

# Post hoc inference via multiple testing

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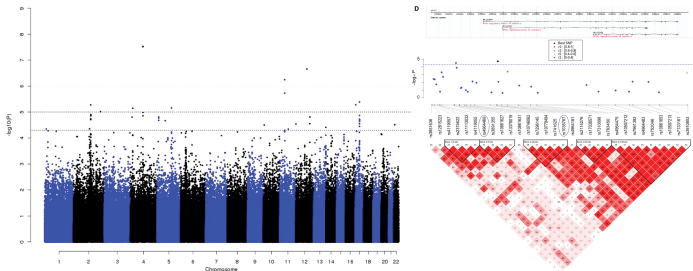
Joint work with Gilles Blanchard and Etienne Roquain

MCP 2017, UC Riverside

# Outline

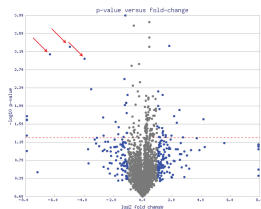
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- 2 Joint Family-Wise Error Rate control for post hoc inference
  - A novel risk measure: JER
  - JER control based on Simes' inequality
- 3 Adaptive Joint Family-Wise Error Rate control
  - Calibration of a rejection kernel
  - Numerical experiments: known dependence, linear kernel

# Genome-Wide Association Studies



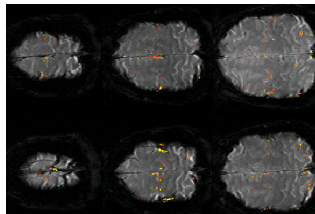
# Other motivating examples

## Cancer studies



Differential gene expression analyses

## Neuroimaging



Activation of brain regions

## Typical analysis steps

- 1 define a list of candidates using a **multiple testing procedure**
- 2 refine this list based on **prior knowledge** (gene pathways, brain regions)

## Limitations

- Initial selection does not take advantage of **available prior knowledge**
- **No formal risk assessment** can be made on the resulting candidate sets

# Multiple testing: notations

- $\mathcal{H} = \{1, \dots, m\}$   $m$  null hypotheses to be tested
- $\mathcal{H}_0 \subset \mathcal{H}$ : true null hypotheses,  $\mathcal{H}_1 = \mathcal{H} \setminus \mathcal{H}_0$
- $(p_i)_{1 \leq i \leq m}$ :  $p$ -values

## Multiple testing procedures

Aim at building from the data a set  $R$  of rejected hypotheses satisfying a statistical guarantee, e.g. controlling:

- $(k)$ -Family-Wise Error Rate:  $k\text{-FWER} = \mathbb{P}(|R \cap \mathcal{H}_0| > k - 1)$
- False Discovery Rate:  $\text{FDR} = \mathbb{E} \left( \frac{|R \cap \mathcal{H}_0|}{|R| \vee 1} \right)$

Most procedures used in applications are **thresholding procedures**:

$$R = \{i \in \mathcal{H}, p_i \leq \hat{t}\}$$

# Post hoc inference

Goal: Confidence statements for the number of true/false positives on **any number of arbitrary rejection sets**, possibly selected after data analysis

## Formal objective

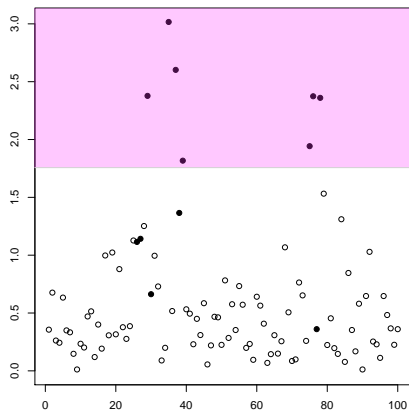
Find  $\overline{V}_\alpha, \overline{S}_\alpha$  such that  $\forall R \subset \{1 \dots m\}$ ,

$$\mathbb{P}(|R \cap \mathcal{H}_0| \geq \overline{V}_\alpha(R)) \geq 1 - \alpha$$

$$\mathbb{P}(|R \cap \mathcal{H}_1| \leq \overline{S}_\alpha(R)) \geq 1 - \alpha$$

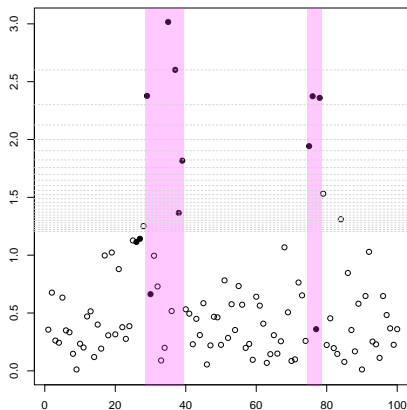
# Post hoc inference in a nutshell

## Classical multiple testing



$\text{FDR} \leq 25\%$

## Post hoc inference



With probability  $\geq 75\%$   
 $|R \cap \mathcal{H}_1| \geq 2$  and  $|R' \cap \mathcal{H}_1| \geq 1$

# State of the art: Goeman and Solari (2011)

Existing post hoc procedures<sup>1</sup> are based on *closed testing*<sup>2</sup>

- Require testing all  $2^m - 1$  possible intersections between the  $m$  original hypotheses!
- Not feasible for  $m \geq 20$  or 30.

In practice: “shortcuts”

- computationally efficient procedures (complexity  $\sim m \log(m)$ )
- increased conservativeness and/or narrower applicability:
- Simes' shortcut: valid under positive dependence between hypotheses (PRDS)

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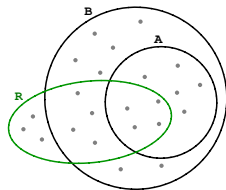
<sup>1</sup>Multiple testing for exploratory research. *Stat. Science* (2011)

<sup>2</sup>Marcus, Peritz and Gabriel, *Biometrika* (1976).



# Joint Family-Wise Error Rate (JER)

## Intuition



Given  $A$  and  $B$  such that:

- $|A \cap \mathcal{H}_0(P)| \leq 5$
- $|B \cap \mathcal{H}_0(P)| \leq 7$

Then we can guarantee:

$$|R \cap \mathcal{H}_1(P)| \geq 1$$

## Definition

Let  $\mathfrak{R} = (R_k)_{k=1\dots m}$  be a *reference family* of rejection sets. Then

$$\text{JER}(\mathfrak{R}) = \mathbb{P}(\exists k \in \{1, \dots, m\}, |R_k \cap \mathcal{H}_0| \geq k)$$

Consequently,  $\mathfrak{R}$  is said to control JER at level  $\alpha \in [0, 1]$  if:

$$\mathbb{P}(\forall k \in \{1, \dots, m\}, |R_k \cap \mathcal{H}_0| \leq k - 1) \geq 1 - \alpha$$

# Post hoc inference through JER control

## JER control

$$\mathbb{P}(\forall k \in \{1, \dots, m\}, |R_k \cap \mathcal{H}_0| \leq k - 1) \geq 1 - \alpha$$

## Upper bound on the number of false positives

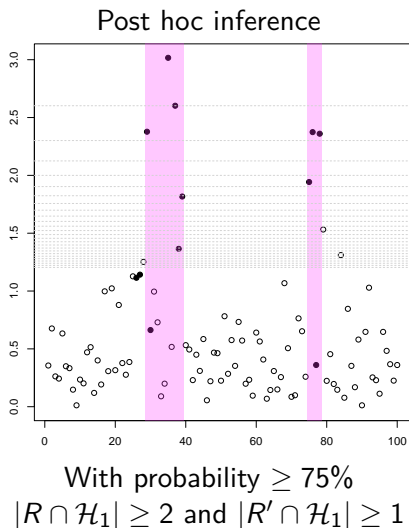
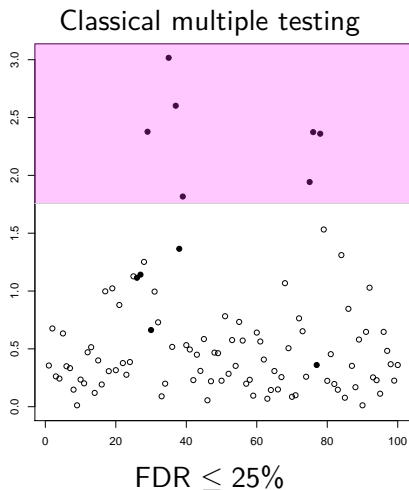
Given a JER controlling family  $(R_k)_{k=1\dots m}$ , with probability larger than  $1 - \alpha$ , for **any** rejection set  $R$ ,

$$|R \cap \mathcal{H}_0| \leq |R| \wedge \min_{1 \leq k \leq |R|} \{|R \cap (R_k)^c| + k - 1\}$$

## Applicable to

- data-driven rejection sets
- any number of rejection sets

# Illustration



How can JER control be achieved?

# Simes' inequality <sup>3</sup>

If the  $p$ -values  $(p_i)$ ,  $1 \leq i \leq m$ , are PRDS then

$$\mathbb{P}(\exists k \in \{1, \dots, m_0\} : q_{(k)} \leq \alpha k / m_0) \leq \alpha,$$

where  $q_{(1)} \leq \dots \leq q_{(m_0)}$  denote the ordered  $p$ -values under  $H_0$

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<sup>3</sup>R. J. Simes. *Biometrika* 73.3 (1986), pp. 751–754.

# Simes-based JER control

## Corollary of Simes' inequality

Under PRDS, JER control at level  $\alpha$  is achieved by the Simes reference family:

$$R_k = \{1 \leq i \leq m : p_i \leq \alpha k/m\}, 1 \leq k \leq m$$

## Proposition (Post hoc bound for the Simes family)

Under PRDS, with probability larger than  $1 - \alpha$ , for any  $R$ ,

$$|R \cap \mathcal{H}_0| \leq |R| \wedge \min_{1 \leq k \leq |R|} \left\{ \sum_{i \in R} \mathbf{1}\{p_i > \alpha k/m\} + k - 1 \right\}.$$

- We recover the bound obtained by Goeman and Solari (2011)
- JER: a generic device to build post hoc bounds

## Dependence-free JER control?

Under arbitrary dependence, with probability larger than  $1 - \alpha$ , for any  $R$ ,

$$|R \cap \mathcal{H}_0| \leq |R| \wedge \min_{1 \leq k \leq |R|} \left\{ \sum_{i \in R} \mathbf{1}_{\{p_i > \alpha / C_m k / m\}} + k - 1 \right\},$$

$C_m = \sum_{k=1}^m k^{-1} \sim \log(m)$ : Hommel's correction factor for dependency<sup>4</sup>

Dependence-free adjustment is not a sensible objective

- implies adjusting to a worst case dependency
- very conservative (cf Benjamini-Yekutieli for FDR control)

We want to be **adaptive** to dependency

<sup>4</sup>G Hommel. "Tests of the overall hypothesis for arbitrary dependence structures". Biometrische Zeitschrift 25.5 (1983), pp. 423–430.

# Sharpness and conservativeness of the Simes family

Simes' equality is sharp under independence, but **conservative under positive dependence**.

## Conservativeness of JFWER control under PRDS

Toy example: Gaussian equi-correlation, white setting ( $m_0 = m = 1,000$ ):  
Test statistics  $\sim \mathcal{N}(0, \Sigma)$  with  $\Sigma_{ii} = 1$  and  $\Sigma_{ij} = \rho$  for  $i \neq j$ .

Equi-correlation level: $\rho$	0	0.1	0.2	0.4	0.8
Achieved JFWER $\times \alpha^{-1}$	0.99	0.85	0.72	0.42	0.39

Can we build a family achieving **sharper** JFWER control?

We want to be **adaptive** to dependency

# JER control with $\lambda$ adjustment

## Rejection kernel

Consider the reference family:

$$R_k = \{1 \leq i \leq m : p_i \leq t_k(\alpha)\}, 1 \leq k \leq m,$$

where  $t_k(0) = 0$  and  $t_k(\cdot)$  is non-decreasing and left-continuous on  $[0, 1]$

- Example (Simes family):  $t_k(\alpha) = \alpha k/m$

The associated *rejection kernel* is the collection of  $(t_k(\lambda)_{k=1\dots m})$  for all  $0 \leq \lambda \leq 1$

## Single-step $\lambda$ adjustment

$$\lambda(\alpha) = \max \left\{ \lambda \geq 0 : \mathbb{P} \left( \min_{1 \leq k \leq K} \left\{ t_k^{-1} \left( p_{(k:\mathcal{H})} \right) \right\} \leq \lambda \right) \leq \alpha \right\}.$$

The family  $\mathfrak{R}_{\lambda(\alpha)}$  controls JER at level  $\alpha$ .



## Calculating the adjustment factor $\lambda(\alpha)$

$$\lambda(\alpha) = \max \left\{ \lambda \geq 0 : \mathbb{P} \left( \min_{1 \leq k \leq K} \left\{ t_k^{-1} \left( p_{(k:\mathcal{H})} \right) \right\} \leq \lambda \right) \leq \alpha \right\}$$

Calculating  $\lambda(\alpha)$  requires the knowledge of the distribution of  $(p_{(k:\mathcal{H})})_k$ !

Using Monte-Carlo approximation if the joint null distribution is known

- see below example of Gaussian equi-correlation
- more in G. Blanchard, P. Neuvial, E. Roquain (2017), arxiv:1703.02307

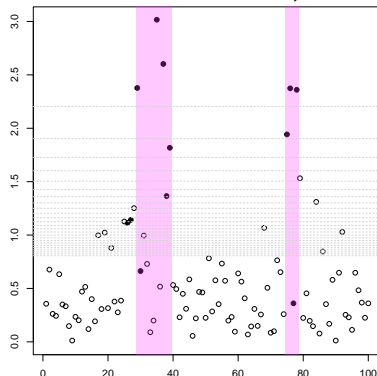
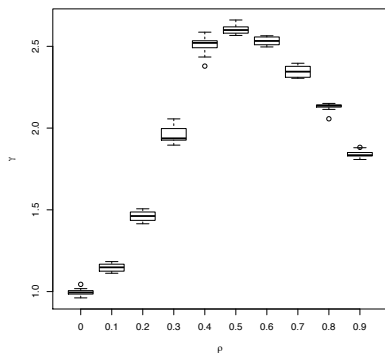
Permutation testing is justified in some applications, including:

- differential expression analyses
- GWAS with discrete (case/control) or quantitative phenotype

(restriction: the reference thresholds  $t$  must be deterministic)

# JER control with $\lambda$ adjustment for the linear kernel

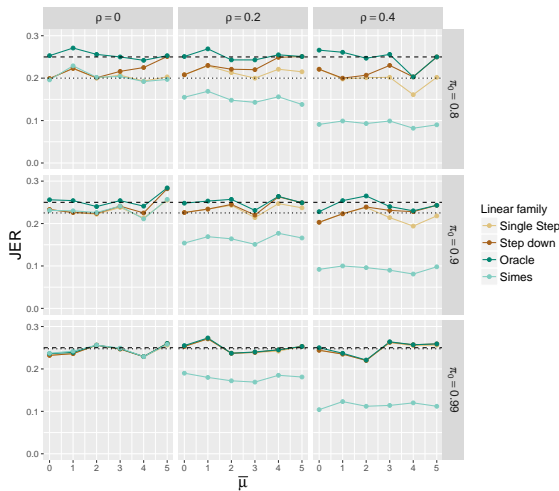
Example under positive dependency (Gaussian equi-correlation)



With probability  $\geq 1 - \alpha = 75\%$ :

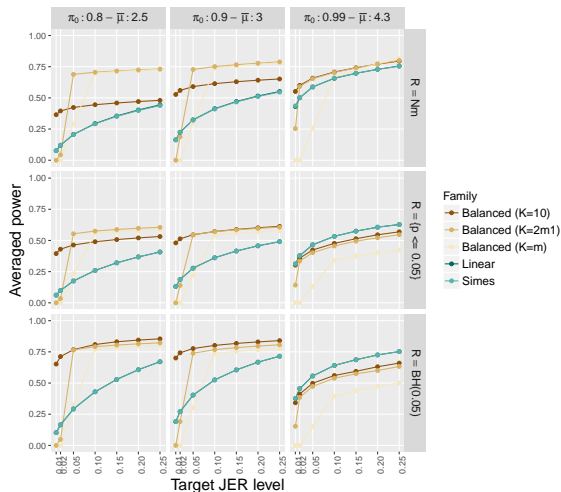
$t_k(\alpha)$	Lower bound on $ R \cap \mathcal{H}_1 $
$\alpha k/m$	$ R \cap \mathcal{H}_1  \geq 2$ and $ R' \cap \mathcal{H}_1  \geq 1$
$\alpha\lambda(\alpha)k/m$	$ R \cap \mathcal{H}_1  \geq 3$ and $ R' \cap \mathcal{H}_1  \geq 2$

# JER control under Gaussian equi-correlation



- $X_i \sim \mathcal{N}(0, 1)$  under  $H_0$
- $X_i \sim \mathcal{N}(\bar{\mu}, 1)$  under  $H_1$
- $\text{cor}(X_i, X_j) = \rho$  for  $i \neq j$
- $\alpha = 0.25$

# Estimation power for under Gaussian equi-correlation



- $X_i \sim \mathcal{N}(0, 1)$  under  $H_0$
- $X_i \sim \mathcal{N}(\bar{\mu}, 1)$  under  $H_1$
- $\text{cor}(X_i, X_j) = \rho$  for  $i \neq j$
- $\bar{\mu} = 2$
- Estimation power:  $E(\bar{S}(\mathcal{H}_1))/m_1$

# Conclusions

## Summary

- JER: a new risk measure for multiple testing
- generalizes existing post hoc procedures
- can be used to build post hoc inference procedures

## Results not discussed here

- Other choices for the kernel
- Step-down procedures
- Control of  $\mathbb{P}(\forall k \in \{1, \dots, K\}, |R_k \cap \mathcal{H}_0| \leq \zeta_k)$
- Detection power: connection to “higher criticism” in a sparse setting

## Ongoing/future works

- Applications to GWAS, differential expression and neuro-imaging
- Structured rejection sets: algorithms and statistical results
- Software and visualization tools


# Thanks

- Etienne Roquain, Paris 6 University, France
- Gilles Blanchard, Potsdam University, Germany

## Reference

G. Blanchard, P. Neuvial, E. Roquain (2017), *Post hoc inference via joint family-wise error rate control* Arxiv preprint:1703.02307

## Funding

- CNRS PEPS FaSciDo (2015-2016)
-  project JCJC SansSouci (2016-2019)

We are hiring a postdoc!