Continous Testing for Poisson Processes Intensities

F. Picard⋆, P. Reynaud-Bouret∘, E. Roquain‡,

⋆ *Laboratoire de Biométrie et Biologie Évolutive*, Univ. Lyon 1,
∘ *Laboratoire J.A. Dieudonné*, Univ. Nice,
‡ *Laboratoire de Probabilités et Modèles Aléatoires*, Univ. Paris 6.

September 2017

Outline

Observations are random sets of points

- We observe two independent sets of peaks location:

$$N_A = \{T_1, \ldots, T_{n_A}\} \quad \text{and} \quad N_B = \{T_1, \ldots, T_{n_B}\}.$$

- We model those sets by two heterogeneous Poisson processes with intensity λ_A, λ_B in $L^2[0,1]$.
- For any interval $I \subseteq [0,1]$,

$$N_A(I) \sim \mathcal{P}\left(\int_I \lambda_A(t)dt\right) \quad \text{and} \quad N_B(I) \sim \mathcal{P}\left(\int_I \lambda_B(t)dt\right)$$

Aim

Testing $\lambda_A = \lambda_B$ and detecting zones where $\lambda_A \neq \lambda_B$

Global and local strategies

- The first strategy would be to test $\{\lambda_A = \lambda_B\}$, but lacks of sensitivity (yes / no answer)
- Scan Statistics : sliding windows and the global Type-I error control
  $\rightarrow$ Asymptotic expansions of distribution tails
  $\rightarrow$ No strict testing framework
  $\rightarrow$ No real interpretation in terms of multiple testing
  $\rightarrow$ No satisfying FDR control yet

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  $\rightarrow$ No satisfying FDR control yet
- **Our strategy is local testing**
  $\rightarrow$ Non asymptotic, non parametric
  $\rightarrow$ We provide a complete testing framework
  $\rightarrow$ We fill the gap between sliding windows and multiple testing
  $\rightarrow$ We provide a formal definition of the FDR in continuous time

Avé les mains

- Consider an interval $I \in [0,1]$, and suppose that $\lambda_A = \lambda_B$ on I
- Given $N_A(I) + N_B(I) = n(I)$, $N_A(I) \sim \mathcal{B}(n(I), 1/2)$

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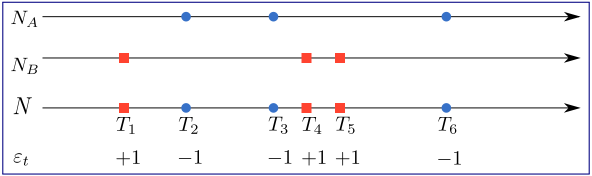
- Given $N_A(I) + N_B(I) = n(I)$, $N_A(I) \sim \mathcal{B}(n(I), 1/2)$
- Our strategy is to perform **conditional** testing, given $N = N_A + N_B$.
- $\lambda = \lambda_A + \lambda_B$ becomes a nuisance parameter
- The challenge is to do it for every possible window on $[0, 1]$

Definition of the joint process

- From (N_A, N_B) we define the couple (N, ε)
- $N = N_A \cup N_B$ is the **joint process** of intensity $\lambda = \lambda_A + \lambda_B$,
- and where $\varepsilon = (\varepsilon_T)_{T \in N}$ is a **set of marks**:

$$\varepsilon_T = \begin{cases} +1, & \text{if } T \in N_A, \\ -1, & \text{if } T \in N_B. \end{cases}$$



Conditional distribution of the marks

- Conditionally to N, the distribution of the marks is:

$$\mathbb{P}(\varepsilon_T = +1 | N) = \frac{\lambda_A(T)}{\lambda_A(T) + \lambda_B(T)}$$

- We introduce notation:

$$\forall t \in [0,1],\ \theta(t) = \frac{\lambda_A(t) - \lambda_B(t)}{\lambda_A(t) + \lambda_B(t)}.$$

- Conditionally to N, the distribution of the marks becomes:

$$\varepsilon_T | N \sim 2\mathcal{B}\left(\frac{\theta(T)+1}{2}\right) - 1,$$

Nuisance parameters and conditional testing

- The distribution of the joint process (N, ε) can be re-parametrized:

$$(N, \varepsilon) \sim \mathbb{P}_{\theta,\lambda}$$

- λ and θ are unknown under the null, but are not "really" of interest
- We propose procedures that are **conditional to the observed joint process** N.

Reparametrization of the test

Conditional to N, the new hypothesis focuses on ε and becomes $\theta = 0$.

An infinite set of local null hypothesis

- We propose a functional testing framework : $\lambda_A = \lambda_B$ or $\theta = 0$.
- The global strategy corresponds to the **global null** hypothesis.

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- We consider **local hypothesis**:

$$H_{0,t} : \left\{\theta(t) = 0\right\} \quad \text{against } H_{1,t} : \quad \left\{\theta(t) \neq 0\right\}.$$

- The null hypothesis corresponding to

$$\left\{\forall t \in J,\, \theta(t) = 0\right\} \Leftrightarrow \left\{\mathcal{H}_0\left\{J\right\} = \bigcap_{t \in J} H_{0,t}.\right\}$$

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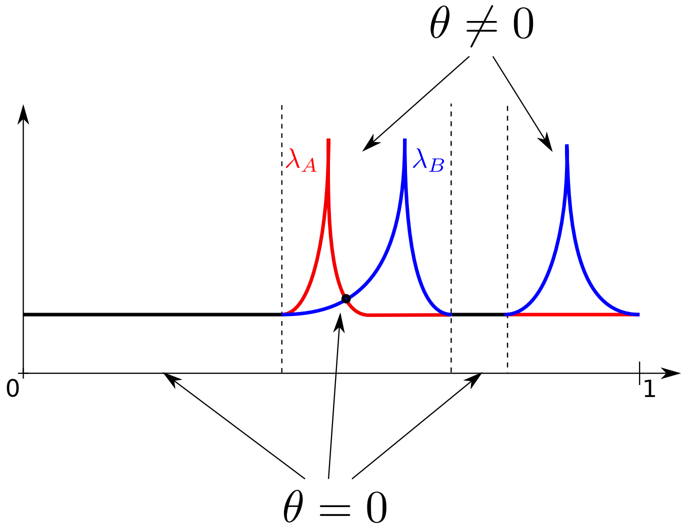
- The *global null* hypothesis corresponds to $\mathcal{H}_0\left\{[0,1]\right\}$.
- The null function on $[0,1]$ is denoted by θ_0 in the sequel.

Local testing with a cartoon



Definition of scanning windows

- We introduce a resolution parameter η that is fixed
- Using the **continuous testing** framework, we perform a whole *continuum* of tests for each interval of length η contained in $[0, 1]$.
- We will distinguish sets of points (denoted by t) from sets of windows center (denoted by x)

$$\forall x \in \mathcal{X}_\eta = [\eta/2, 1 - \eta/2],\ I_\eta(x) = [x - \eta/2, x + \eta/2]$$

Our multiple testing procedures are based on single tests on $\mathcal{H}_0 \left\{ I_\eta(x) \right\}$ for all possible window centers

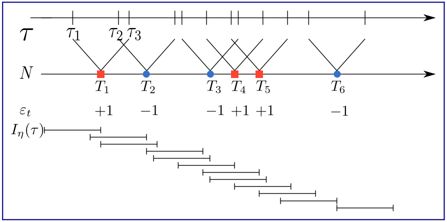
Is continuous testing computationally tractable ?

- Each observation T_i has a span η and will be used by the testing procedure on $[T_i - \eta/2, T_i + \eta/2]$
- There exists a partition τ of $\mathcal{X}_\eta$ consisting in M intervals and with inner breaks given by

$$\boldsymbol{\tau} = \left(\bigcup_{T \in N} \{T - \eta/2\} \cup \{T + \eta/2\} \right) \bigcap \mathcal{X}_\eta,$$

- The set τ is chosen as the center of the observed windows

$]\tau_{m-1}, \tau_m]$ are homogeneous intervals in terms of *composition* $N \cap I_\eta(x)$



Outline

1. Point Process modeling of Genomic features
2. Test statistics and associated p-value process
3. Two error rates in continuous time
4. Simulations
5. Application
6. Conclusions

Count or position-based statistics

- The easiest possibility is to use the count and the p-value is explicit

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- Define a statistics based an estimator of:

$$\|\lambda_A - \lambda_B\|^2_{I_\eta(x)} = \int_{I_\eta(x)} \Big(\lambda_A(s) - \lambda_B(s)\Big)^2 ds$$

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- Kernel-based statistics is ($n = N([0,1])$):

$$S_\eta(x) = \frac{1}{n(n-1)} \sum_{T \neq T' \in N \cap I_\eta(x)} K_h\left(T - T'\right) \varepsilon_T \varepsilon_{T'}$$

- Small increase in performance in pratice

Conditional testing and the p-value process

- We are interested in the distribution of $S_\eta(x)$ under $H_0\{I_\eta(x)\}$:

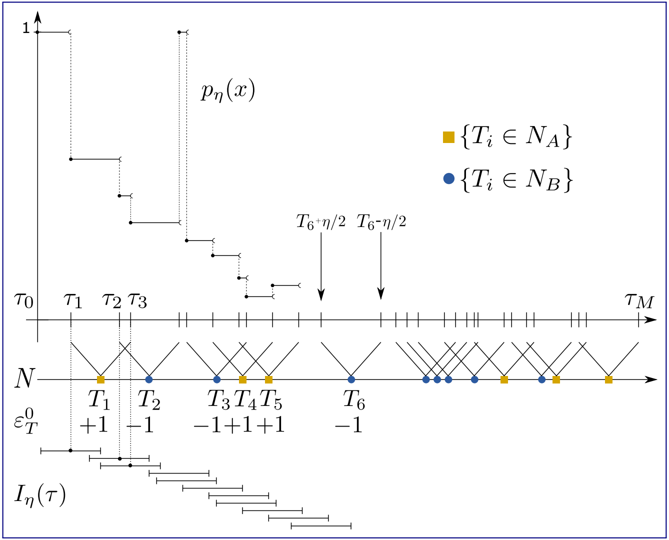
$$\forall x \in \mathcal{X}_\eta,\ \ F_{\theta_0,N}(s;x) = \mathbb{P}_{\theta_0}\Big(S_\eta(x) \geq s|N\Big)$$

- Since the intensities are heterogeneous, we rather consider p-values (normalize between $[0,1]$):

$$\forall x \in \mathcal{X}_\eta,\ \ p_\eta(x) = F_{\theta_0,N}\Big(S_\eta(x);x\Big)$$

- Since $S_\eta(x)$ is piece-wise constant, $\Big(p_\eta(x)\Big)_x$ is a piece-wise constant process on [0,1].

The p-value process with a cartoon



Conditional Monte-Carlo approximation of the p-values

- Sample B independent draws of i.i.d. Rademacher sets of marks:

$$\varepsilon^b := (\varepsilon_T^b)_{T \in N}, \text{ for } b = 1, \ldots, B$$

- Label the observed marks such that $\varepsilon^0 := (\varepsilon_T)_{T \in N}$, (first term of a $B+1$-sample of marks)
- The conditional distribution given N of the Rademacher process is:

$$\varepsilon_T^b | N \sim 2\mathcal{B}(1/2) - 1,$$

- We obtain the estimated p-value process

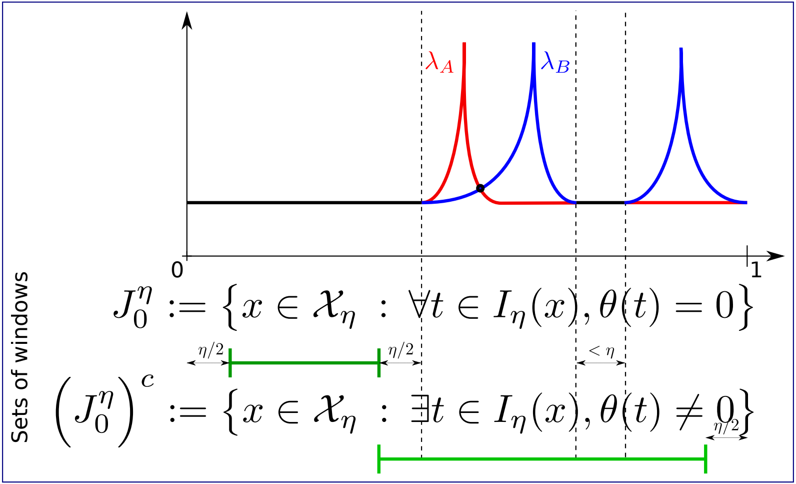
$$\widehat{p}_\eta(x) = \frac{1}{B+1}\left(1 + \sum_{b=1}^{B} 1_{\left\{S_\eta^b(x) \geq S_\eta^0(x)\right\}}\right).$$

This parametrization guarantees that under $H_0\{I_\eta(x)\}$:

$$\forall \alpha \in [0,1], \ \mathbb{P}_{\theta,\lambda}\left(\widehat{p}_\eta(x) \leq \alpha\right) \leq \alpha.$$

Outline

Approximation Sets



Acceptation and Rejection Sets

- u is a threshold potentially depending on the data.
- A multiple testing procedure is defined by a **rejection set**:

$$\mathcal{R}_\eta(u) := \{x \in \mathcal{X}_\eta \ : \ p_\eta(x) < u\},$$

- The set of **accepted windows** is denoted by

$$\mathcal{A}_\eta(u) := \{x \in \mathcal{X}_\eta \ : \ p_\eta(x) \geq u\}.$$

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- $\mathcal{A}_\eta(u)$ is an approximation of

$$J_0^\eta := \left\{x \in \mathcal{X}_\eta \ : \ \forall t \in I_\eta(x), \theta(t) = 0\right\}$$

Challenge

How to evaluate the quality of threshold u ?

False Positive Windows and the continuous FWER

- The target is the set of **false positive windows**

$$J_0^\eta \cap \mathcal{R}_\eta(u)$$

- Its size can be measured by its Lebesgue measure:

$$\Lambda\big(J_0^\eta \cap \mathcal{R}_\eta(u)\big)$$

- The **Family-Wise Error Rate** in continuous time can be defined by

$$\mathsf{FWER}_{\theta,\lambda}^\eta(u) = \mathbb{P}_{\theta,\lambda}\Big(\Lambda\big(J_0^\eta \cap \mathcal{R}_\eta(u)\big) > 0\Big).$$

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Calibrate $u^\alpha \in [0,1]$ such that $\mathrm{FWER}_{\theta,\lambda}^\eta(u^\alpha)$ is controlled at level α

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$$\mathrm{FDR}_{\theta,\lambda}^{\eta}(v) = \mathbb{E}_{\theta,\lambda}\left(\frac{\Lambda\left(J_0^\eta \cap \mathcal{R}_\eta(v)\right)}{\Lambda\left(\mathcal{R}_\eta(v)\right)}\right)$$

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Aim

Calibrate $v^\alpha \in [0,1]$ such that $\mathrm{FDR}_{\theta,\lambda}^\eta(v^\alpha)$ is controlled at level α

Controlling the FWER in continuous time - 1

- The starting point is that we have for all u,

$$\begin{aligned}\left\{J_0^\eta \cap \mathcal{R}_\eta(u) \neq \emptyset\right\} &= \left\{\exists x \in J_0^\eta \,:\, p_\eta(x) < u\right\} \\ &= \left\{\inf_{x \in J_0^\eta} \{p_\eta(x)\} < u\right\}.\end{aligned}$$

- Control the FWER by learning the distribution of the min. p-values under the null.
- Consider the conditional α-quantile of the min. p-value process on $[0,1]$:

$$U_{J_0^\eta}^\alpha = \min\left\{u \in [0,1] \,:\, \mathbb{P}_{\theta_0}\left(\inf_{x \in J_0^\eta}\{p_\eta(x)\} \leq u \,\middle|\, N\right)\right\}.$$

Controlling the FWER in continuous time - 2

- But the set of windows J_0^η is unknown: **Choose the worst-case scenario**
- We compute the quantile of the min. of the p-value process on $\mathcal{X}_\eta$:

$$U^\alpha_{\mathcal{X}_\eta} = \min\left\{u \in [0,1] \,:\, \mathbb{P}_{\theta_0}\left(\inf_{x\in\mathcal{X}_\eta}\{p_\eta(x)\} \leq u \,\middle|\, N\right)\right\}.$$

- This **ensures the control of the FWER at level** α
- This procedure can be extended to step-down approaches.

FWER-Adjusted p-value process: the min-p procedure

- In practice we would like to use the *adjusted* p-value process:

$$\forall x \in \mathcal{X}_\eta, \;\; q_\eta(x) = F^{\min}_{\theta_0,N}\Big(p_\eta(x)\Big)$$

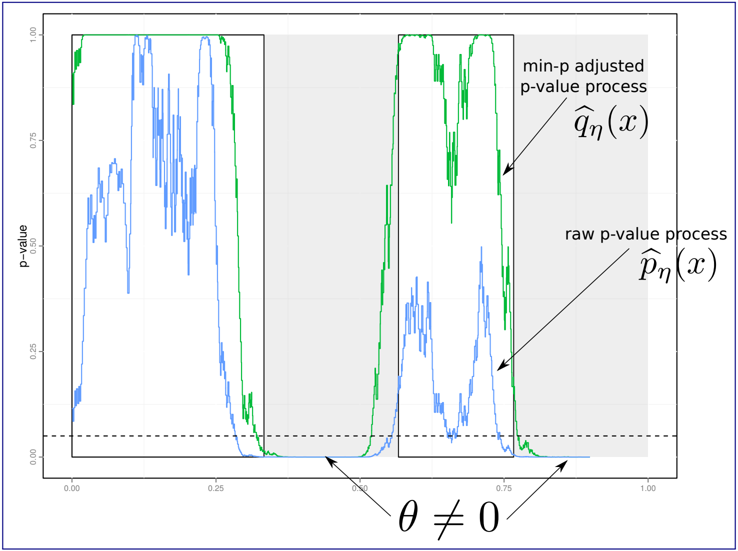
- This requires to compute the distribution of the min-p under the null

$$\forall z \in [0,1], \; F^{\min}_{\theta_0,N}(z) = \mathbb{P}_{\theta_0,N}\left(\inf_{x \in \mathcal{X}_\eta} \{p_\eta(x)\} \leq z \;\middle|\; N\right)$$

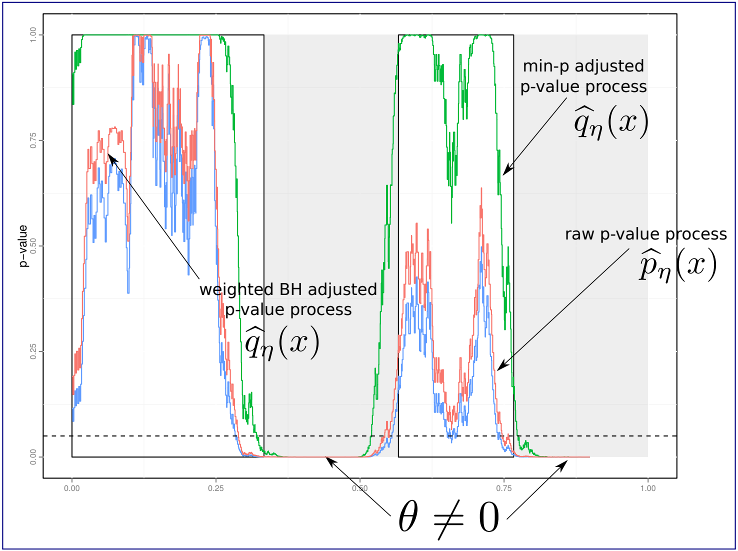
- In practice we control the FWER using:

$$\forall x \in \mathcal{X}_\eta, \;\; \widehat{q}_\eta(x) = \widehat{F}^{\min}_{\theta_0,N}\Big(\widehat{p}_\eta(x)\Big)$$

The min-p procedure with a cartoon



The weighted BH procedure with a cartoon



Control of the FDR, a heuristic inspired by Blanchard et al.

- For a given threshold v (eventually depending on everything !),

$$FDR^{\eta}_{\theta,\lambda}(\mathcal{R}(v)) = \mathbb{E}_{\theta,\lambda}\left(\frac{\Lambda\left(J_0^{\eta} \cap \mathcal{R}(v)\right)}{\Lambda\left(\mathcal{R}(v)\right)}\right)$$

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- If one could find a v such that $\frac{\Lambda(\mathcal{R}(v))}{\Lambda(\mathcal{X}_\eta)} \geq \frac{v}{\alpha}$, then (as if v was deterministic)

$$FDR^{\eta}_{\theta,\lambda}(\mathcal{R}(v)) \leq \frac{\alpha}{\Lambda(\mathcal{X}_\eta)} \int_{J_0^{\eta}} \frac{\mathbb{P}_{\theta,\lambda}\left(p_\eta(x) \leq v\right)}{v} d\Lambda(x).$$

$$\leq \frac{\alpha\Lambda(J_0^{\eta})}{\Lambda(\mathcal{X}_\eta)} \leq \alpha.$$

A weighted step-up BH procedure

- Hence one needs the largest v such that $\frac{\Lambda(\mathcal{R}(v))}{\Lambda(\mathcal{X}_\eta)} \geq \frac{v}{\alpha}$,
- Let τ be the partition that defines the windows:

$$\Lambda\left(\mathcal{R}_\eta(v)\right) = \sum_{m=0}^{M-1} (\tau_{m+1} - \tau_m) 1_{\{p_\eta(\tau_m) \leq v\}}.$$

- Compute the weights $w_m = (\tau_{m+1} - \tau_m)/(1-\eta)$
- Denote $\{p_m, 1 \leq m \leq M\} = \{p_\eta(\tau_m), 0 \leq m \leq M-1\}$ and order this p-values in increasing order $p_{\sigma(1)} \leq \cdots \leq p_{\sigma(M)}$ for an appropriate permutation σ of $\{1, \ldots, M\}$;
- Consider $\widehat{k} = \max\{k \in \{1, \ldots, M\} \ : \ p_{\sigma(k)} \leq \alpha \sum_{l=1}^{k} w_{\sigma(l)}\}$
- Compute V^α as $\alpha \sum_{l=1}^{\widehat{k}} w_{\sigma(l)}$.

BH-adjusted p-value process

- Let us denote by $(q_\eta(x))_{x\in\mathcal{X}_\eta}$ the adjusted p-values of the step-up procedure:
$$q_\eta(x) = \min_{k:p_{\sigma(k)}\geq p_\eta(x)} \left\{ \frac{p_{\sigma(k)}}{\sum_{l=1}^{k} w_{\sigma(l)}} \right\}.$$
- The decision at level α is simply to reject the nulls corresponding to windows $I_\eta(x)$ with *adjusted* p-values lower than α.
- We can check that
$$\mathcal{R}_\eta(V^\alpha) = \{x \in \mathcal{X}_\eta \ : \ q_\eta(x) \leq \alpha\}.$$

Theorem

For the one-sided case with the p-values based on the $N_A(I_\eta(x))$, the FDR of $\mathcal{R}^{wBH}$ is controlled by α.

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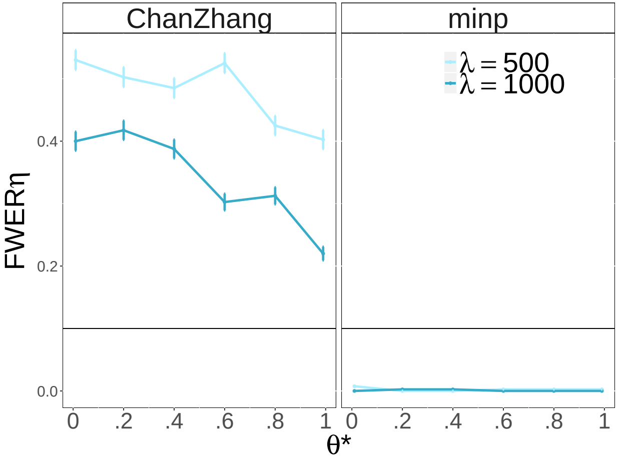

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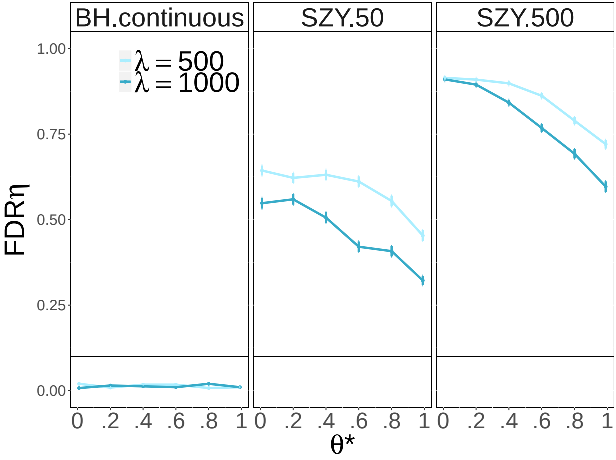
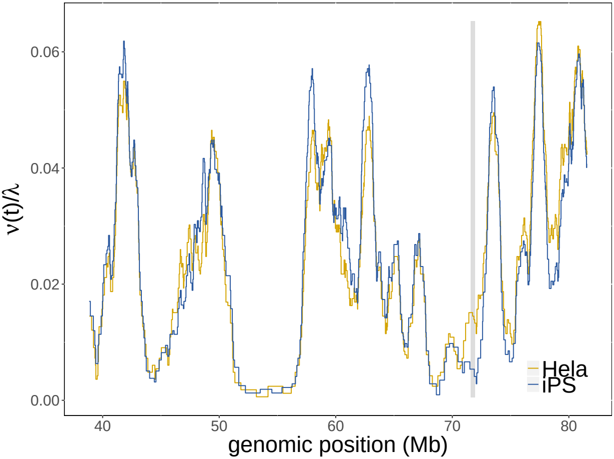


Outline

Density of replication origins along chromosome 16



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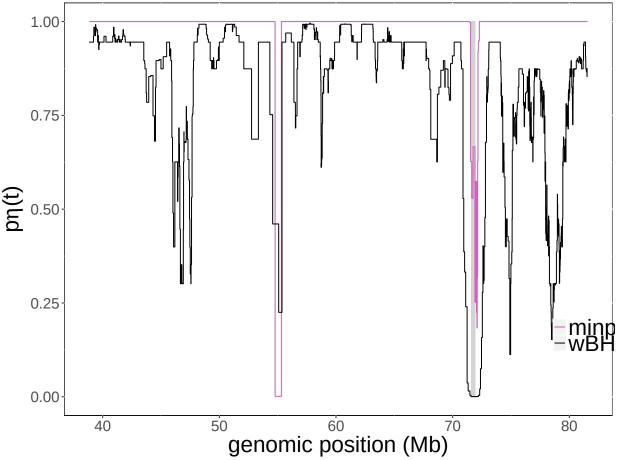

Outline

Perspectives of our work

- We provide a framework to locally compare Poisson processes intensities
- How procedures control the FWER and the FDR in continuous time
- This framework can be extended to one-sided hypothesis, and one-sample testing (homogeneity)
- Provides a new look on scanning statistics (lack of proper definition for FDR)
- Calibration of the windows size η
- Extension to 2D / 3D scans ?