` belong, `lN.1` is $t - t_l$ and `i1` is isi_1.

Smoothing spline (1)

- Since cellular biophysics does not provide much guidance on how to build $\eta(t - t_l, isi_1)$ we have chosen to use the nonparametric smoothing spline (Wahba, 1990; Gu, 2002) approach implemented in the `gss` (general smoothing spline) package of Chong Gu for `R`.
- $\eta(t - t_l, isi_1)$ is then uniquely decomposed as:

$$\eta(t - t_l, isi_1) = \eta_\emptyset + \eta_l(t_t - l) + \eta_1(isi_1) + \eta_{l,1}(t - t_l, isi_1)\,.$$

- Where for instance:

$$\int \eta_1(u)du = 0\,,$$

the integral being evaluated on the definition domain of the variable isi_1.

Smoothing spline (2)

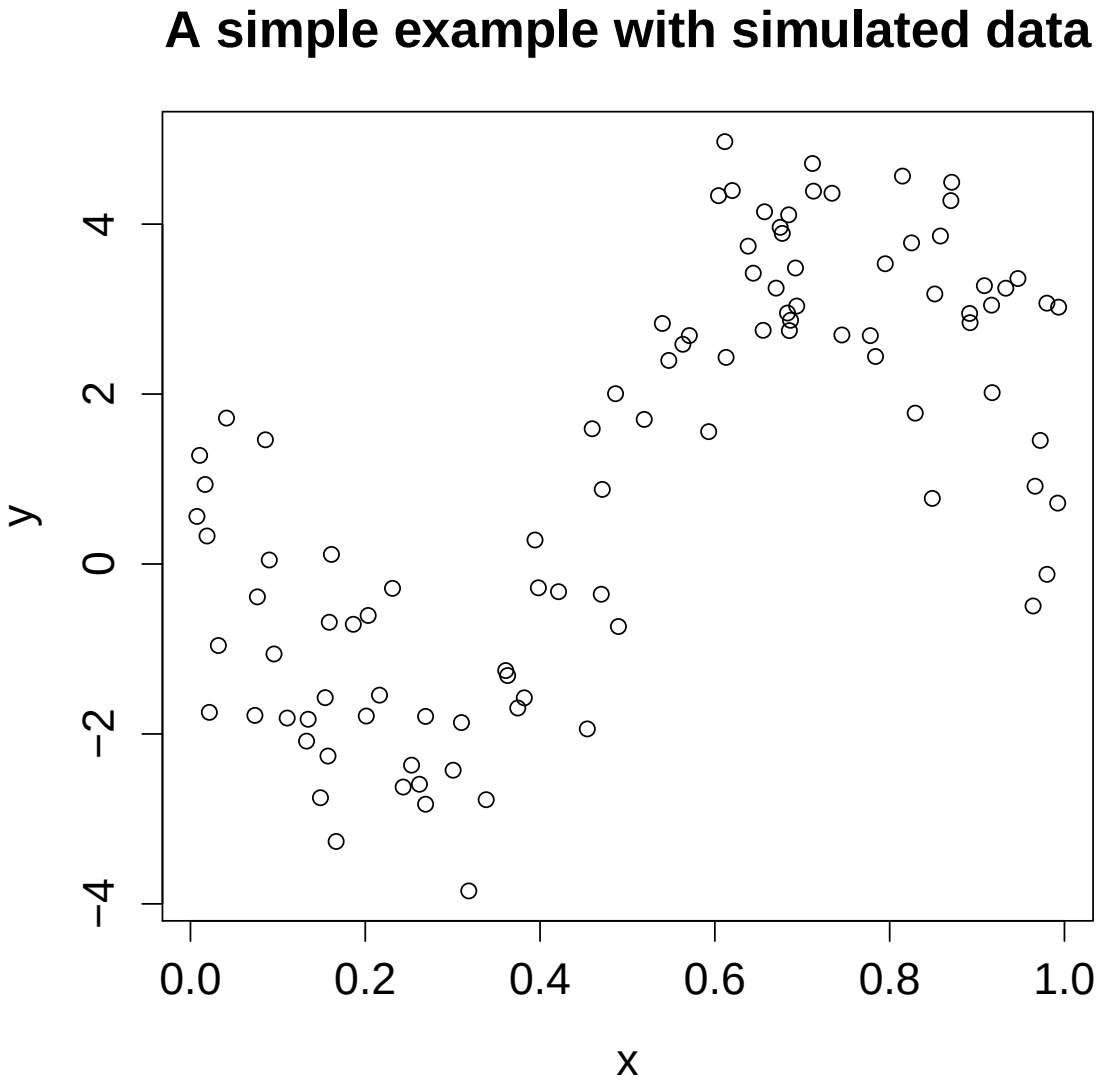
Given data:

$$Y_i = \eta(x_i) + \epsilon_i, \quad i = 1, \ldots, n\,,$$

where $x_i \in [0, 1]$ and $\epsilon_i \sim \mathrm{N}(0, \sigma^2)$, we want to find η_ρ minimizing:

$$\frac{1}{n}\sum_{i=1}^{n}(Y_i - \eta_\rho(x_i))^2 + \rho \int_0^1 \left(\frac{d^2\eta_\rho}{dx^2}\right)^2 dx\,.$$

Smoothing spline (3)



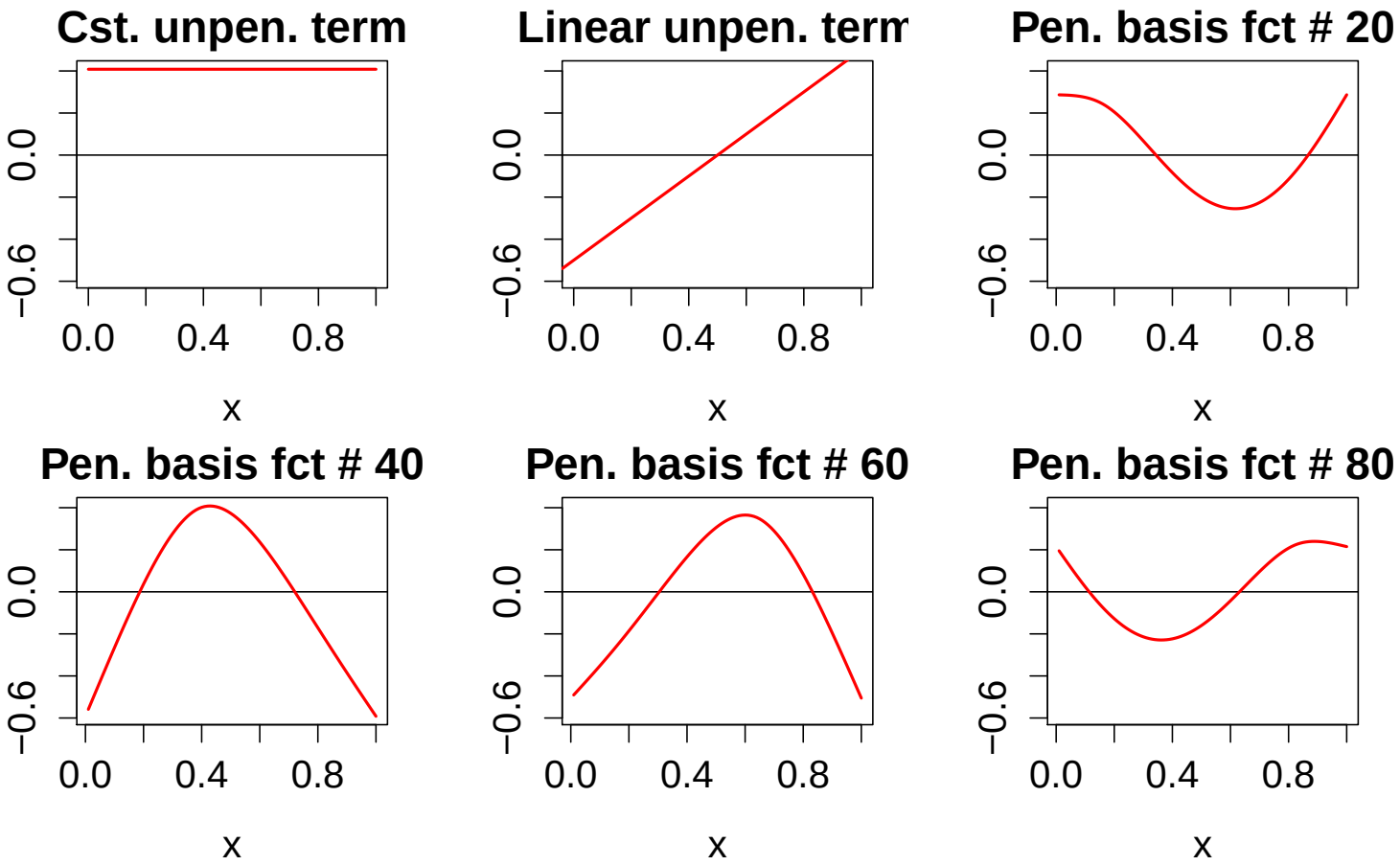
Smoothing spline (4)

It can be shown (Wahba, 1990) that, for a given ρ, the solution of the functional minimization problem can be expressed on a finite basis:

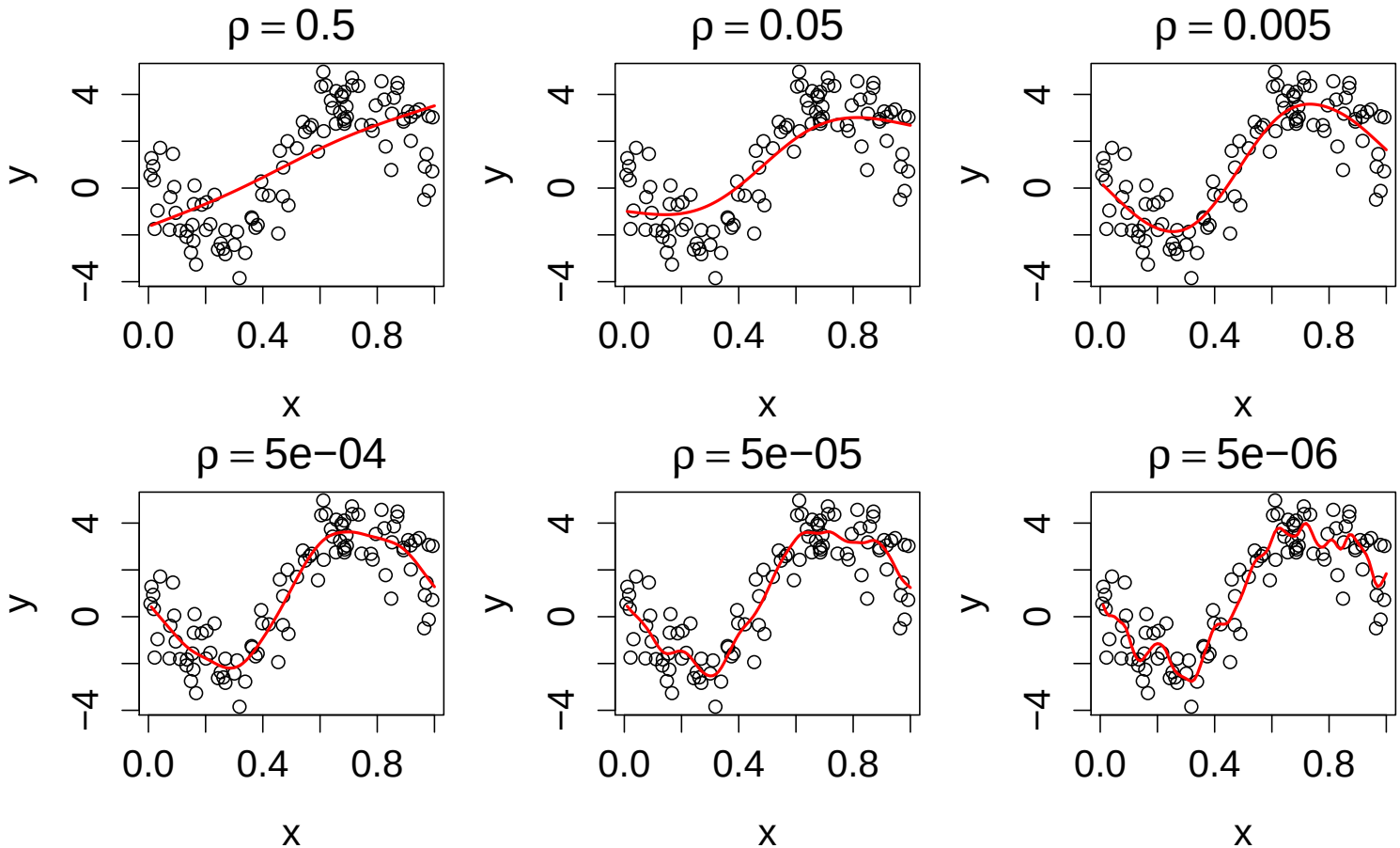
$$\eta_\rho(x) = \sum_{\nu=0}^{m-1} d_\nu \, \phi_\nu(x) + \sum_{i=1}^{n} c_i \, R_1(x_i, x) \, ,$$

where the functions, $\phi_\nu()$, and $R_1(x_i,)$, are known.

Smoothing spline (5)



Smoothing spline (6): What about ρ?



Smoothing spline (7): Cross-validation

Ideally we would like ρ such that:

$$\frac{1}{n}\sum_{i=1}^{n}(\eta_\rho(x_i) - \eta(x_i))^2$$

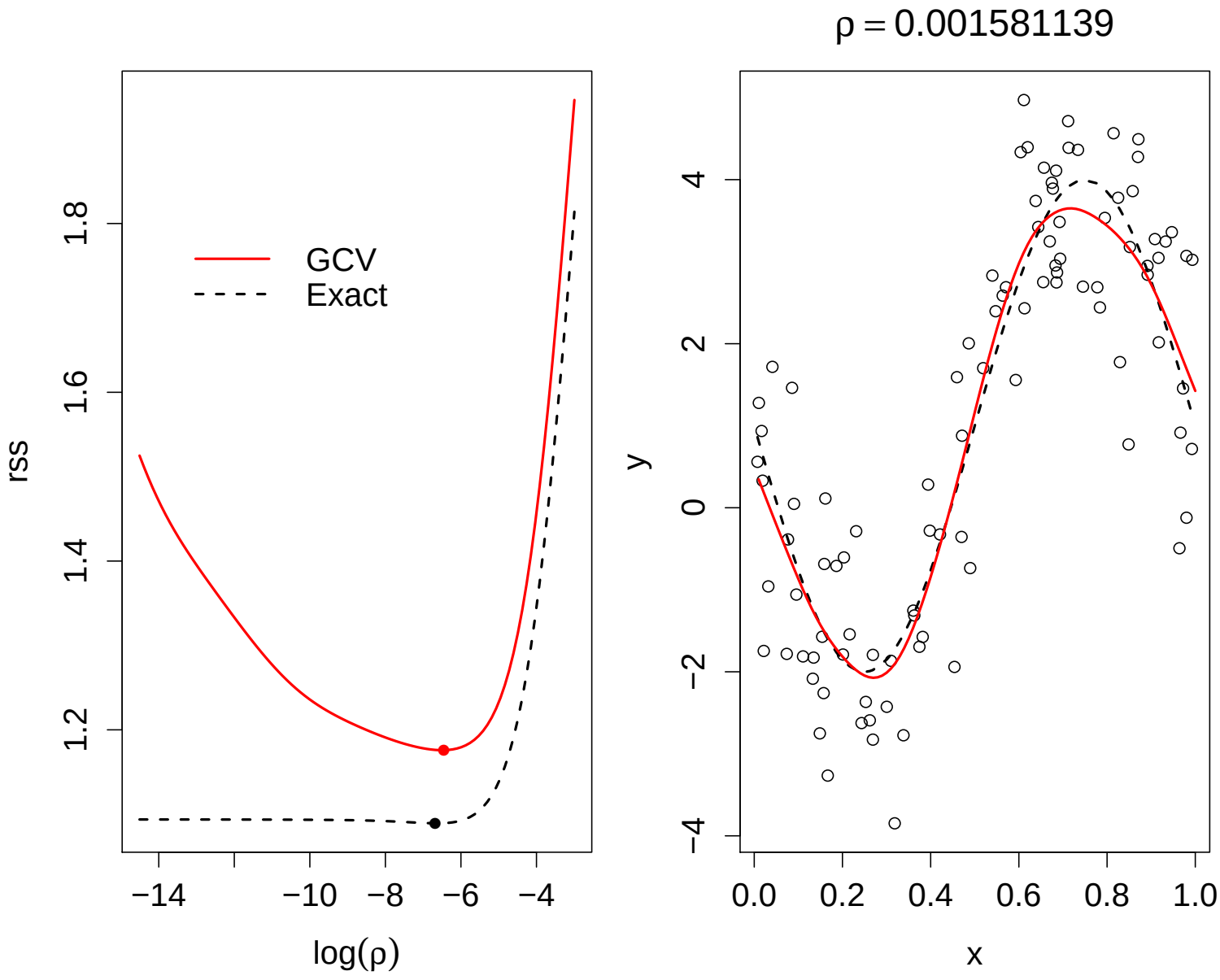
is minimized... but we don't know the true η. So we choose ρ minimizing:

$$V_0(\rho) = \frac{1}{n}\sum_{i=1}^{n}(\eta_\rho^{[i]}(x_i) - Y_i)^2\,,$$

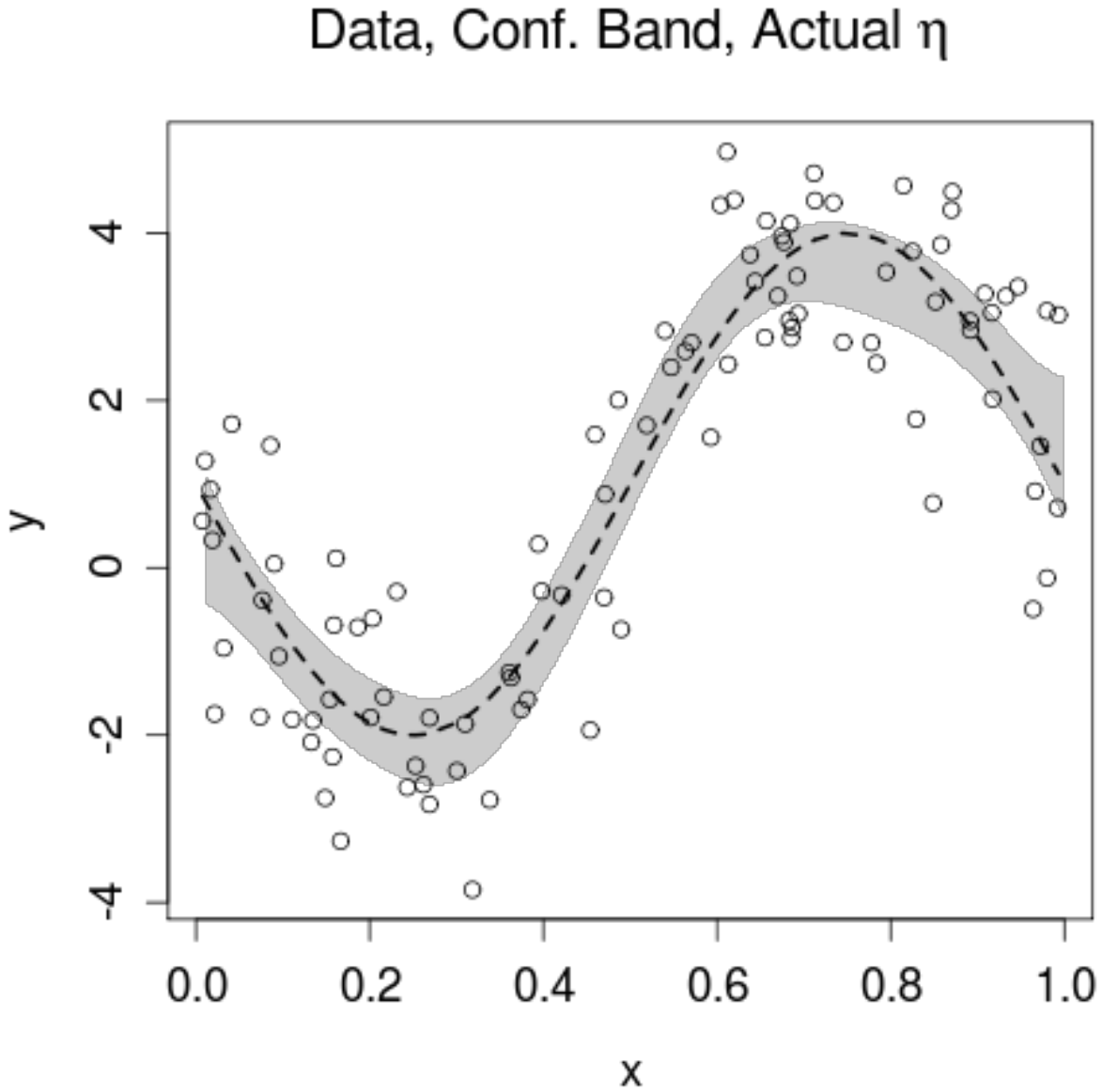
where $\eta_\rho^{[k]}$ is the minimizer of the "delete-one" functional:

$$\frac{1}{n}\sum_{i\neq k}(Y_i - \eta_\rho(x_i))^2 + \rho\int_0^1 \left(\frac{d^2\eta_\rho}{dx^2}\right)^2 dx\,.$$

Smoothing spline (8)



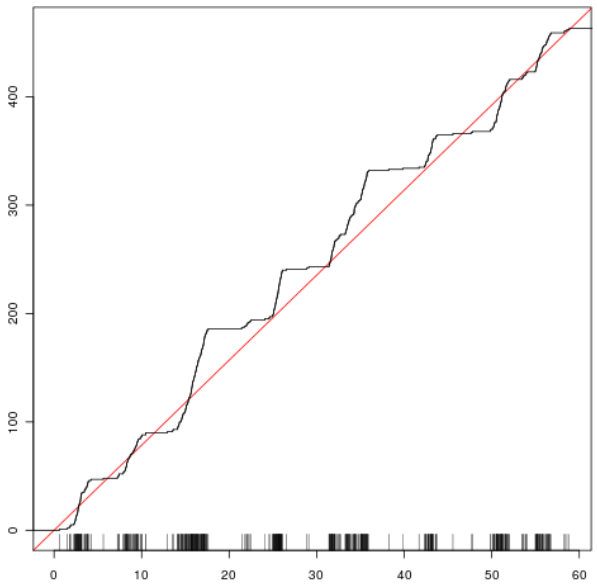
The theory (worked out by Grace Wahba) also gives us confidence bands

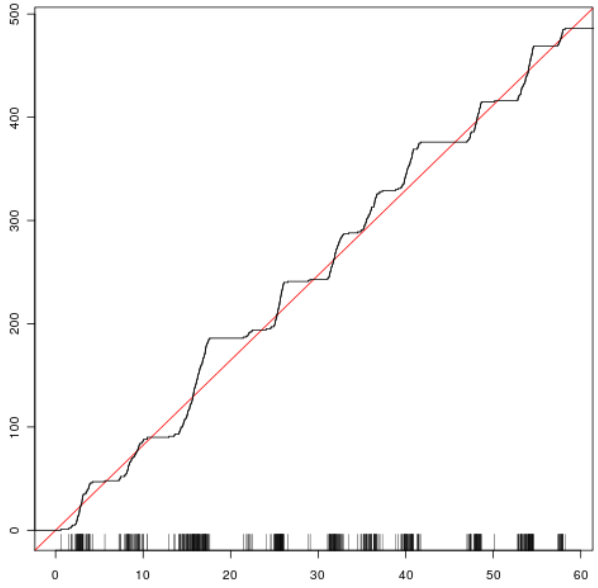


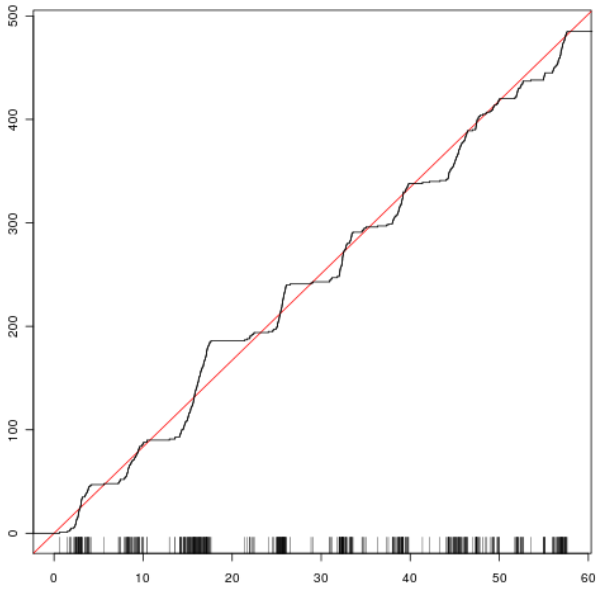
Going back to the real train

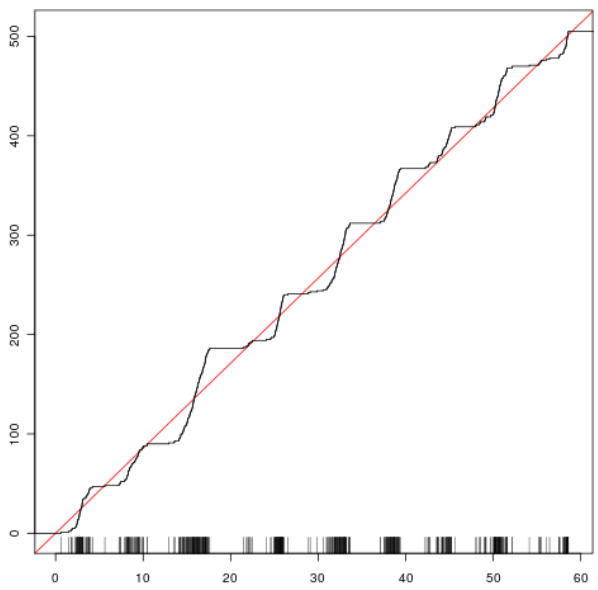
- On the next figure the actual spike train you saw previously will be shown again.
- Three other trains will be shown with it. The second half ($t \geq 29.5$) of each of these trains has been simulated.
- The simulation was performed using the same model obtained by fitting the first half of the data set.

Which one is the actual train?









Towards the candidate model

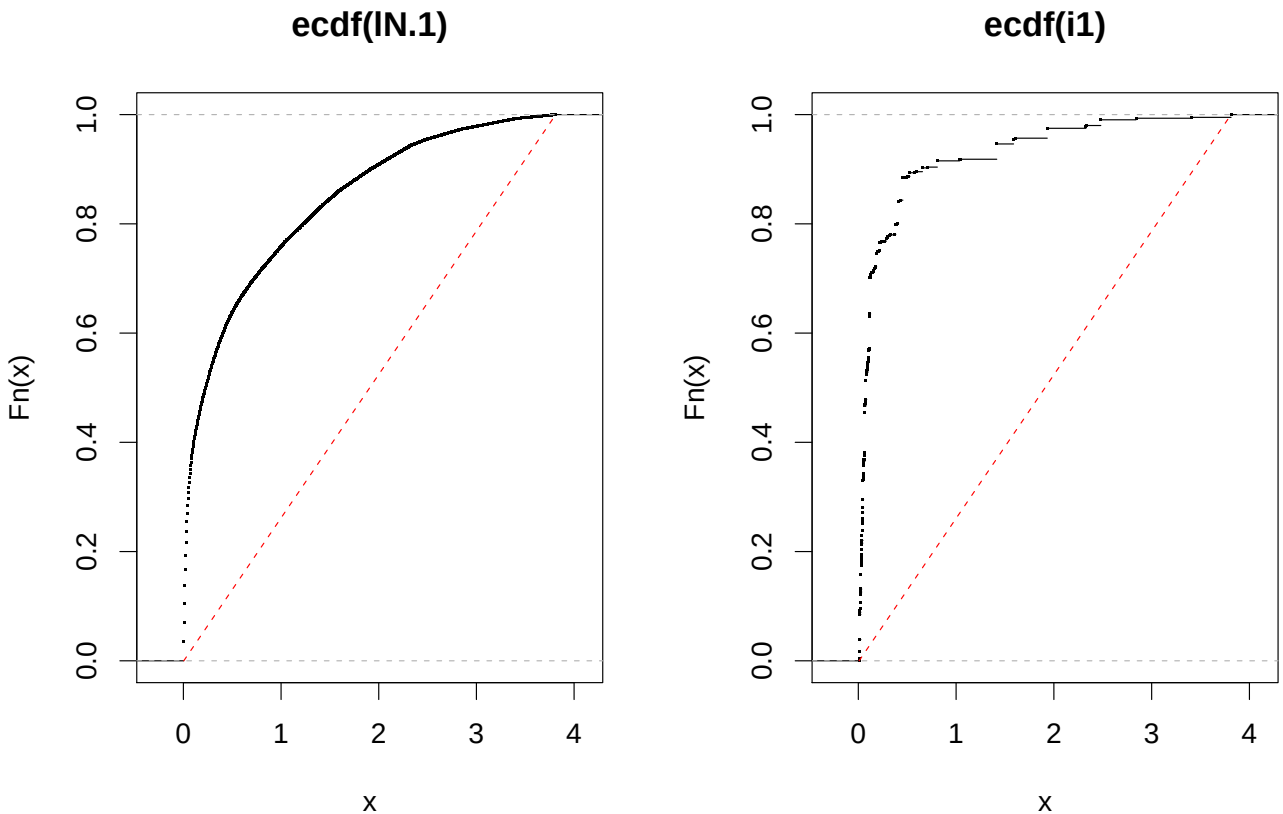
- We said previously that we would start with a 2 variables model:

$$\eta(t - t_l, isi_1) = \eta_\emptyset + \eta_l(t_t - l) + \eta_1(isi_1) + \eta_{l,1}(t - t_l, isi_1)\,.$$

- Since we are using non-parametric method we should not apply our tests to the data used to fit the model. Otherwise our P-values will be wrong.
- We therefore systematically split the data set in two parts, fit the same (structural) model to each part and test it on the other part.

An important detail (1)

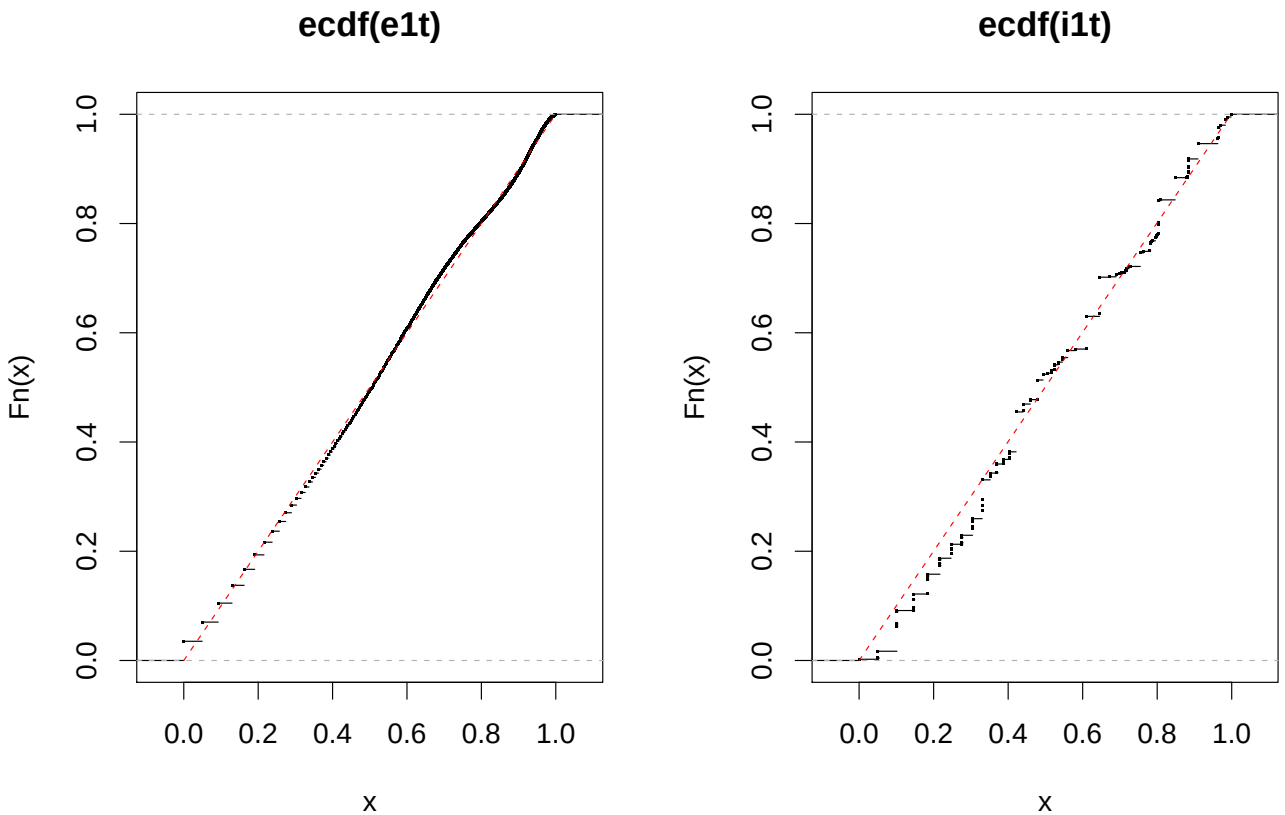
The distributions of our variables, $t - t_l$ and isi_1 are very non-uniform:



For reasons we do not fully understand yet, fits are much better if we map our variables onto uniform ones.

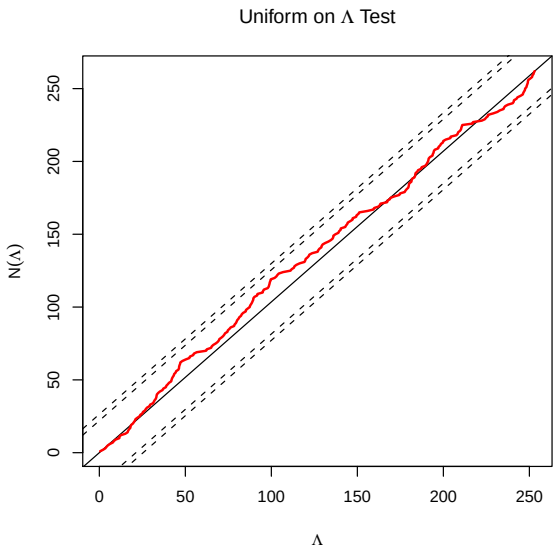
An important detail (2)

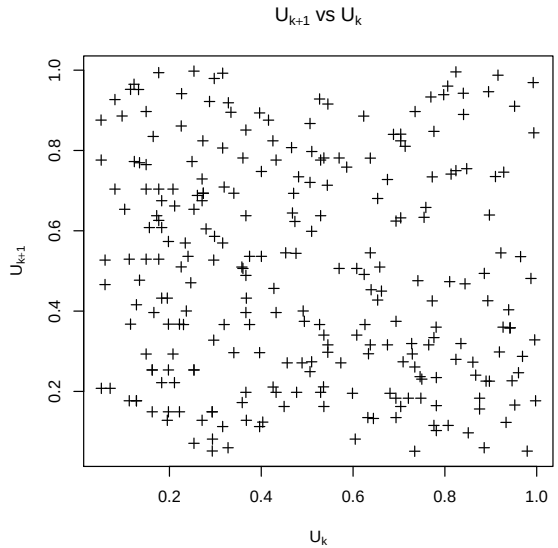
We therefore map our variables using a smooth version of the ECDF estimated from the first half of the data set.

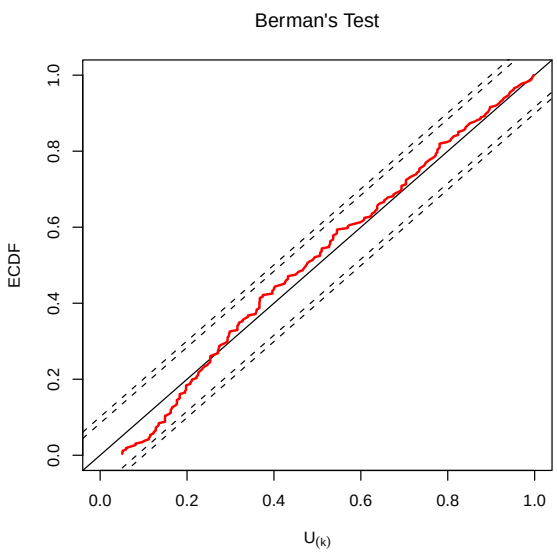


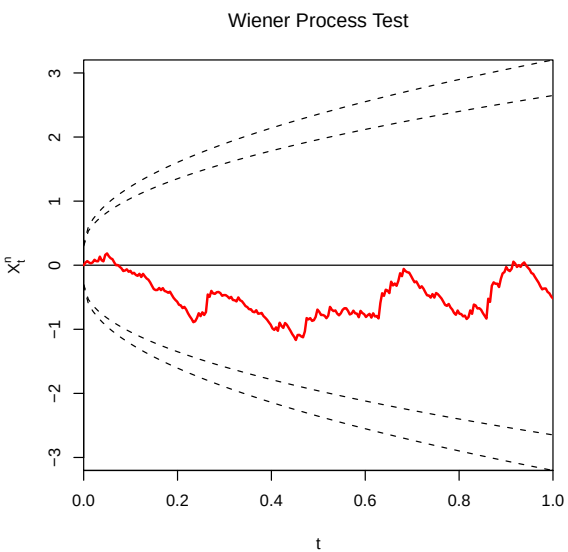
These mapped variables ECDFs are obtained from the whole data set.

Fit Early Test Late

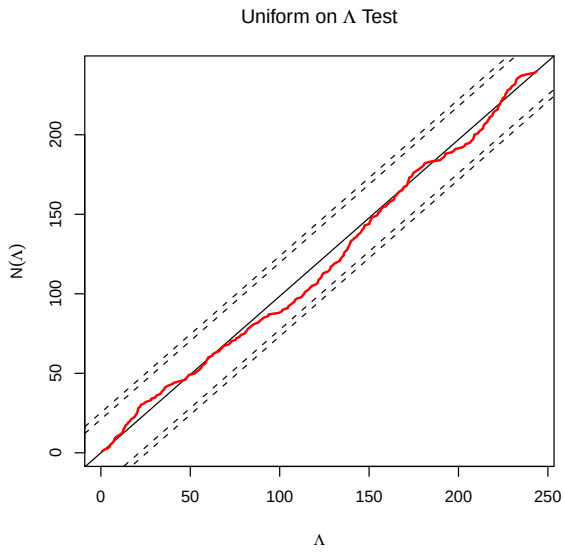


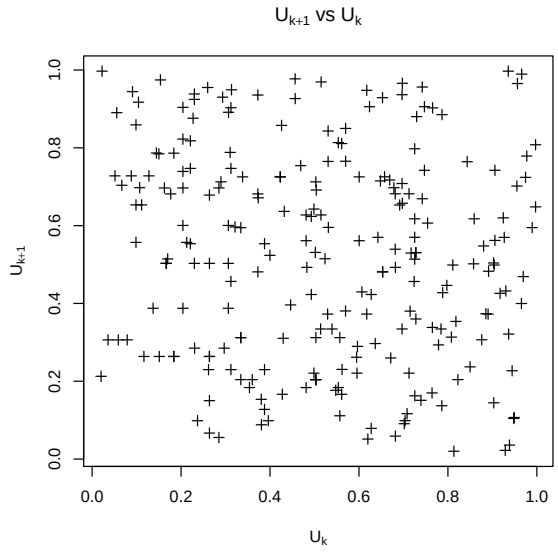


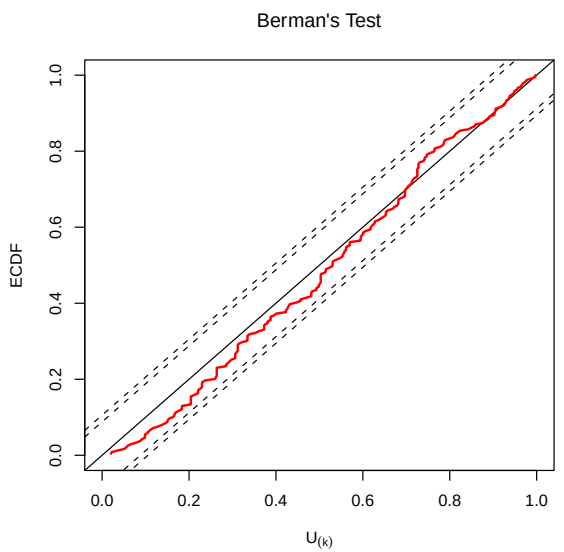


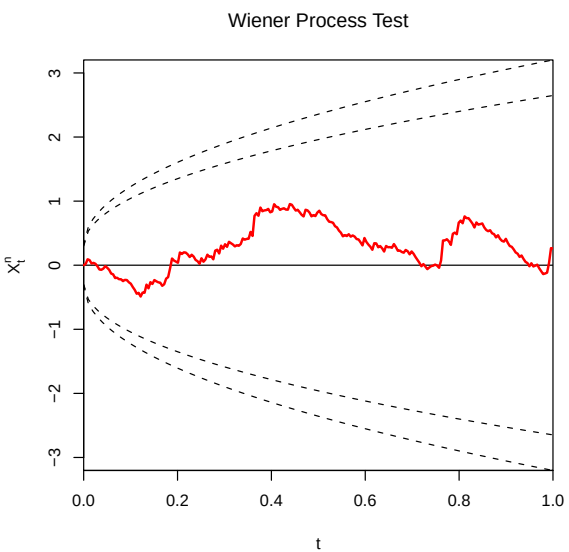


Fit Late Test Early

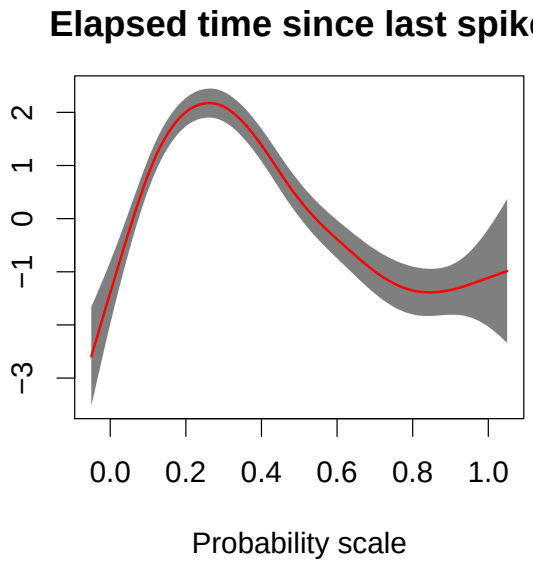


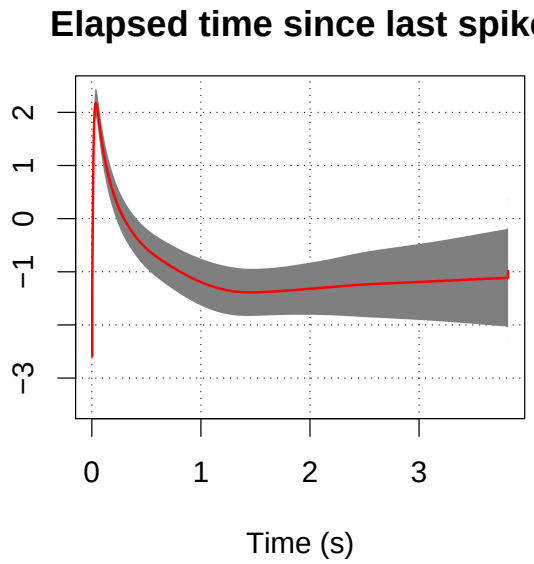


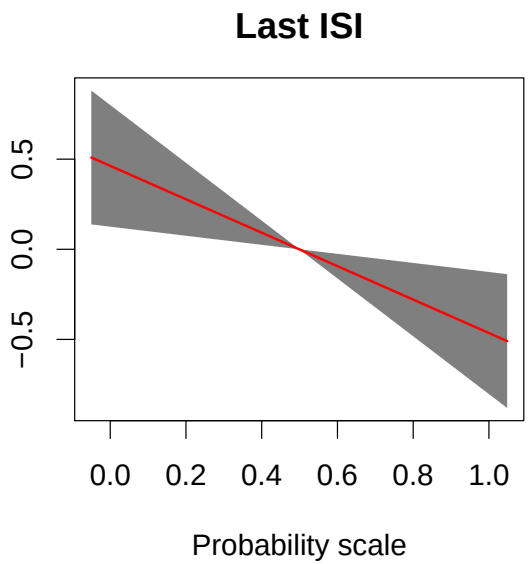


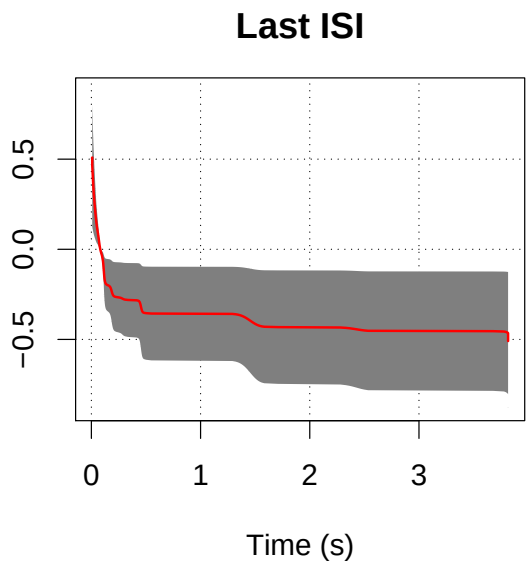


The functional forms: Uni-variate terms

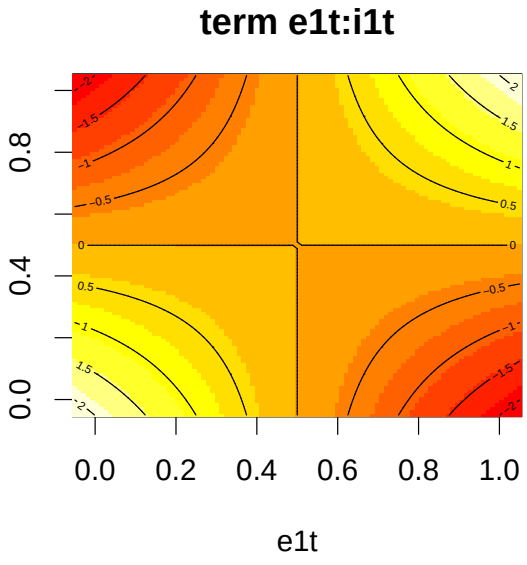


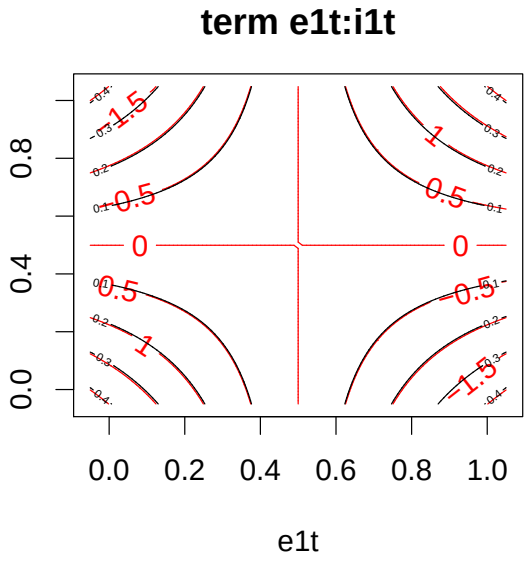


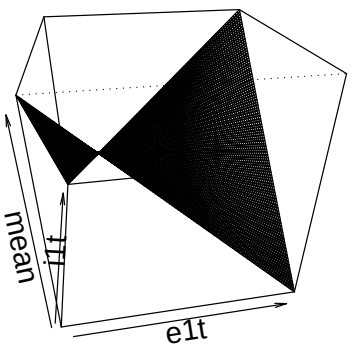


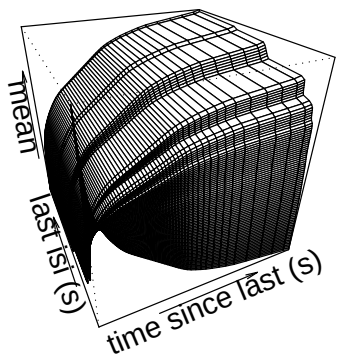


The functional forms: Interaction term









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- Roberto Fernandez for his kind invitation.
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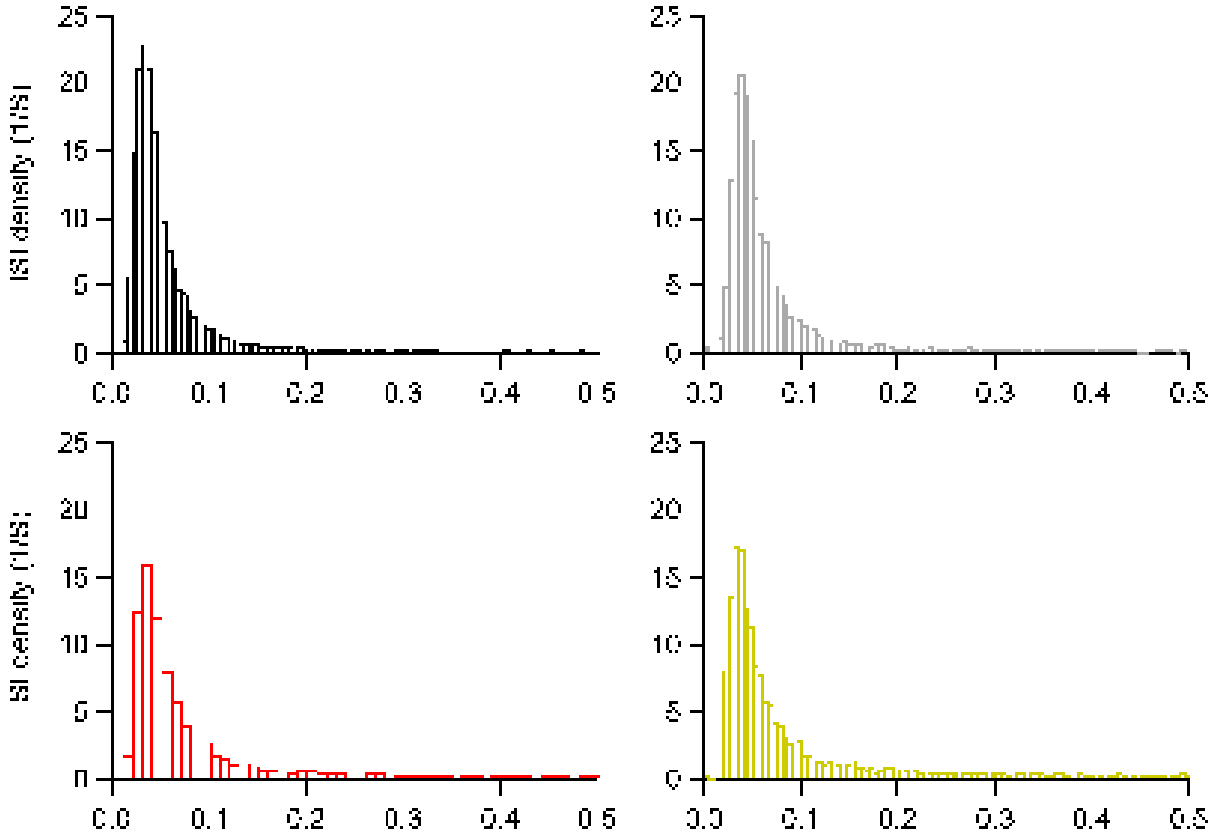
- Chong Gu for developing the `gss` package and for collaborating on this conditional intensity estimation problem.
- The `R` guys for making such a wonderful data analysis tool.
- Vilmos Prokaj, Olivier Faugeras and Jonhatan Touboul for pointing Donsker's theorem to me.
- You guys for listening to me up to that point.

A Model for spike trains: Actual spike trains are not Poisson



Example of Inter Spike Interval (ISI) densities obtained from 4 simultaneously recorded Projection Neurons.

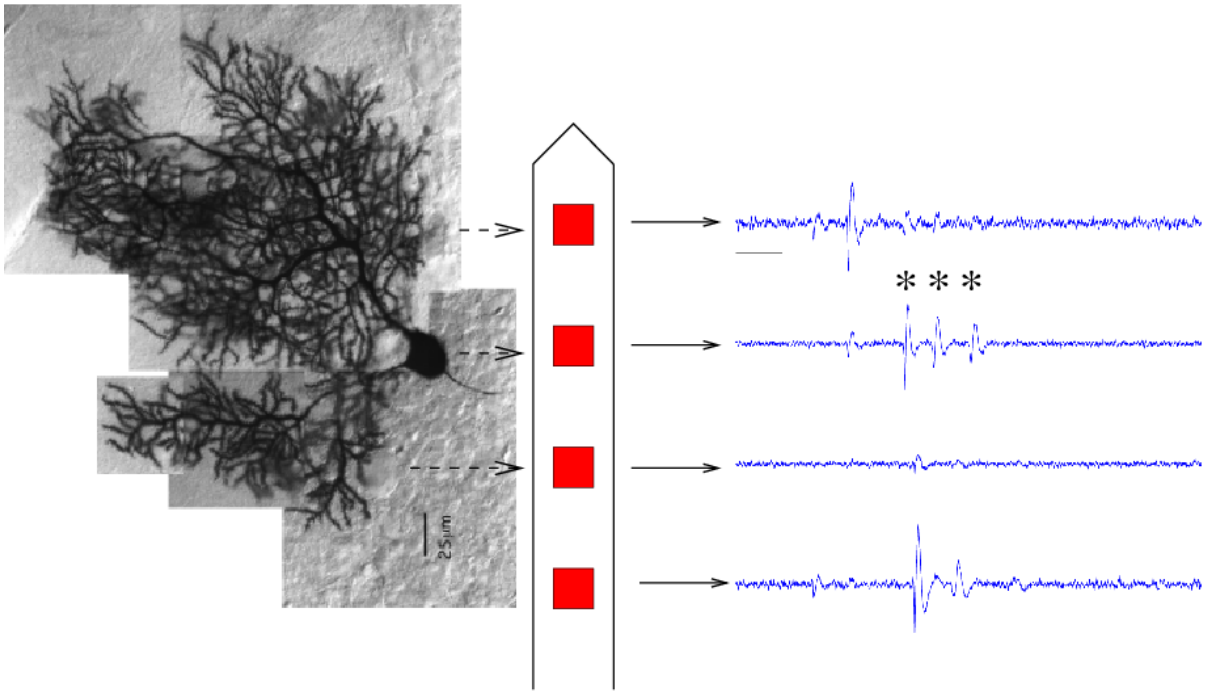
A Model for spike trains: Log-normal density

Empirical ISI densities are better described by a log-normal density than by a Poisson density :

$$\pi_{isi}\left(ISI = isi \mid S = s, F = f\right) = \frac{1}{isi \cdot f \cdot \sqrt{2\pi}} \cdot \exp\left[-\frac{1}{2} \cdot \left(\frac{\ln isi - \ln s}{f}\right)^2\right]$$

where, S is a scale parameter (measured in sec) and F is a dimensionless shape parameter.

Spike shapes are not (always) stationary



Recording form rat sagittal cerebellar slices, along the Purkinje cell layer. Right: $***$, 3 consecutive spikes from a single Purkinje cell. Scale bar: 10 ms. Recording made M. Delescluse.

Description of the amplitude dependence on the ISI

We will describe the spike amplitude, **a**, dependence upon the *ISI* with an exponential relaxation (Fee et al, 1996):

$$\mathbf{a}\left(isi\right) = \mathbf{p} \cdot \left(1 - \delta \cdot \exp\left(-\lambda \cdot isi\right)\right)$$

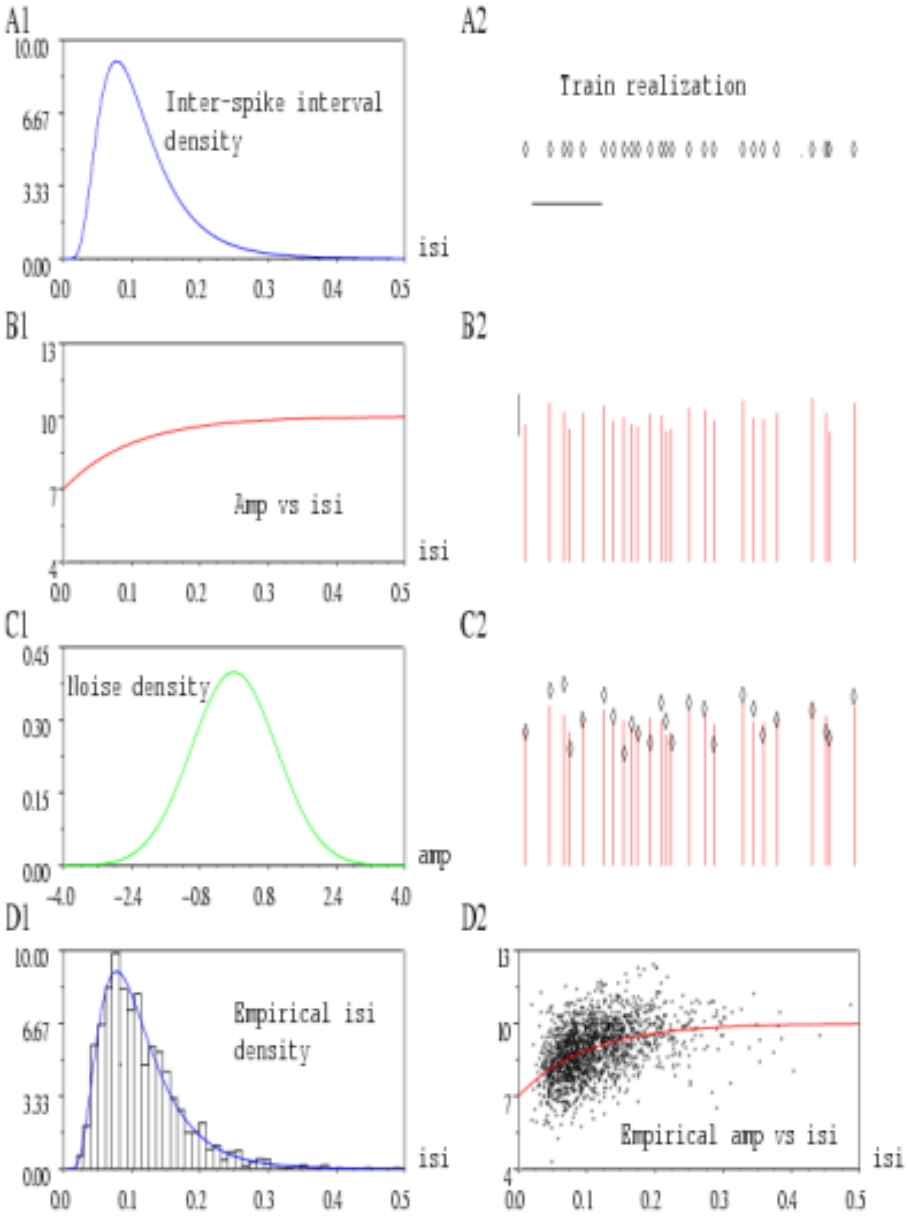
where **p** is the maximal peak amplitude, δ is the maximal modulation and λ is the inverse of the relaxation time constant.

A data generation model

We will now adopt the following data generation model:

- The discharge statistics of individual neurons is described by a log-normal point process.
- The spike amplitudes generated by a single neuron depends on the elapsed time since the last spike of the same neuron. This dependence is an exponential relaxation.
- The background noise is Gaussian, white and statistically independent of the spikes.

Ideal single neuron data according to our model



We will not enter into details here but it is very easy to maximize the likelihood of such data, or, in other words, to find the most likely parameter values given the data.

Notations for multi-neuron data

- We will use Θ to designate the full list of model parameters:

$$\Theta = (\mathbf{P}_1, \Delta_1, \Lambda_1, S_1, F_1, \ldots, \mathbf{P}_K, \Delta_K, \Lambda_K, S_K, F_K) \ .$$

- We will formalize our ignorance of the origin of each spike, j, by attaching to it a label, $L_j \in \{1, \ldots, K\}$. $l_j = 3$, means that spike, j, is attributed to neuron 3 of the model.
- We will call configuration, C, the set of labels:

$$C = (L_1, \ldots, L_N)^T \ .$$

  There are K^N different configurations.

The "Bayesian" approach (1)

- We will adopt the Bayesian approach to statistical inference.
- We want here to obtain values and *confidence intervals*, for our model parameters, Θ and for the configuration, C. More generally we will try to obtain probability density functions for Θ and C.
- The Bayesian approach is based on the following identities:

$$\begin{aligned} Prob\,(data, c, \theta) &= Prob\,(data, c \mid \theta) \cdot Prob\,(\theta)\ , \\ &= Prob\,(\theta, c \mid data) \cdot Prob\,(data)\ . \end{aligned}$$

- The last identity leads to:

$$Prob\,(\theta, c \mid data) = \frac{Prob\,(data, c \mid \theta)\ Prob\,(\theta)}{Prob\,(data)}.$$

- $Prob\,(data, c \mid \theta)$ is nothing else than the likelihood function.

The "Bayesian" approach (2)

- The denominator or normalizing constant can be rewritten as:

$$Prob\,(data) = \sum_{c \in \mathcal{C}} \int d\theta\, Prob\,(data, c \mid \theta) \cdot Prob\,(\theta)\ ,$$

  where $\mathcal{C}$ is the set of all configurations.
- The quantity $Prob\,(\theta)$ is called the prior density on model parameters.

Problems of the Bayesian approach

- We are interested in getting: $Prob\,(\theta, c \mid data)$, for then we can obtain an answer to any question like: What is the *posterior probability* of configuration c? It is "simply": $\int d\theta\, Prob\,(\theta, c \mid data)$.
- But to get $Prob\,(\theta, c \mid data)$ we need to compute the normalizing constant:

$$Prob\,(data) = \sum_{c \in \mathcal{C}} \int d\theta\, Prob\,(data, c \mid \theta) \cdot Prob\,(\theta)\ ,$$

  which requires a continuous summation on the parameters space and a discrete one on a set with K^N elements! This is much too large for realistic situations where $K \sim 10$ and $N \sim 1000$!
- How shall we do?

Did somebody else already solve our problem?

- Before scratching our heads for too long or, even worst, giving up our nice data generation model, we could look if someone else already solved our problem.
- In such situations it seems a good idea to look at what physicists did since these guys are extremely gifted to write down problems they can't explicitly solve... Before finding a way around them.
- In our case, statistical physics turned out to be the right field to explore... in particular the Potts model.

What is a Potts model? (1)

- A Potts model on an $N \times N$ square lattice is network whose nodes can have $q \geq 2$ possible values.
- The energy of a Potts model configuration (or *micro state*) is given by:

$$E\left(c = \{I_{1,1}, \ldots, I_{N,N}\}\right) = -J \sum_{\textit{neighboring pairs}} \delta_{I_{i,j}, I_{i',j'}} ,$$

where δ is the Kroenecker symbol.

What is a Potts model? (2)

- The probability to find the lattice in a particular configuration is given by the Boltzmann distribution:

$$\pi_{Bolztmann,\beta}(c) = \frac{\exp(-\beta E(c))}{Z_\beta},$$

with $\beta = (kT)^{-1}$,

$$Z_\beta = \sum_{c \in \mathcal{C}} \exp(-\beta E(c))$$

is the normalizing constant or partition function and the set $\mathcal{C}$ of all configurations has q^{N^2} elements.

The problems of Potts models

- Physicists are interested in computing expected values, because these are the quantities they can measure experimentally.
- They want for instance to get the expected energy which is formally obtained with:

$$\langle E \rangle_\beta = \sum_{c \in \mathcal{C}} \frac{E(c) \exp(-\beta E(c))}{Z_\beta} .$$

- But such expected value calculations always involve summations over sets whose number of elements are too large.

Its solution

- In 1953, Metropolis et al found the solution to the expectation computation problem.
- The idea is to generate a Markov chain on the configurations set:

$$\left\{c^1, c^2, \ldots, c^M\right\} .$$

- This Markov chain is generated such that:

$$\lim_{M\to\infty} \frac{1}{M} \sum_{j=1}^{M} E\left(c^{(j)}\right) = \langle E \rangle_\beta \ ,$$

where $c^{(j)} \in \left\{c^1, c^2, \ldots, c^M\right\}$ stands for the configuration "visited" by the chain at step j.

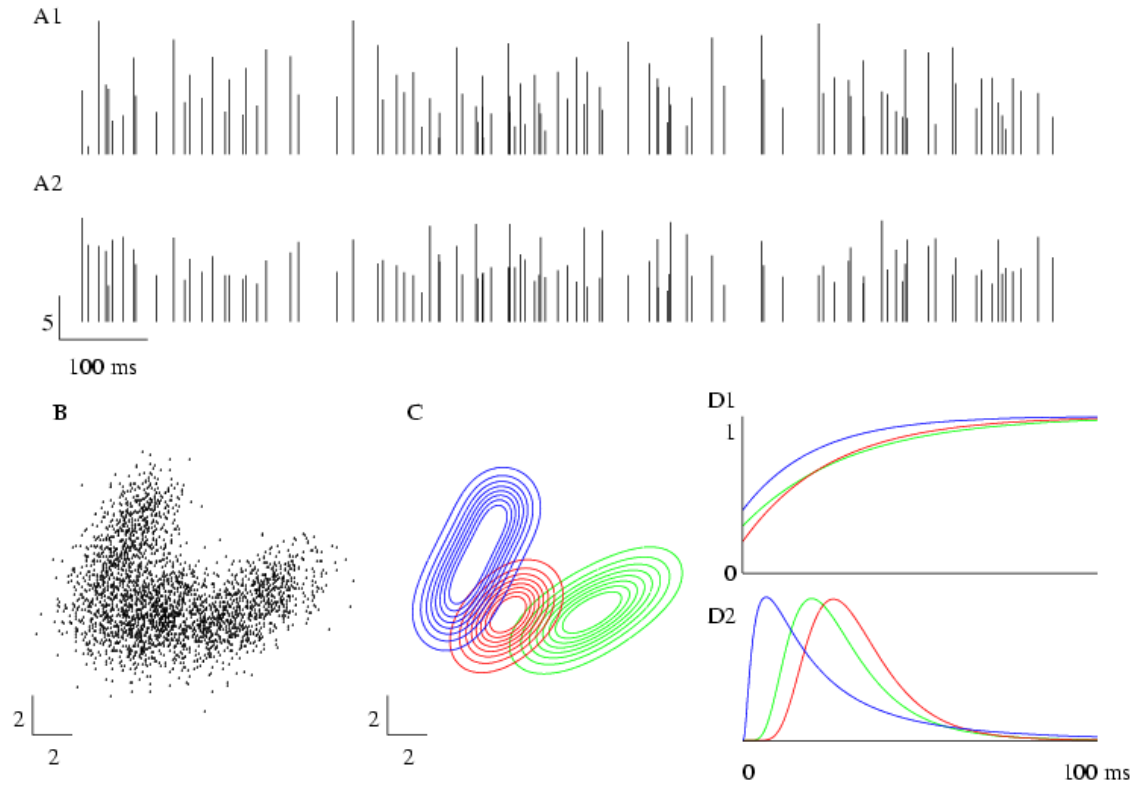
An adaptation of the physicists' solution to our spike sorting problem

- Following Metropolis et al, as well aw many physicists and statisticians after them we will generate a Markov chain on our configuration set and on our model parameter space:

$$\left\{c^1, c^2, \ldots, c^M\right\} \times \Theta\,.$$

- We won't detail here how we precisely build this Markov chain. It just takes time and patience!
- The general class of methods we are implementing here is called Dynamic Monte Carlo by physicists and Markov Chain Monte Carlo (MCMC) by statisticians.

An example on simulated data



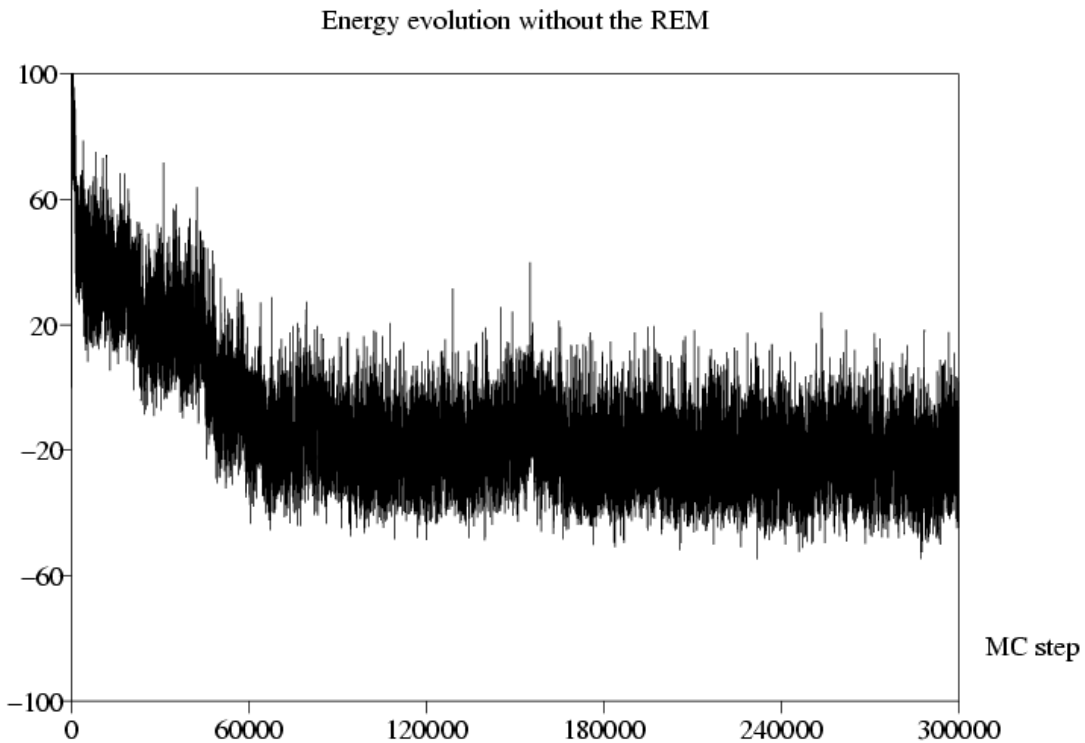
A, Data from 2 electrodes with 3 active neurons. We will use (and show) only the peak amplitudes of the spikes. B, The peak amplitude of each spike on the second recording site is shown against its peak amplitude on the first. C, Ideal iso-density plots of the 3 neurons. D, Amplitude dynamics and *ISI* densities of the 3 neurons.

Energy evolution: evidence for slow relaxation

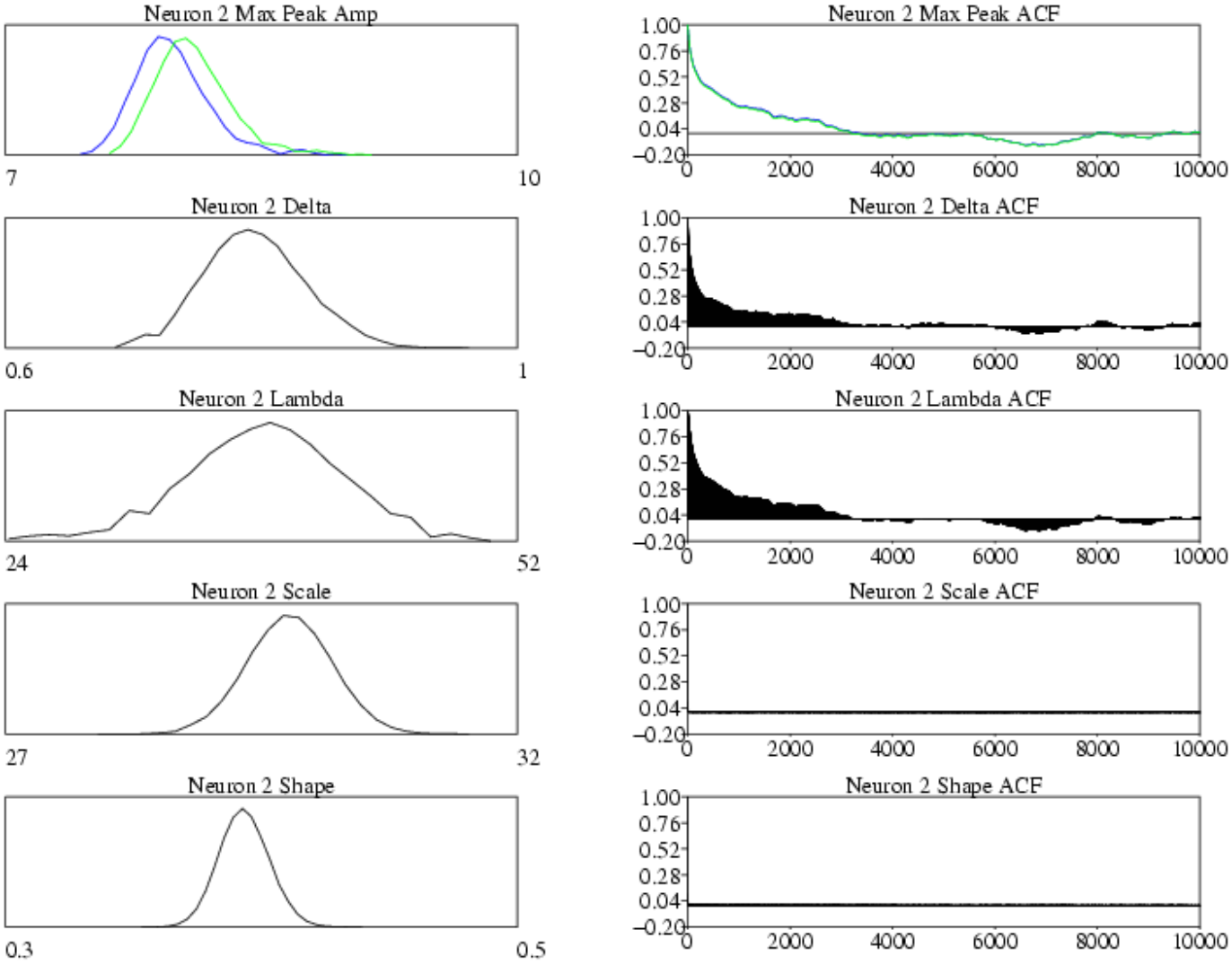
By analogy with Physics we define the energy of our spike train as follows:

$$E(c, \theta) = -\ln\left[Prob(data, c \mid \theta)\ Prob(\theta)\right]$$

and we get:



Posterior density of the amplitude parameters of the red neuron



Removing the slow relaxation: a spin glass analogy

- The slow relaxation means that our algorithm has a relatively high computational cost.
- We can again look at Statistical Physics to see if some similar problems were described and solved.
- They were indeed found with spin glasses which in the case of Potts model look like:

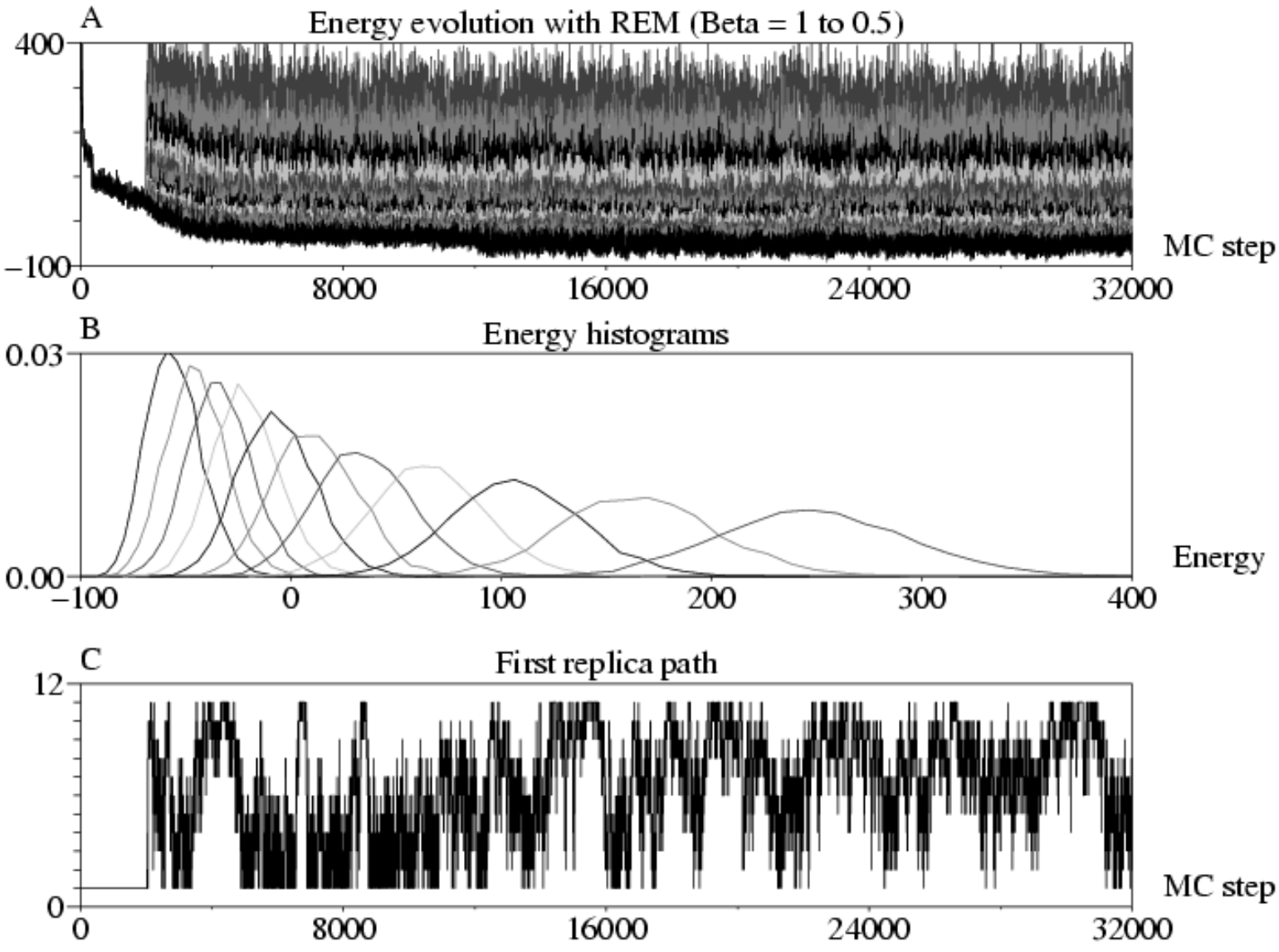
$$E\left(c = \{l_{1,1}, \ldots, l_{N,N}\}\right) = - \sum_{\textit{neighboring pairs}} J\left(l_{i,j}, l_{i',j'}\right) \delta_{l_{i,j}, l_{i',j'}} ,$$

where $J\left(l_{i,j}, l_{i',j'}\right)$ is the realization of a *random variable* (typically Gaussian with mean 0 and SD 1).

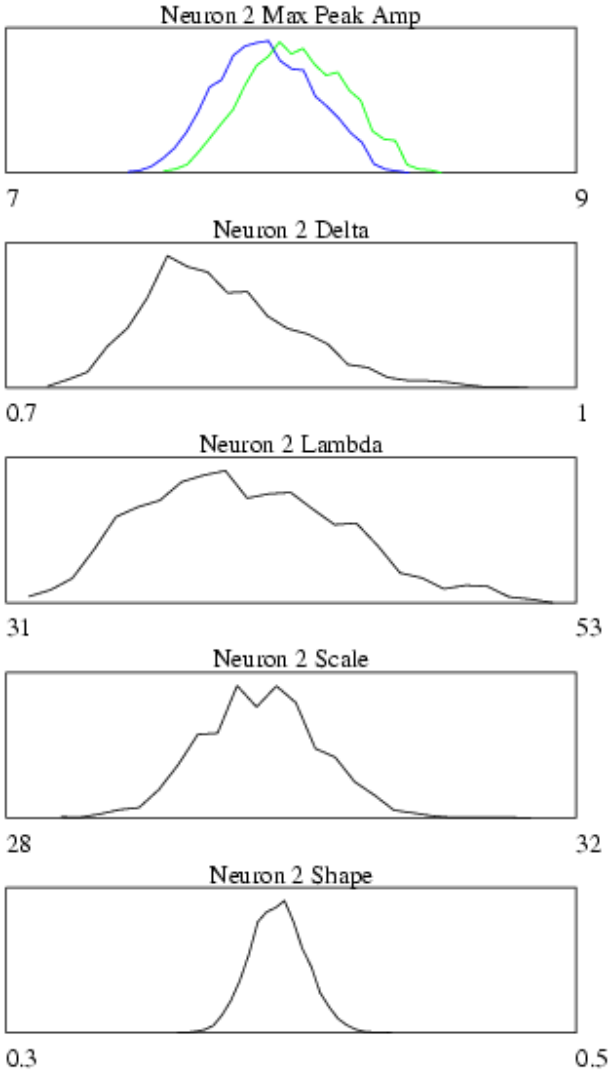
One spin glass solution to the slow relaxation

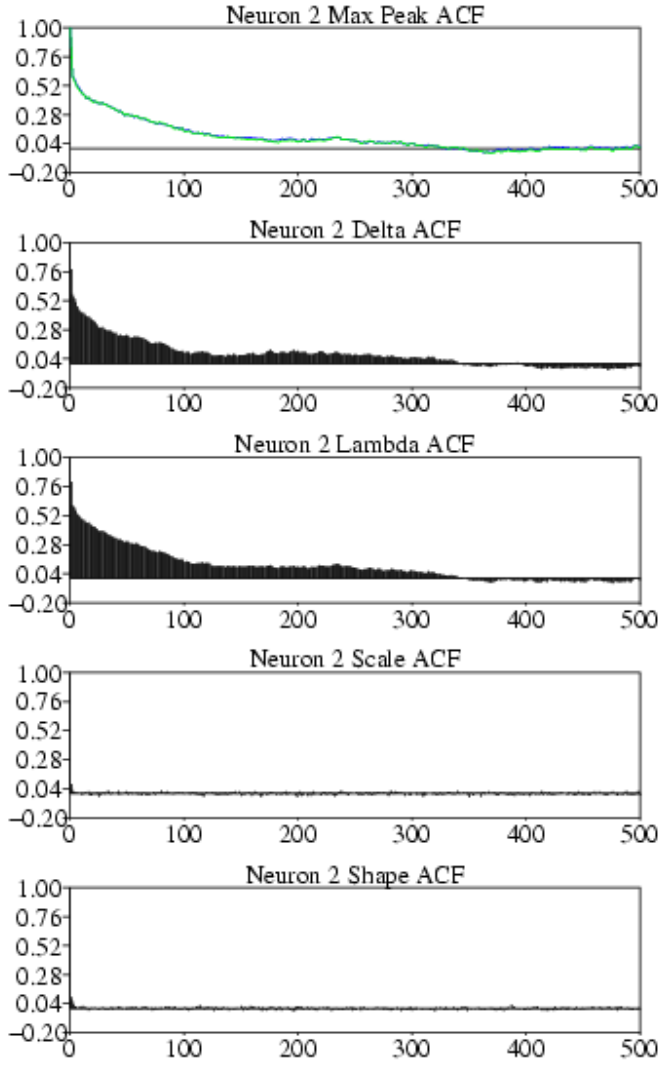
- One trick developed by physicists (in fact, statisticians found it first) is to generate parallel Markov chains on the same configuration space but with Boltzmann distributions corresponding to different temperatures.
- Some exchange between the configurations of different chains (at different temperatures) are then used.
- The idea is to exploit the "fast" configuration space exploration of the chain at high temperature which is less sensitive to local energy minima.
- This technique is known as: the Replica Exchange Method (REM), the Parallel tempering Method or the Metropolis Coupled MCMC.

Implementation of the REM

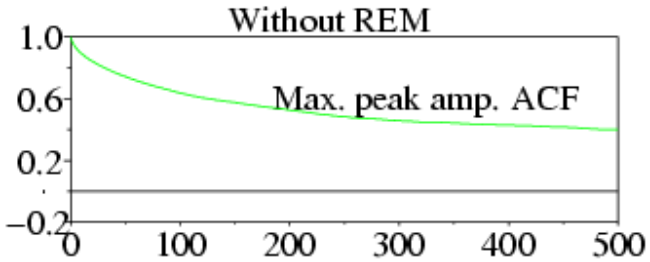


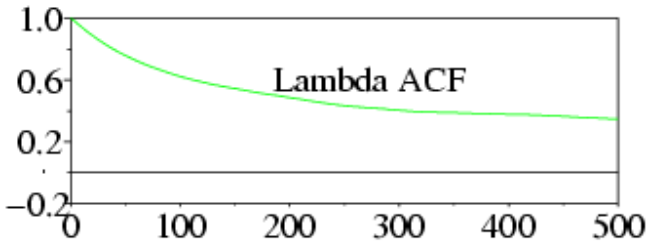
Posterior density of the amplitude parameters of the red neuron with the REM

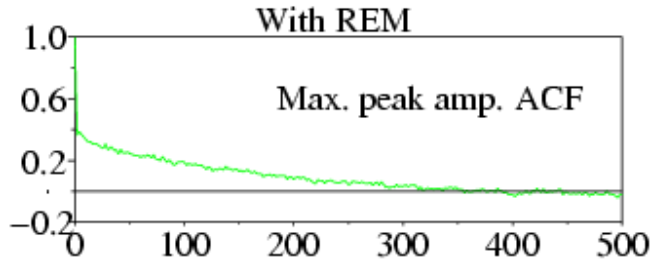


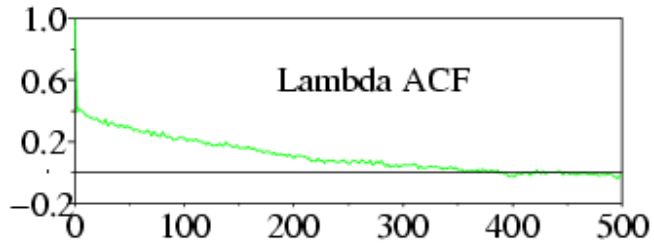


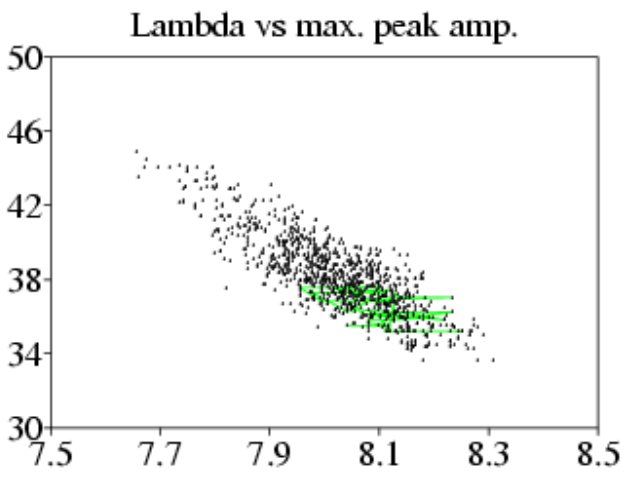
Why does the REM work?

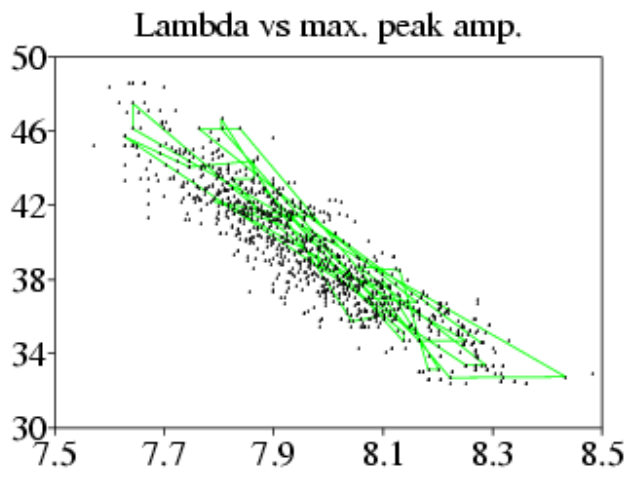




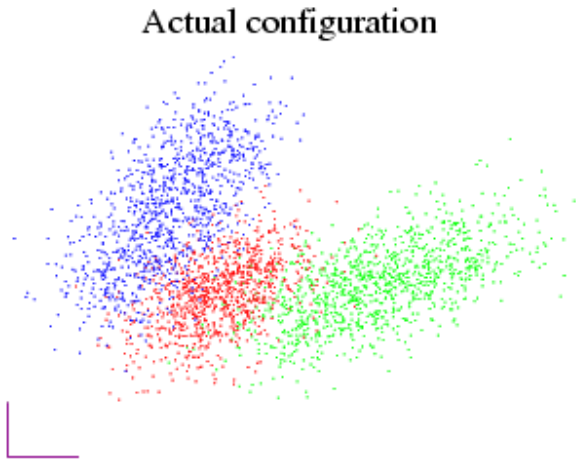


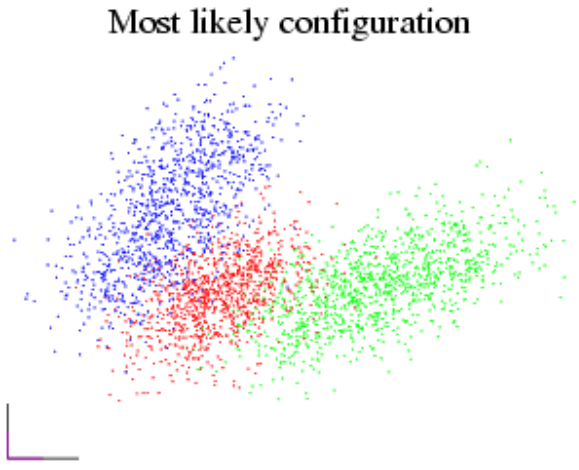


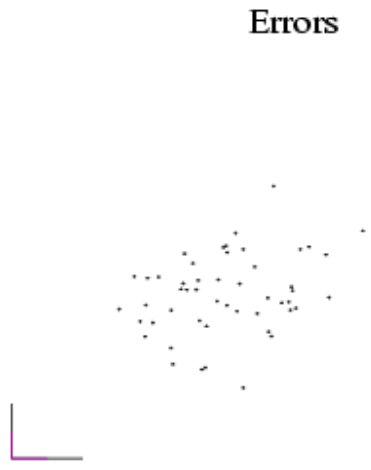




Do we get good sorting?







We end up with 50 errors for 2966 spikes.