# Hawkes process as models for some genomic data

### P. Reynaud-Bouret

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January 27th, Institut Curie

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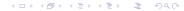


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- 2 The probabilistic model(s)
- 3 Parametric estimation







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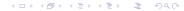
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### TRE

Transcription Regulatory Elements = "everything" that may enhance or repress gene expression

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Why just DNA ? RNA etc ...

# A simplified/informal vision

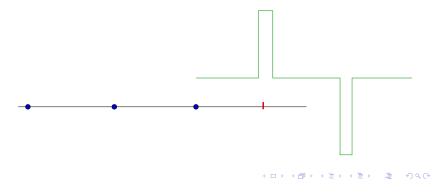
# A simplified/informal vision

How can we explain the positions of the occurrences of one event (motifs, TRE, etc) wrt the others and itself ?

Spontaneous apparition

- Spontaneous apparition
- Self-interaction

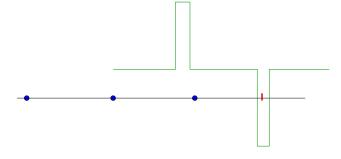
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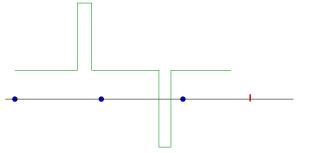
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Maximal sensible interaction distance: 5 000 - 10 000 bases because of the 3d DNA structure

Point process

N= random countable set of points of  $\mathbb{R}$  (here).

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 $N_A$  number of points of N in A,  $N_t = N_{[0,t]}$ ,  $dN_t = \sum_{T \text{ point de } N} \delta_T \cdot \int f(t) dN_t = \sum_{T \in N} f(T)$ 

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#### Intensity

 $t o \lambda(t)$  represents the probability to have a point at time t conditionnally to the past before t (s < t)

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ightarrow \lambda(t)$  represents the probability to have a point at time t conditionnally to the past before t (s < t)

"Past" contains in particular the previous occurrences of points. NB : here  $\mathbb R$  is the DNA strand. The "past" may be interpreted as what has already been read in a prescribed direction (e.g. 5'-3' or 3'-5').

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Biological motivation

The probabilistic model(s)

Parametric estimation

Adaptive estimation

## The simple Hawkes process

The intensity  $\lambda(t)$  is given by

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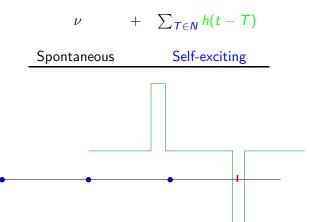
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Spontaneous



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 $u + \sum_{T \in N} h(t - T)$ Spontaneous Self-exciting

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Spontaneous Self-exciting

The most classical case corresponds to h > 0 (see Hawkes (1971)) and a stationary version exists if  $\int h < 1$ . There is also in this specific case a branching / cluster process representation (see Hawkes and Oakes (1974)).

#### The simple Hawkes process

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$$\left( \nu + \sum_{T \in N} h(t-T) \right)_{+}$$

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One can actually consider any 1-Lipschitz modification, there is still a stationary version of it if  $\int |h| < 1$  (Brémaud and Massoulié (1996)).

# The Hawkes process interaction with itself + an additional interaction

 $\lambda(t) =$ 

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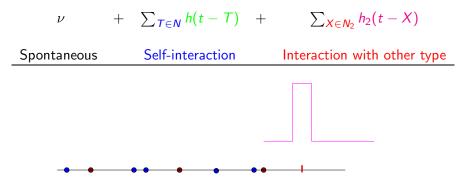
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Spontaneous

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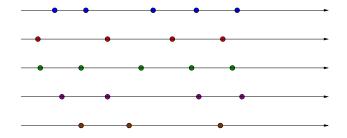
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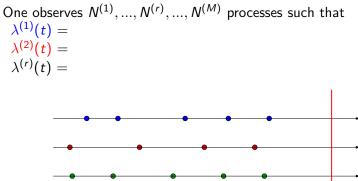
$$\lambda(t) = \begin{pmatrix} \nu & + \sum_{T \in N} h(t - T) + \sum_{X \in N_2} h_2(t - X) \end{pmatrix}_+$$

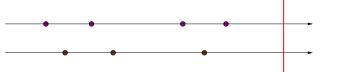
SpontaneousSelf-interactionInteraction with other typeIf h is null and if  $N_2$  is fixed (no reciprocal interaction), then N is aPoisson process given  $N_2$ .

One observes  $N^{(1)}, ..., N^{(r)}, ..., N^{(M)}$  processes such that

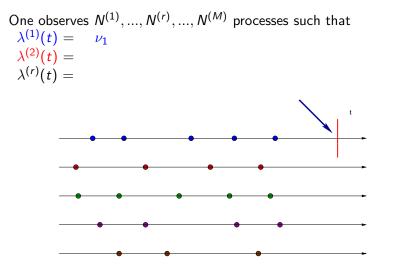


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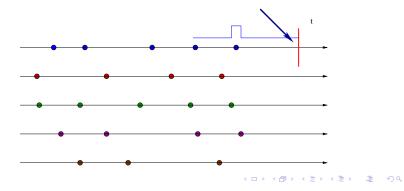


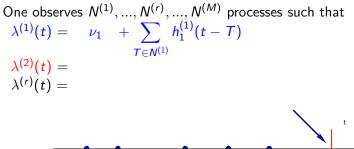
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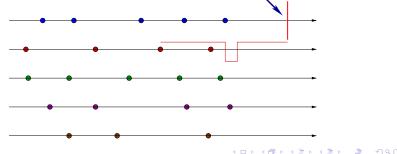


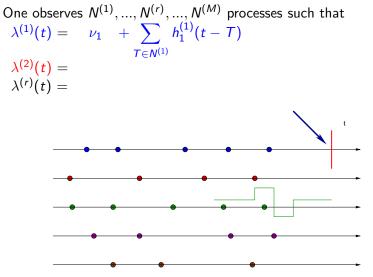
One observes  $N^{(1)}, ..., N^{(r)}, ..., N^{(M)}$  processes such that  $\lambda^{(1)}(t) = \nu_1 + \sum_{T \in N^{(1)}} h_1^{(1)}(t - T)$  $\lambda^{(2)}(t) =$ 



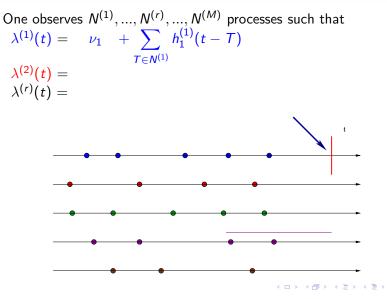




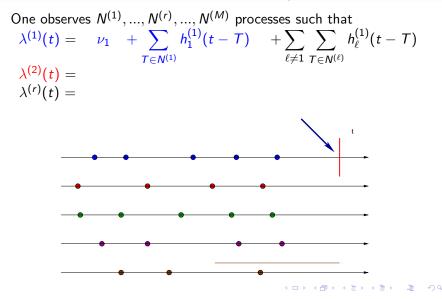


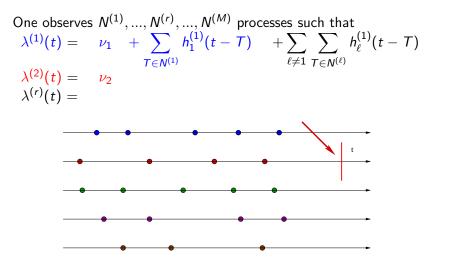


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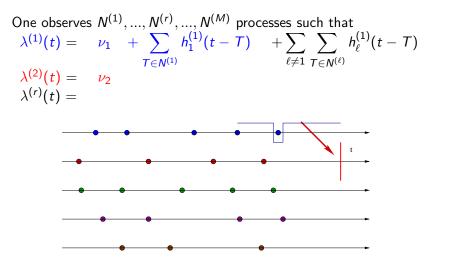


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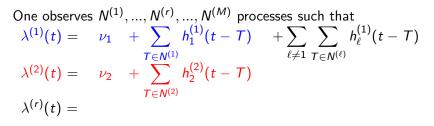


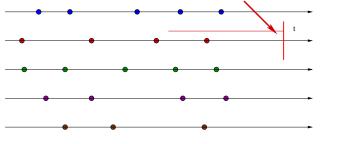


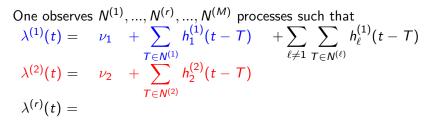
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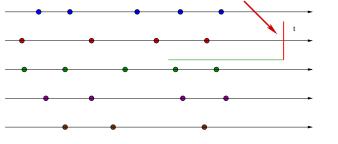


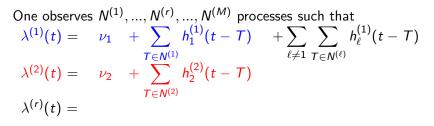
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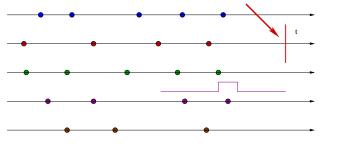


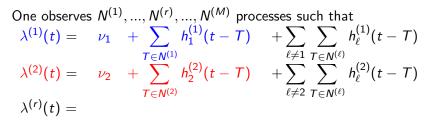


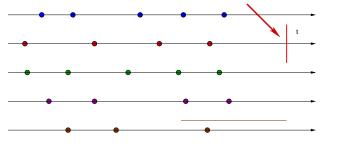








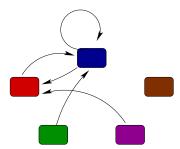




Link with graphical model of local independence (see Didelez (2008))

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

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

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

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Exponential

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

Multiplicative shape but no guarantee of a stationary version

Adaptive estimation

#### Maximum likelihood estimation

• Only the shape of the intensity is necessary.

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- Given the "past" before 0, for one process observed until time *T*,

$$L_{\mathcal{T}}( heta) = \int_0^{\mathcal{T}} \ln(\lambda_{ heta}(t)) dN_t - \int_0^{\mathcal{T}} \lambda_{ heta}(t) dt.$$

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- not necessary to have a stationary version, it depends on the considered asymptotics.
- Consistence, asymptotic normality under smooth conditions, see Ogata and Akaike (1982), Ozaki (1979) or Andersen et al (1993).

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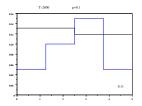
- Only the shape of the intensity is necessary.
- Given the "past" before 0, for one process observed until time  $\mathcal{T}$ ,

$$L_T( heta) = \int_0^T \ln(\lambda_ heta(t)) dN_t - \int_0^T \lambda_ heta(t) dt.$$

- maximizing gives  $\hat{\theta}$ .
- If several processes or  $n \text{ sample} \rightarrow \text{sum}$
- not necessary to have a stationary version, it depends on the considered asymptotics.
- Consistence, asymptotic normality under smooth conditions, see Ogata and Akaike (1982), Ozaki (1979) or Andersen et al (1993).
- Even tests of the nullity of  $h_{\ell}^{(r)}$  and access to a graphical model (see Carstensen et al (2010)).

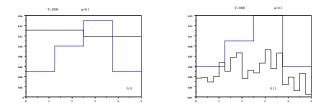
Adaptive estimation

#### Model choice



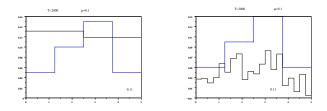
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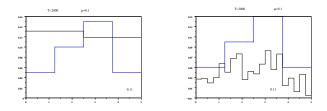


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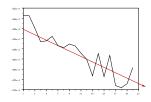
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# AIC criterion

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- Hence no clear access to favoured or avoided distance as some one of the second distance and the second distance and the second distance are second distance.

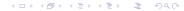


## • We want to perform an adaptive estimation of the functions *h*!





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- → penalized model selection (Birgé and Massart, see Massart course in St Flour (2007))
- but also, thresholding or Lasso methods.

Biological motivation

Adaptive estimation

## Least-square contrast for one process

#### • The meaningful quantity is $\lambda(t)$ .

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- Let  $\eta$  be an intensity candidate.

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• We will minimize  $\gamma_T$  for precise shape of intensity candidates.

## Least-square contrast on a toy model

Let [a, b] an interval of  $\mathbb{R}^+$ .

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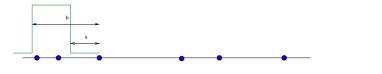
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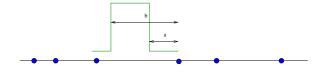
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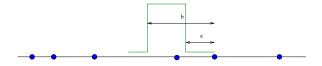
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# For the simple Hawkes process

• 
$$\mathbb{L}_2 = \begin{cases} f = (\mu, g) : \text{Supp}(g) = [0, A], \|f\|^2 = \mu^2 + \int_0^A g^2(x) dx < +\infty \end{cases}$$
  
•  $s = (\nu, h)$  to estimate



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•  $\hat{s}_m = \arg \min_{f \in S_m} \gamma_T(f)$ . no close formula in general.

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# Risk study

#### Only for simple Hawkes process

Risk The risk of  $\hat{s}$  is  $\mathbb{E}(||s - \hat{s}||^2)$ .

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- $\bullet \to {\rm compromise:}$  the best (or oracle) in a family is the one that minimizes the sum.

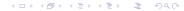
#### Joint work with S. Schbath (2010). Only for simple Hawkes process

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#### Models

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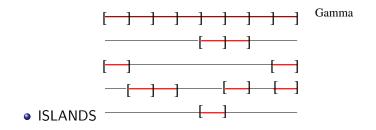
- NESTED Regular dyadic partitions constructed on  $\Gamma$ .
- REGULAR Regular partitions until a certain prescribed bandwidth
- IRREGULAR All irregular partitions contructed on Γ.

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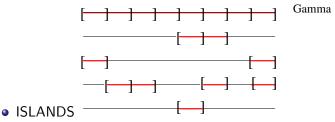


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All models included in  $\Gamma$ . The most adapted to the biological question.

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## Model selection with dimension-based penality(2)

Only for simple Hawkes process Let  $\mathcal{M}_T$  be a family of models  $(m \in \mathcal{M}_T)$ .

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- also adaptive minimax results for Hölder functions.

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- An angle is perfectly clear on the simulations at the correct dimension:

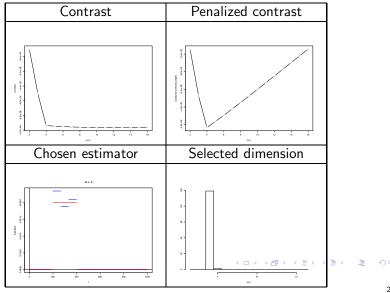
$$-ar{k} = rac{\gamma_{\mathcal{T}}(\hat{s}_{\Gamma}) - \gamma_{\mathcal{T}}(\hat{s}_{1})}{|\Gamma| - 1}$$

and

$$\hat{m} = \operatorname{argmin}_{m \in \mathcal{M}_T} \gamma_T(\hat{s}_m) + \bar{k}(|m|+1).$$

### Illustration

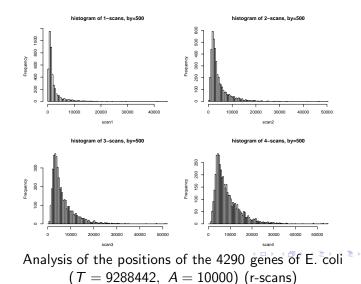
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### On real data

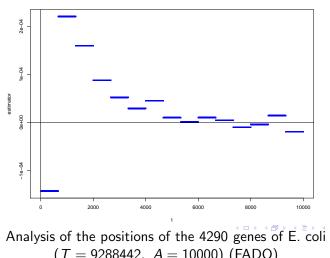
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FADO: m = 15

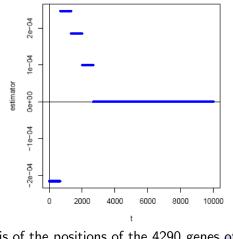
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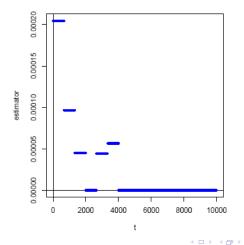


Analysis of the positions of the 4290 genes of E. coli r = 9288442, A = 10000) (Islands)

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#### On real data

#### Only for simple Hawkes process





Analysis of the 1036 occurrences of tataat for E. coli. (T - 9288442, A - 10000) (Islands)

### Disadvantages of the dimension-based penalty method

only for simple Hawkes process! (not more than grid with 15 - 26 bins)

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- only for simple Hawkes process! (not more than grid with 15 26 bins)
- We miss part of the understanding because we do not take external information into account (here interaction tataat genes).

### Poissonian Interaction

Work in progress of Laure Sansonnet.

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- **Q** <u>Parents</u> :  $U_1, ..., U_n$ , *n* iid uniform random variables on [0, T].
- 2 <u>Children</u>: Poisson process with intensity  $\sum_{i=1}^{n} h(t U_i)$ .



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- Computation quite fast. Precision >> Islands

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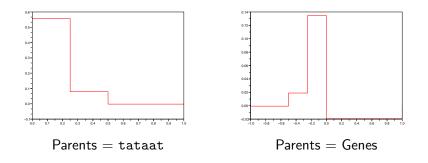
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Cons:

- The presence of Parents will not be explained and is not linked to Children.
- Crucial to say who are the parents/ the children (it is not symetric!).
- For the moment, one cannot explain the Children position, even with an extra spontaneous apparition.



#### Interaction tataat - genes.



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#### Full Multivariate Hawkes processes and lasso procedure

Joint Work with N.R. Hansen (Copenhagen) and V. Rivoirard (Dauphine), in progress.

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Intensity candidate per mark  $\psi_{f}^{(r)}(t) = \mu_{r} + \sum_{\ell} \int_{-\infty}^{t} g_{\ell}^{(r)}(t-u) dN_{u}^{(\ell)}.$ 

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### Full Multivariate Hawkes processes and lasso procedure(2)

Least-square contrast (full form)

 $\gamma_T(f) = \sum_r \gamma_T^{(r)}(f)$  where

$$\gamma_T^{(r)}(f) = -\frac{2}{T} \int_0^T \psi_f^{(r)}(t) dN_t^{(m)} + \frac{1}{T} \int_0^T \psi_f^{(r)}(t)^2 dt.$$

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If each  $g_{\ell}^{(r)}$ 's in f are decomposed on a finite orthonormal family of functions with cardinal K, then

•  $f \to (\mathbf{a}_r)_{r \le M}$  Each  $\mathbf{a}_r$  of size MK + 1.

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$$\gamma_T^{(r)}(f) = -2\mathbf{a}_r^*\mathbf{b}_r + \mathbf{a}_r^*\mathbf{G}\mathbf{a}_r,$$

where

- G is a random observable matrix, independent of the mark r
- $\mathbf{b}_r$  is also a random observable vector.

## Full Multivariate Hawkes processes and lasso procedure(3)

The Lasso criterion can be expressed independently for each mark.

Lasso criterion

$$\hat{\mathbf{a}}_r = \operatorname{argmin}_{\mathbf{a}_r \in \mathbb{R}^{MK+1}} \{-2\mathbf{a}_r^* \mathbf{b}_r + \mathbf{a}_r^* \mathbf{G} \mathbf{a}_r + 2\mathbf{d}_r^* |\mathbf{a}_r|\}$$

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- Oracle inequality with "high" probability possible....

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