Estimation of local independence graphs via Hawkes processes to unravel functional neuronal connectivity

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F. Grammont (Nice), T. Bessaih, R. Lambert, N. Leresche (Paris 6)

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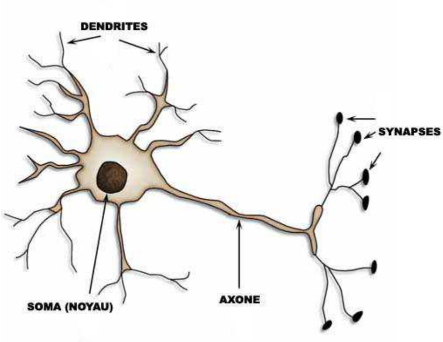
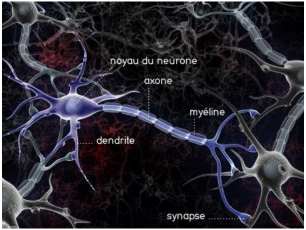
Some basics in Neurosciences

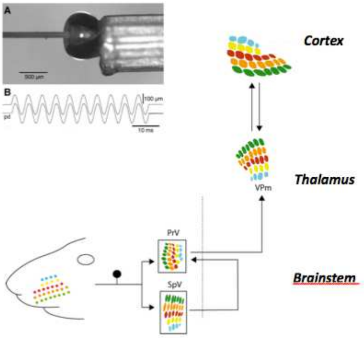


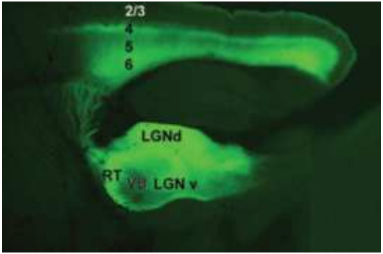
(a) One neuron



(b) Connected neurons

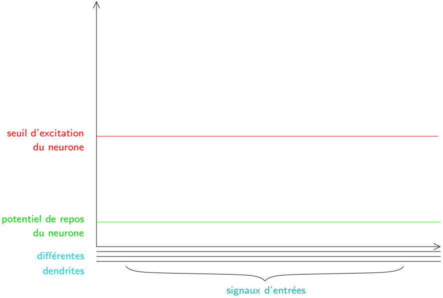
Description of the data (Team RNRP of Paris 6)





Synaptic integration

without synchronisation



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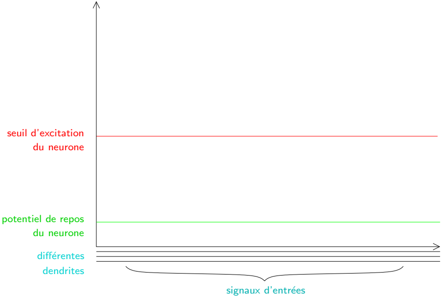

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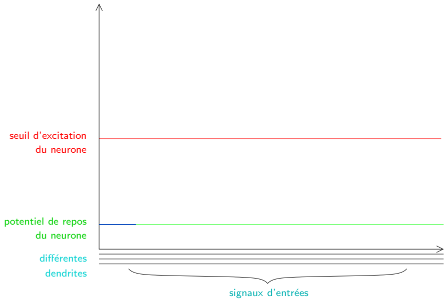

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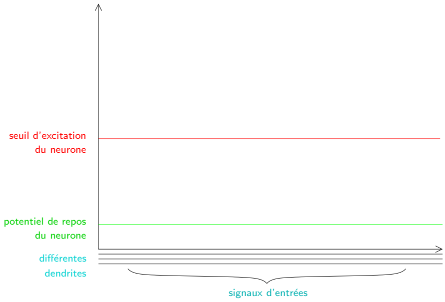

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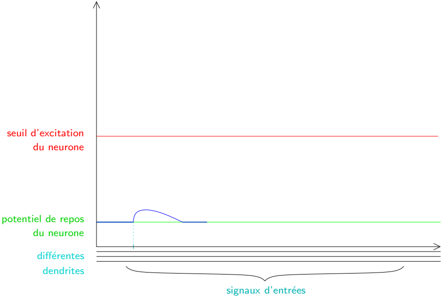

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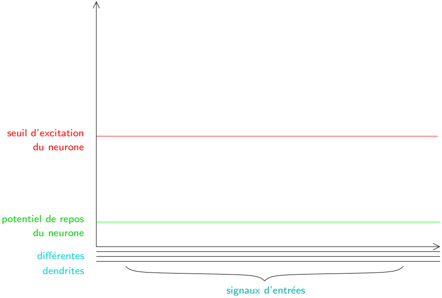

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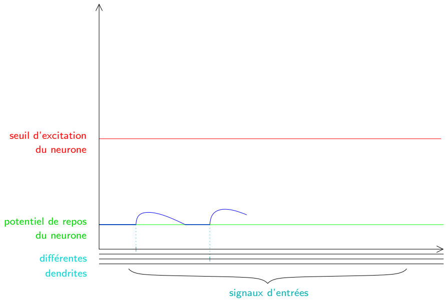

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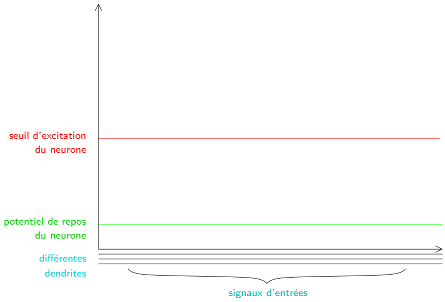

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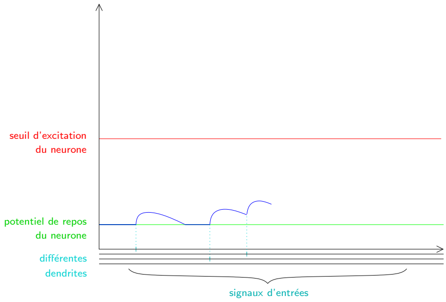

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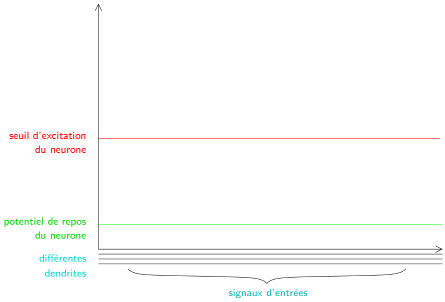

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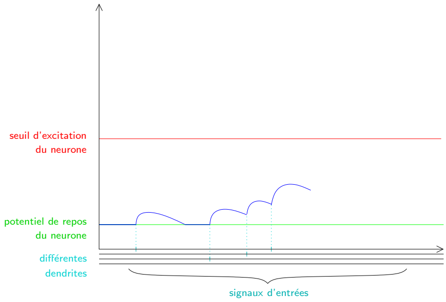

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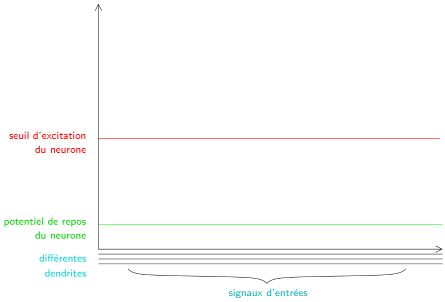

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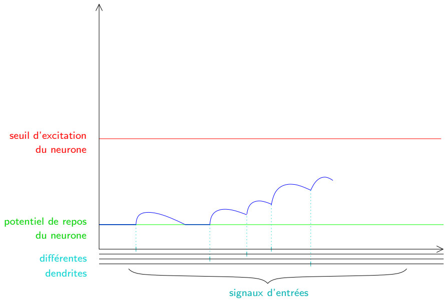

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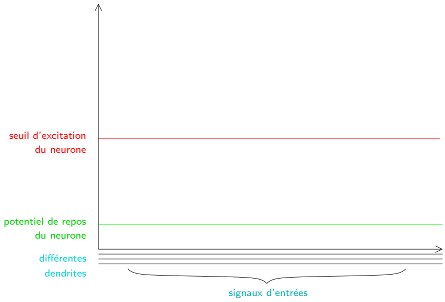

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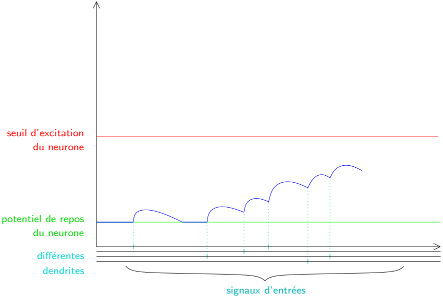

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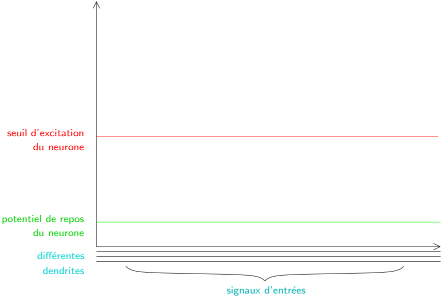

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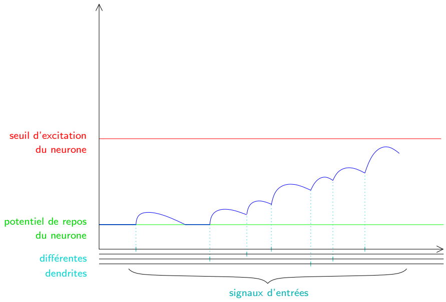

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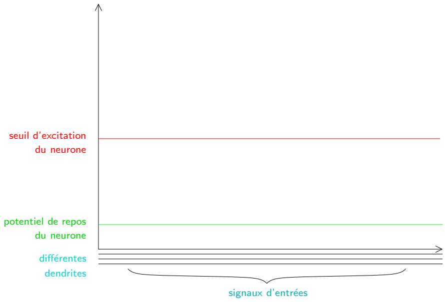

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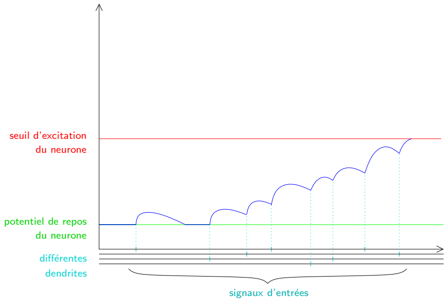

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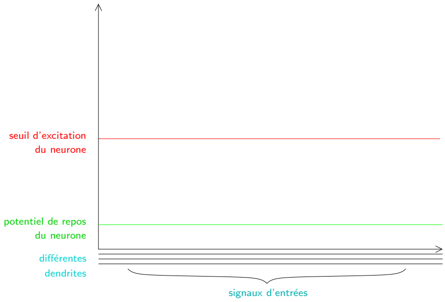

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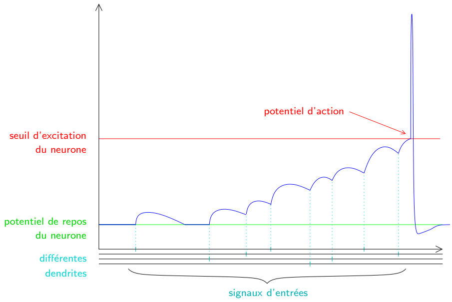

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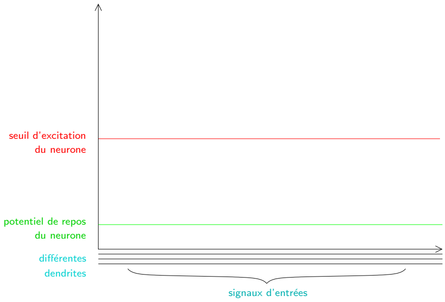

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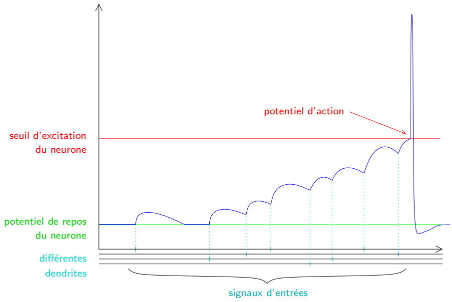

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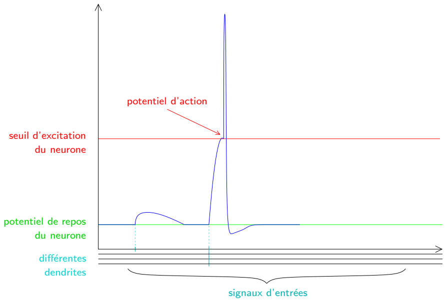

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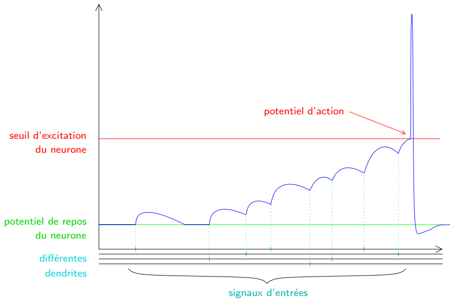

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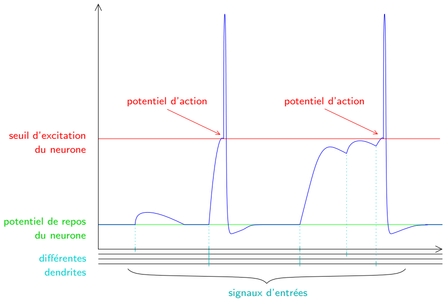
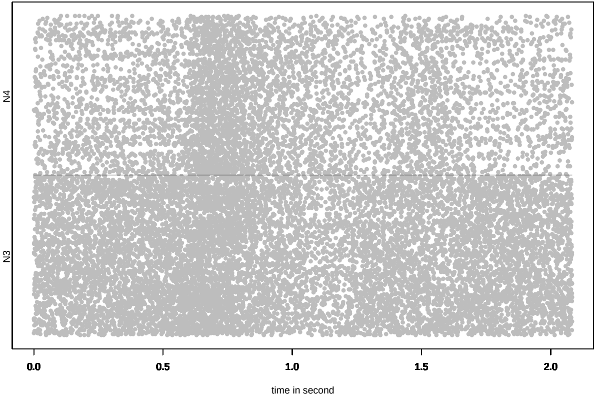


Data = spike trains

monkey trained to touch the correct target when illuminated



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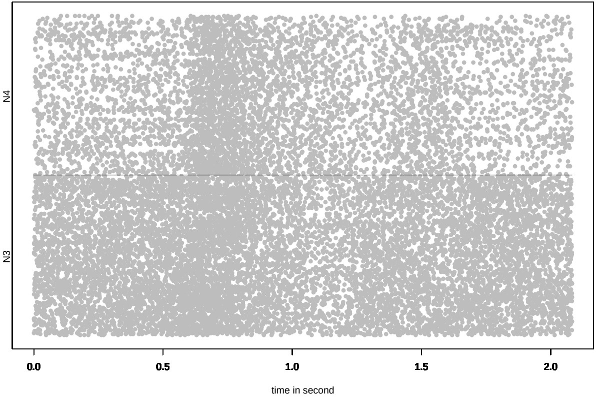
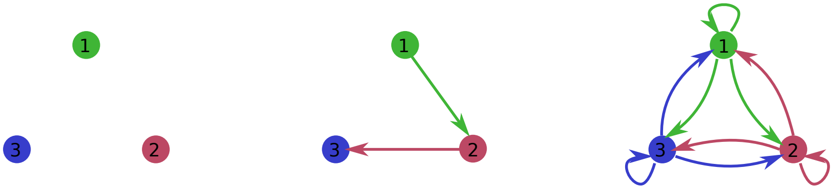


spike = point

$\rightarrow$ point processes

Visual aim

We want to produce that:



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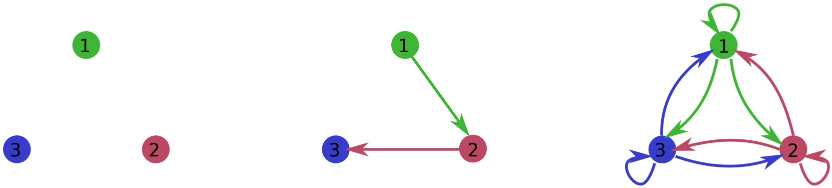


What is the mathematical meaning of it ?

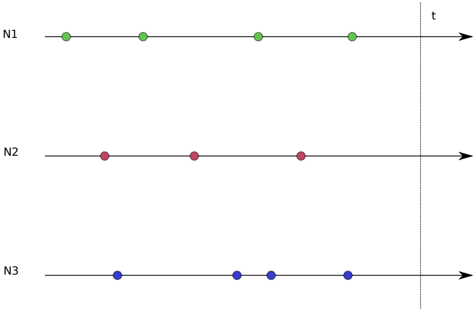
Point processes and conditional intensity

dN point measure $= \sum_{T \in N} \delta_T$

$$\underbrace{dN_t}_{\text{Nbr observed points in } [t, t+dt]} = \underbrace{\overbrace{\lambda(t)}^{\textbf{intensity}}\ dt}_{\text{Expected Number given the past before } t} + \underbrace{\text{noise}}_{\textit{Martingales differences}}$$

$$\begin{aligned} \lambda(t) &= \text{instantaneous frequency} \\ &= \textbf{random}\text{, depends on previous points} \end{aligned}$$

Multivariate Hawkes processes



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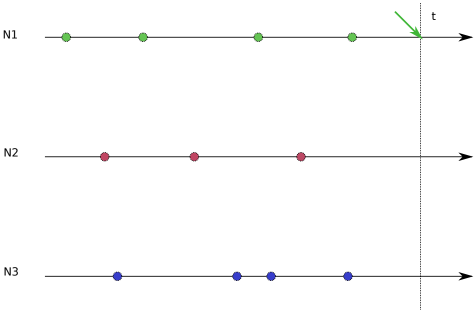

$$\lambda^{(1)}(t) \quad = \quad \underbrace{\nu}_{\text{spontaneous}}$$

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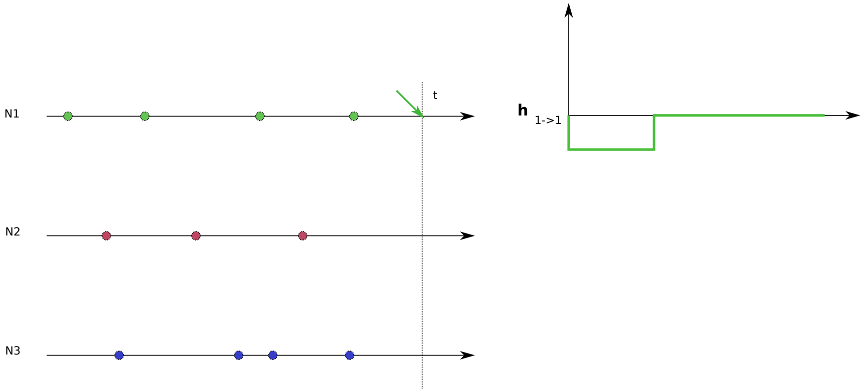

$$\lambda^{(1)}(t) = \underbrace{\nu}_{\text{spontaneous}} + \underbrace{\sum_{\substack{T<t \\ \text{pt de N1}}} h_{1\to 1}(t-T)}_{\text{self-interaction}}$$

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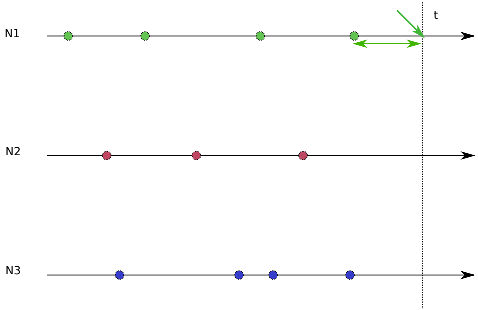

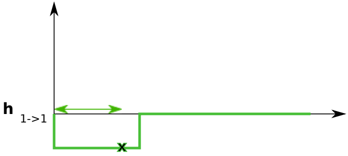

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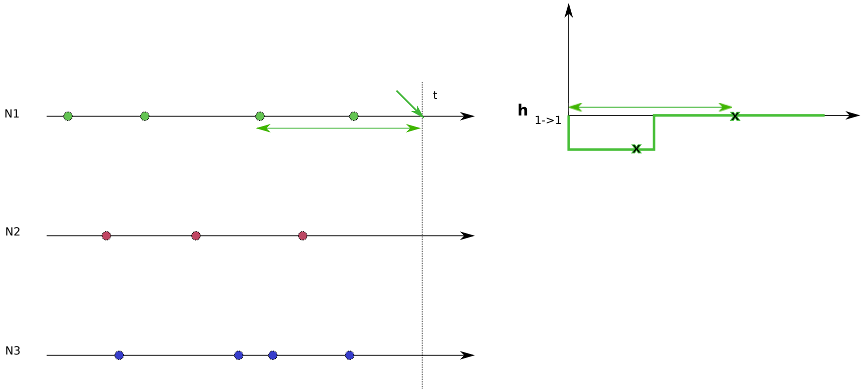

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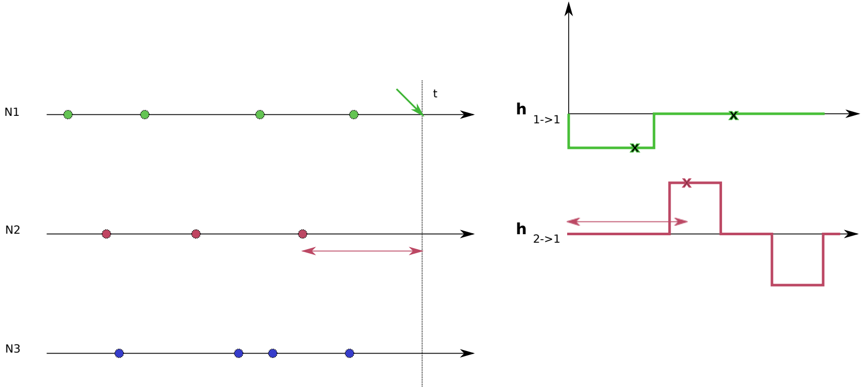

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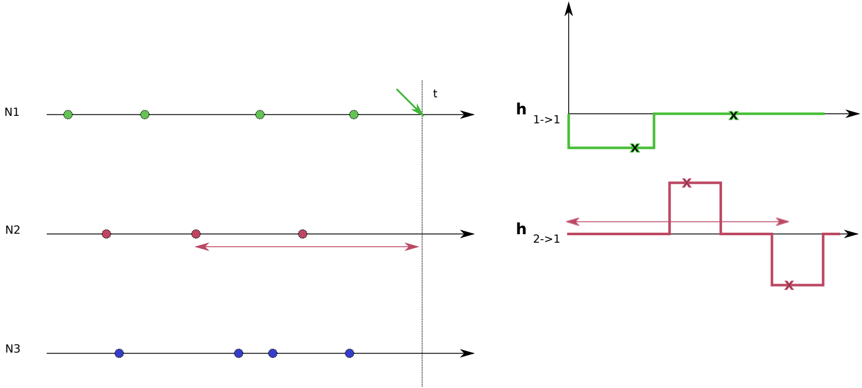

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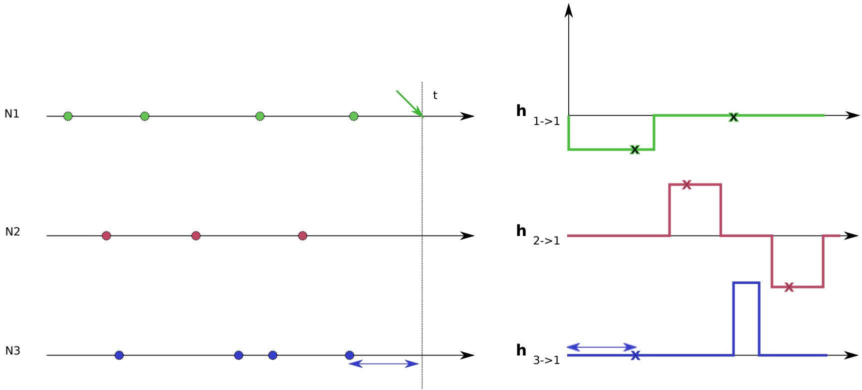

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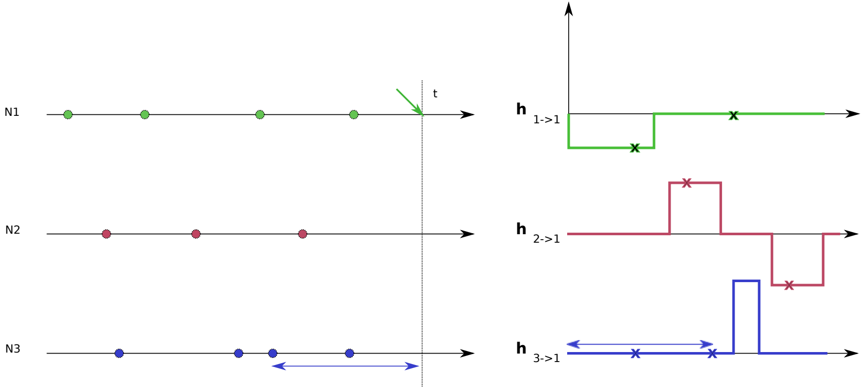

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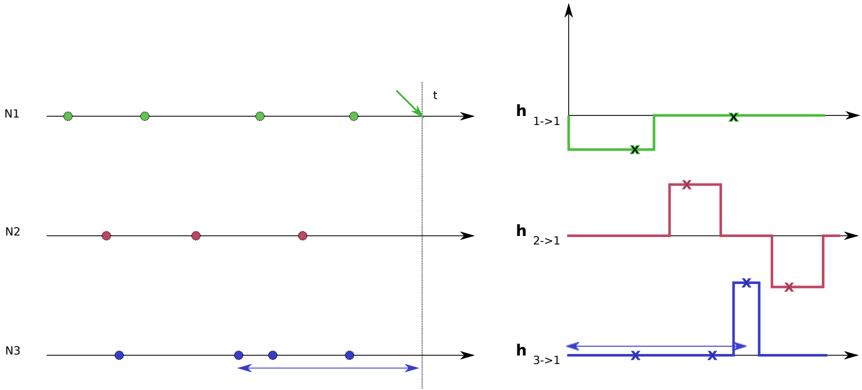

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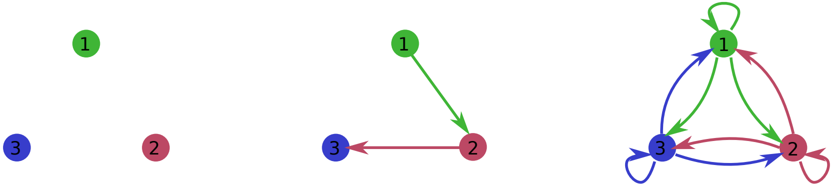
Link Graphical model of local independence

(Didelez (2008))



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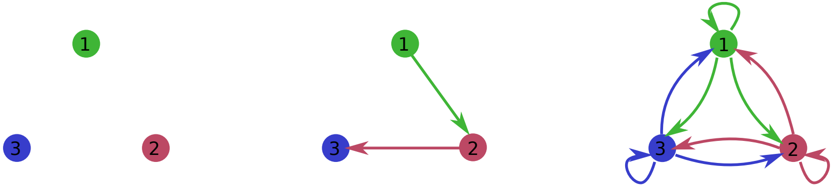

→ (?) functional connectivity graphs in Neurosciences, but also useful in sismology, genomics, marketing, finance, epidemiology ....

More formally

- Only excitation (all the $h_{\ell \to r}$ are positive): for all r,

$$\lambda^{(r)}(t) = \nu_r + \sum_{\ell=1}^{M} \int_{-\infty}^{t-} h_{\ell \to r}(t-u) dN_u^{(\ell)}.$$

Branching / Cluster representation, stationary process if the spectral radius of $\left(\int h_{\ell \to r} dt\right)$ is < 1.

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- Exponential (Multiplicative shape but no guarantee of a stationary version ...)

$$\lambda^{(r)}(t) = \exp\left(\nu_r + \sum_{\ell=1}^{M} \int_{-\infty}^{t-} h_{\ell \to r}(t-u) dN_u^{(\ell)}\right).$$

Previous works

- Maximum likelihood estimates eventually + AIC (Ogata, Vere-Jones etc mainly for sismology, Chornoboy et al., for neuroscience, Gusto and Schbath for genomics)
- Parametric tests for the detection of edge + Maximum likelihood + exponential formula + spline estimation (Carstensen et al., in genomics)
- Univariate processes + ℓ_0 penalty, oracle inequalities (RB and Schbath)
- Maximum likelihood + exponential formula + ℓ_1 "group Lasso" penalty (Pillow et al. in neuroscience)
- Thresholding + tests for very particular bivariate models, oracle inequality (Sansonnet)

Another parametric method : Least-squares

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- Hence one minimizes

$$-2\int_0^T \eta(t)dN_t + \int_0^T \eta(t)^2 dt,$$

for a model $\eta = \lambda_{\mathbf{a}}(t)$

On Hawkes processes

Recall that for the process $N^{(r)}$

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By linearity,

$$\lambda^{(r)}(t) = (\mathbf{R}\mathbf{c}_t)' \mathbf{a}_*^{(r)},$$

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By linearity,

$$\lambda^{(r)}(t) = (\mathbf{Rc}_t)'\mathbf{a}_*^{(r)},$$

with $\mathbf{Rc}_t$ being the renormalized instantaneous count given by

$$(\mathbf{Rc}_t)' = \left(1, \delta^{-1/2}(\mathbf{c}_t^{(1)})', \ldots, \delta^{-1/2}(\mathbf{c}_t^{(M)})'\right),$$

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with $\mathbf{Rc}_t$ being the renormalized instantaneous count given by

$$(\mathbf{Rc}_t)' = \left(1, \delta^{-1/2} (\mathbf{c}_t^{(1)})', \ldots, \delta^{-1/2} (\mathbf{c}_t^{(M)})'\right),$$

and with $\mathbf{c}_t^{(\ell)}$ being the vector of instantaneous count with delay of N_ℓ i.e.

$$(\mathbf{c}_t^{(\ell)})' = \left(N^{(\ell)}_{[t-\delta, t)}, \ldots, N^{(\ell)}_{[t-K\delta, t-(K-1)\delta)}\right).$$

An heuristic for the least-square estimator

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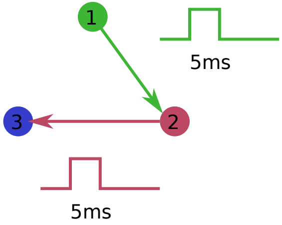
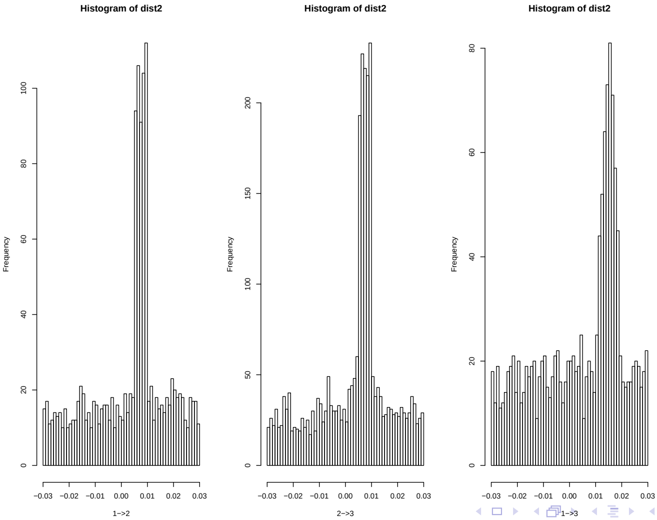
→ simpler formula than Maximum Likelihood Estimators for similar properties

What gain wrt cross correlogramm ?



only 2 non zero interaction functions over 9

What gain wrt cross correlogramm ?



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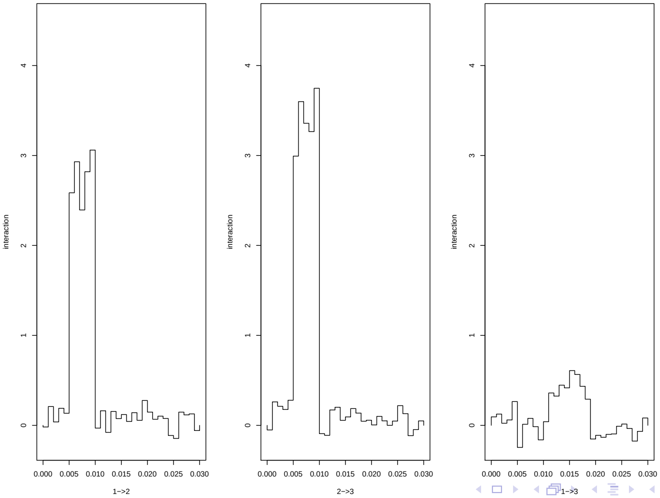

Full Multivariate Hawkes process and ℓ_1 penalty

with N.R. Hansen (Copenhagen), and V. Rivoirard (Dauphine)
The Lasso criterion for each sub-process:

Lasso criterion

$$\begin{aligned}\hat{\mathbf{a}}^{(r)} &= \operatorname{argmin}_{\mathbf{a}}\{\gamma_T(\lambda_{\mathbf{a}}^{(r)}) + \operatorname{pen}(\mathbf{a})\} \\ &= \operatorname{argmin}_{\mathbf{a}}\{-2\mathbf{a}'\mathbf{b}_r + \mathbf{a}'\mathbf{G}\mathbf{a} + 2(\mathbf{d}^{(r)})'|\mathbf{a}|\}\end{aligned}$$

- The crucial choice is the $\mathbf{d}^{(r)}$, should be data-driven !
- The theoretical validation : be able to state that our choice is the best possible choice.
- The practical validation : on simulated Hawkes processes (done), on simulated neuronal networks, on real data (RNRP Paris 6 work in progress)...

Theoretical Validation = Oracle inequality

Let

$$\mathbf{b}^{(r)} = \int_0^T \mathbf{Rc}_t dN^{(r)}(t) \text{ and } \bar{\mathbf{b}}^{(r)} = \int_0^T \mathbf{Rc}_t \lambda^{(r)}(t)dt$$

and

$$\mathbf{G} = \int_0^T \mathbf{Rc}_t(\mathbf{Rc}_t)'dt.$$

Hansen,Rivoirard,RB

If $\mathbf{G} \geq cI$ with $c > 0$ and if

$$\left|\mathbf{b}^{(r)} - \bar{\mathbf{b}}^{(r)}\right| \leq \mathbf{d}^{(r)}, \quad \forall r$$

then

$$\sum_r \|\lambda^{(r)} - \mathbf{Rc}_t\hat{\mathbf{a}}^{(r)}\|^2 \leq \square \inf_{\mathbf{a}} \left\{ \sum_r \|\lambda^{(r)} - \mathbf{Rc}_t\mathbf{a}\|^2 + \frac{1}{c} \sum_{i \in supp(\mathbf{a})} (d_i^{(r)})^2 \right\}.$$

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- In practice small unavoidable bias, possible to correct by two step procedures (OLS on the support of the Lasso estimate).
- Possible to do it with other basis (Fourier) or other linear model (Aalen)

One of the main probabilistic ingredients

Bernstein type inequality for counting processes (H., R.B., R.)

Let $(H_s)_{s\geq 0}$ be a predictable process and
$M_t = \int_0^t H_s(dN_s - \lambda(s)ds)$. Let $b > 0$ and $v > w > 0$.
For all $x, \mu > 0$ such that $\mu > \phi(\mu)$, let
$\hat{V}_\tau^\mu = \frac{\mu}{\mu-\phi(\mu)} \int_0^\tau H_s^2 dN_s + \frac{b^2 x}{\mu-\phi(\mu)}$, where $\phi(u) = \exp(u) - u - 1$.
Then for every stopping time τ and every $\varepsilon > 0$

$$\mathbb{P}\left(M_\tau \geq \sqrt{2(1+\varepsilon)\hat{V}_\tau^\mu x} + bx/3, \quad w \leq \hat{V}_\tau^\mu \leq v \text{ and } \sup_{s\in[0,\tau]} |H_s| \leq b \right)$$
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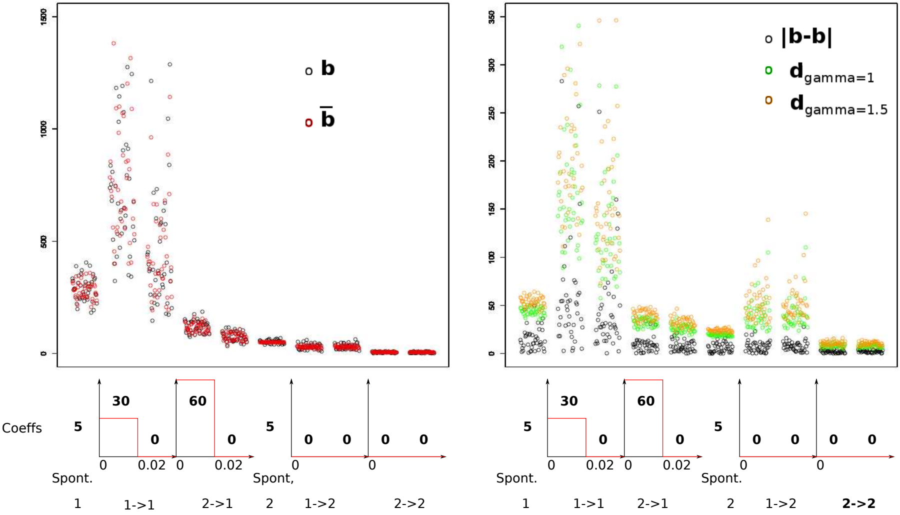
NB : $\hat{V}^\mu_\tau$ is an estimate of the bracket of the martingale, i.e. the martingale equivalent of the variance $\rightarrow$ Gaussian behavior for the main term.
Applied to $\int_0^T \mathbf{Rc}_t \left(dN^{(r)}(t) - \lambda^{(r)}(t)dt\right)$: $\mathbf{d}$ is given by the right hand-side ($x \simeq \gamma \ln(\# param)$) $\rightarrow$ Bernstein Lasso.

Choices of the weights d_λ

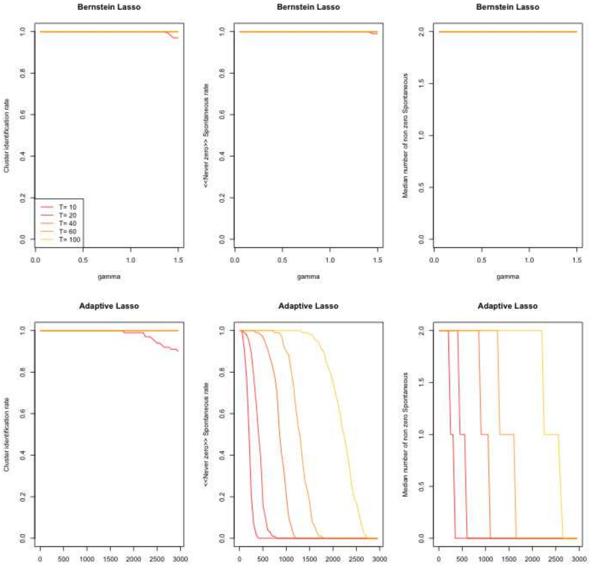


NB : γ larger, d larger and fewer non zero coefficients

NB2: Adaptive Lasso (Zou) $d_\lambda = \gamma / |\hat{a}_\lambda|$

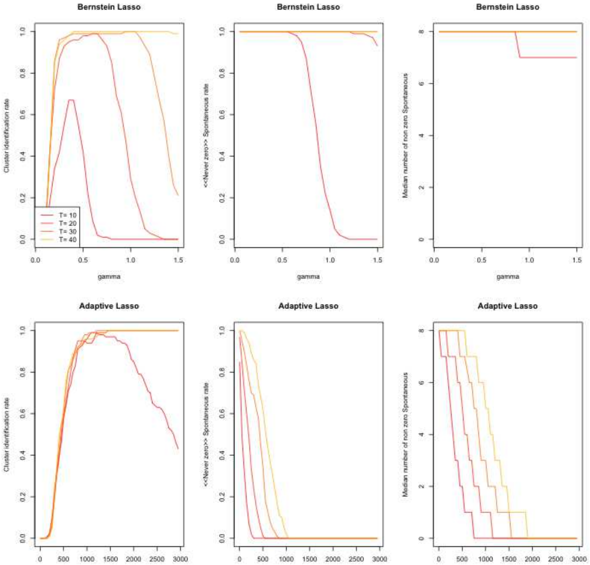
Simulation study - Support recovery

Same experiment

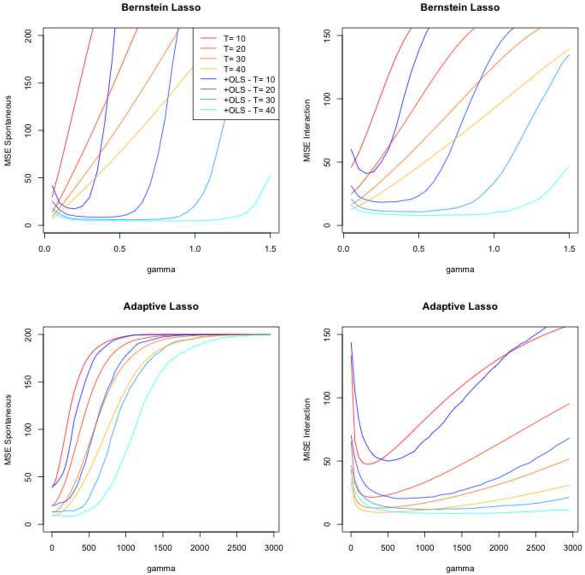


Simulation study - Support recovery

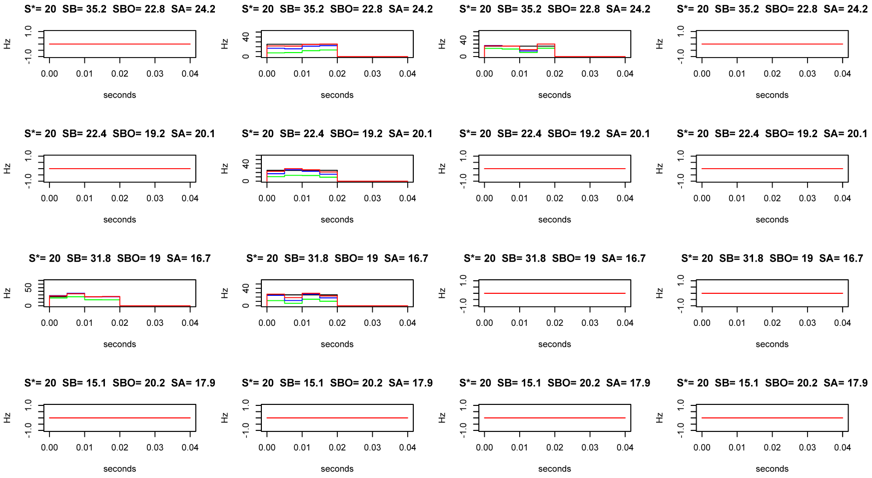
8 Neurons , 3 clusters of dependence, 10 bins per interaction



Simulation study - Influence of the OLS step

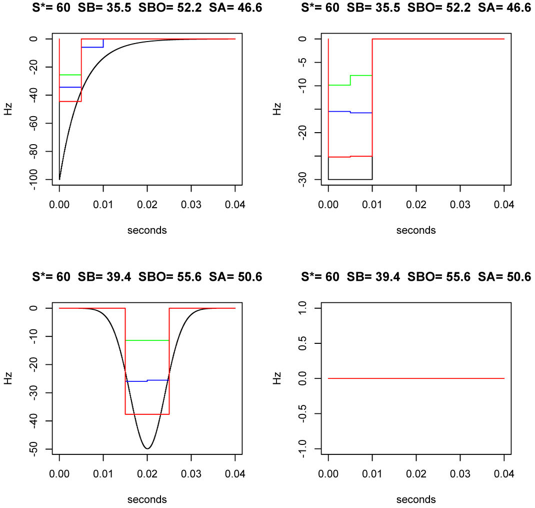


Simulation study - Estimation ($T = 20$, $M = 8$, $K = 8$)



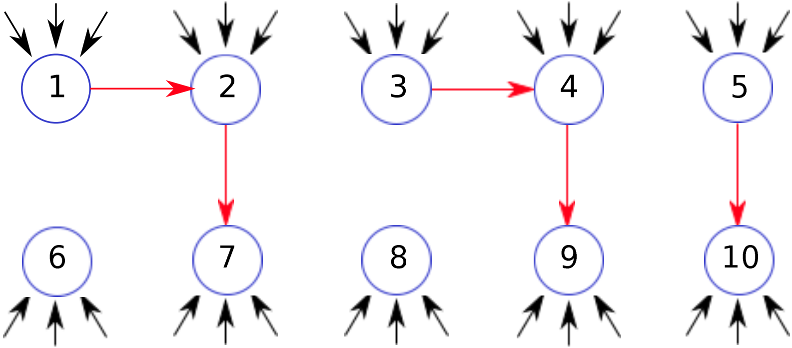
Interactions reconstructed with 'Adaptive Lasso', 'Bernstein Lasso' and 'Bernstein Lasso+OLS'. Above graphs, estimation of spontaneous rates

Another smooth example with inhibition



$T = 20s$

Another (more realistic?) neuronal network: Integrate and Fire



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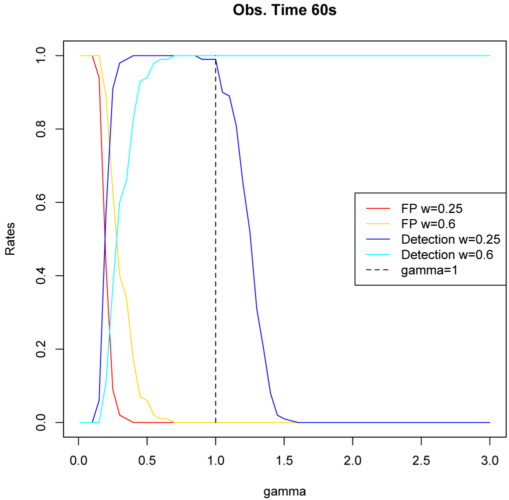

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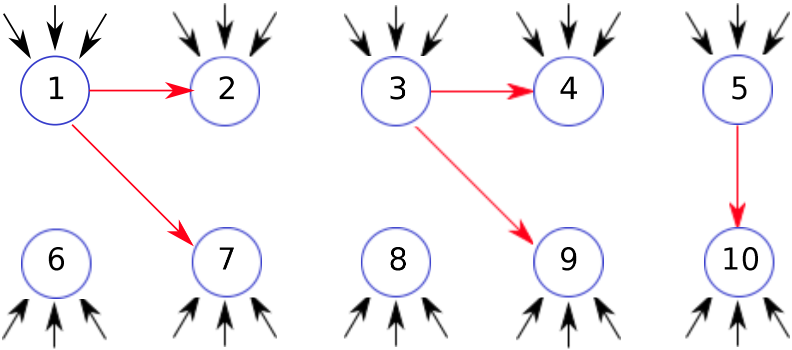

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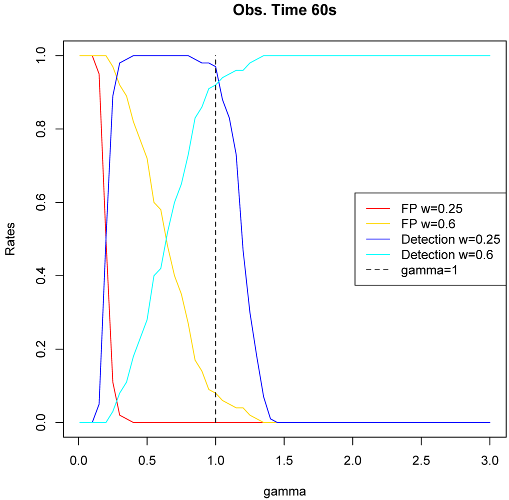

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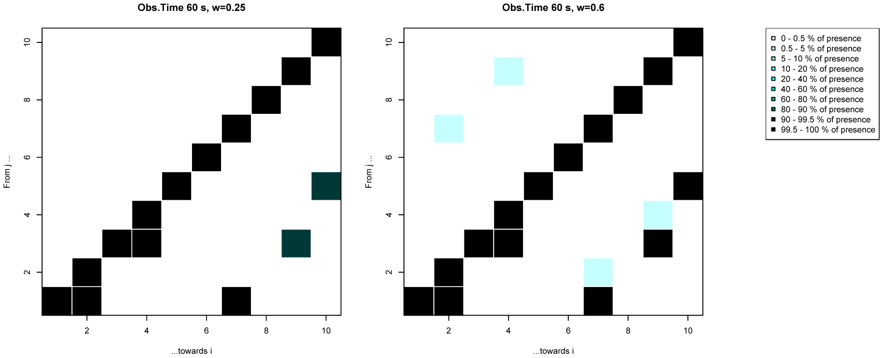

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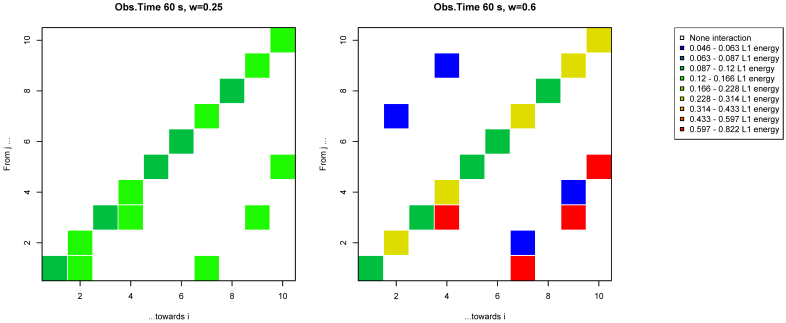

Random networks

Random networks with 7 neurons

- each vertex with $1/7$ chance to be a connection
- $1/2$ chance to be excitatory or inhibitory
- excitation : synaptic weight chosen uniformly in [0.2,0.5]
- inhibition : synaptic weight chosen uniformly in [-0.9,-0.6]

Random networks

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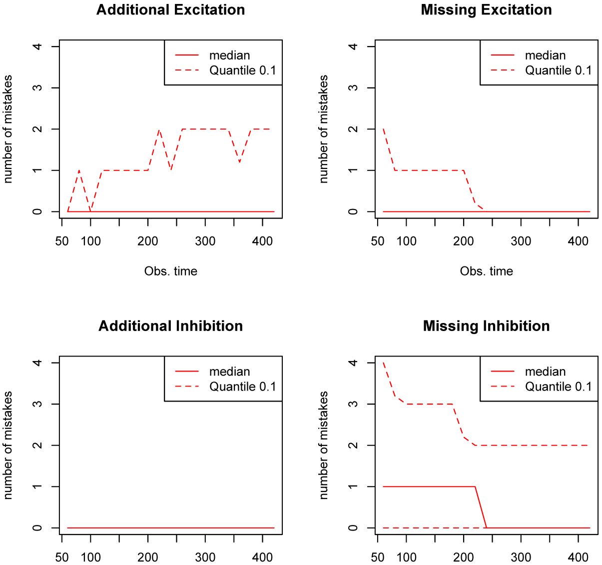

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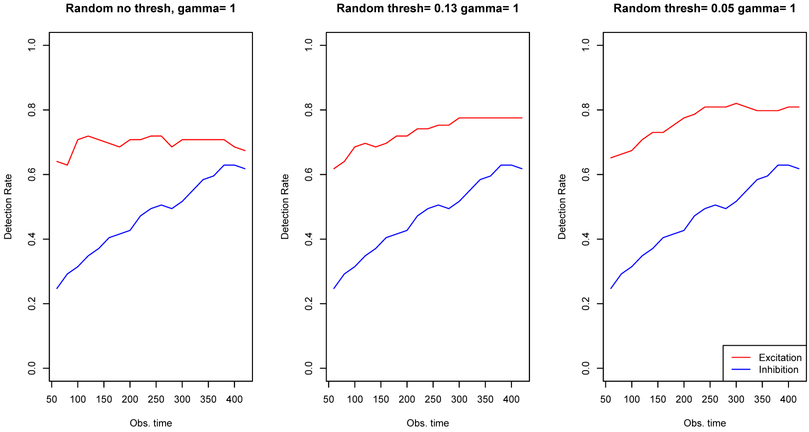
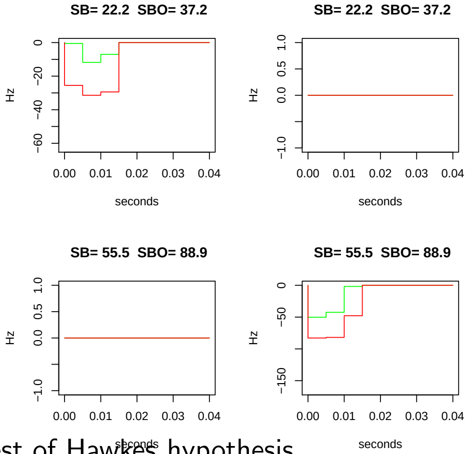


On neuronal data (sensorimotor task)

Joint work with F. Grammont, V. Rivoirard and C. Tuleau-Malot.

30 trials : monkey trained to touch the correct target when illuminated.



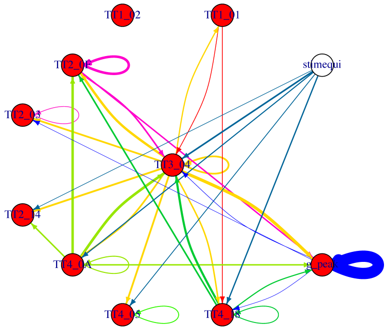
Accept the test of Hawkes hypothesis.

On neuronal data (vibrissa excitation)

Joint work with RNRP (Paris 6). Behavior: stim. at 25-50Hz.

$T = 72s$, 9 Neurons + stimulation + gamma peaks ($M = 11$)

"Neuron"	TT1_01	TT1_02	TT2_0F	TT2_03	TT2_14	TT3_04
Obs. Spikes	241	136	839	951	446	1310
"Neuron"	TT4_0A	TT4_05	TT4_18	stimequi	g_peak	
Obs. Spikes	734	925	1021	2695	1559	

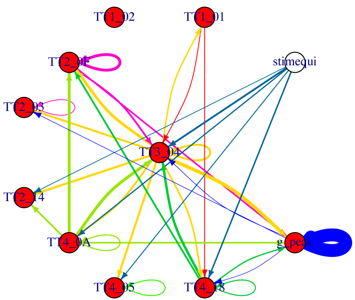


Stability

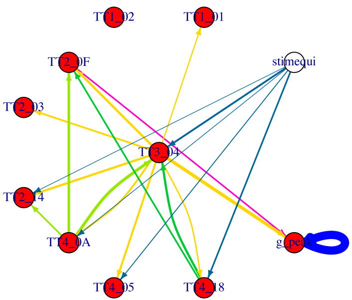
"Neuron"	TT1_01	TT1_02	TT2_0F	TT2_03	TT2_14	TT3_04
Obs. Spikes	241	136	839	951	446	1310
Sim. Spikes	238	135	966	1005	507	1548

"Neuron"	TT4_0A	TT4_05	TT4_18	stimequi	g_peak	
Obs. Spikes	734	925	1021	2695	1559	
Sim. Spikes	816	993	1124	3469	1785	

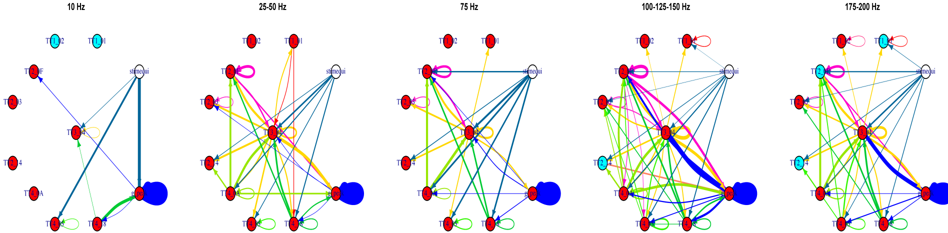
On real data



On simulated data



Evolution of the dependance graph as a fonction of the vibrissa excitation



Also be careful if **G** non invertible .....

Conclusions and Perspectives

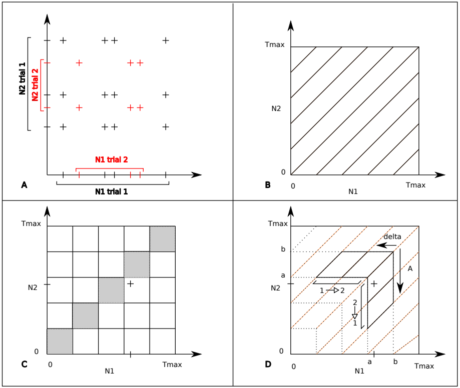
- It is possible to estimate interaction functions and even a graph of possible interactions, to have some mathematical guarantee on it and this even if the Hawkes linear model is not completely true (robustness).
- It is even possible to (non parametrically) test that such interactions exists. However the power of such tests (not studied yet) should be linked to a "distance" to the Hawkes model.
- One of the main issue is the lack of stationarity → a work in progress with F. Picard (Lyon) and C. Tuleau-Malot (Nice) based on segmentation and clustering.

Thank you !

References

- Hansen, N.R., Reynaud-Bouret, P. and Rivoirard, V. *Lasso and probabilistic inequalities for multivariate point processes.* Bernoulli (2015).
- Reynaud-Bouret, P., Tuleau-Malot, C., Rivoirard, V. and Grammont, F. *Goodness-of-fit tests and nonparametric adaptive estimation for spike train analysis* Journal of Mathematical Neuroscience (2014)
- Reynaud-Bouret, P., Rivoirard, V., Tuleau-Malot, C. *Inference of functional connectivity in Neurosciences via Hawkes processes*, 1st IEEE Global Conference on Signal and Information Processing, Austin, Texas (2013).

Link with cross-correlogram and Joint PeriStimulus Histogram



see also Zhang et al (2007) in genomics and Aertsen et al (1989) in Neurosciences