

Introduction aux tests multiples

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M2 Maths & IA
Notes de cours

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Simple testing

- ▶ Data: $X = (X_1, \dots, X_n)$ i.i.d. $\sim \mathcal{N}(\mu, 1)$, $\mu \geq 0$ unknown
- ▶ Question: is $\mu = 0$ (no signal) or > 0 (signal) ?
- ▶ Null hypothesis H_0 : " $\mu = 0$ " versus alternative H_1 : " $\mu > 0$ "
- ▶ Test statistic: $T(X) = n^{-1/2} \sum_{i=1}^n X_i$, under H_0 $T(X) \sim \mathcal{N}(0, 1)$
- ▶ $T(X)$ in the right tail of $\mathcal{N}(0, 1)$ \Rightarrow unrealistic \Rightarrow reject H_0
- ▶ So we reject H_0 if $T(X)$ is "large": the rejection region \mathcal{R} is the event $\{T(X) > c\}$ with c to be determined

Test of level α

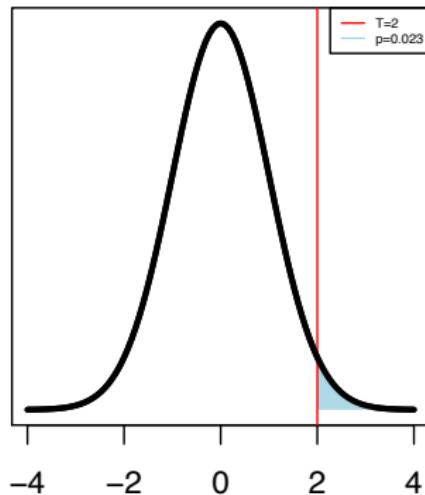
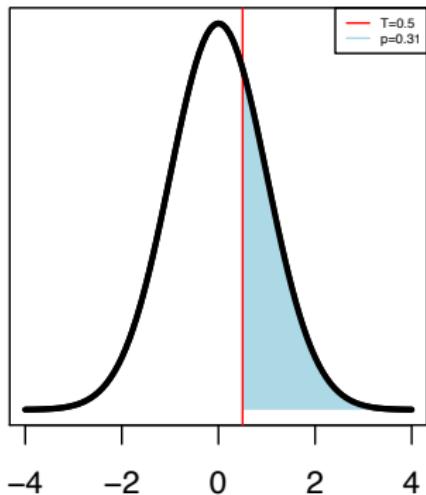
Choice of the rejecting threshold

Goal:

Control the type I error = \mathbb{P} of a wrong rejection = \mathbb{P} of a false positive

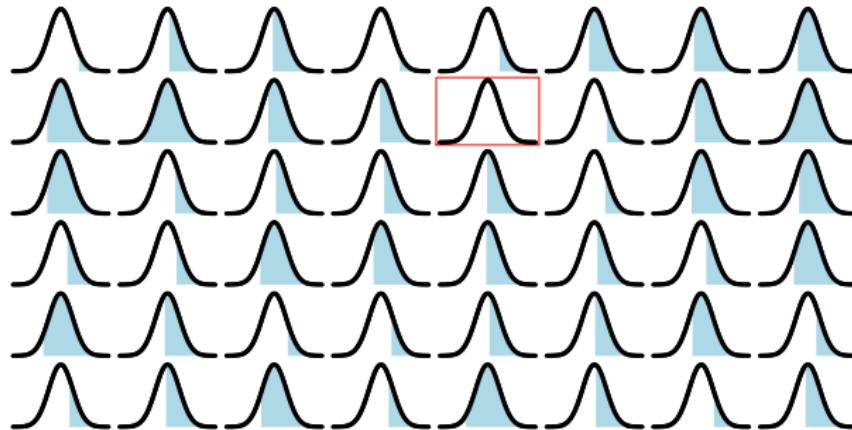
- ▶ “level α ” means type I error = $\mathbb{P}_{H_0}(T(X) > c) \leq \alpha$
- ▶ $\Rightarrow c \geq q_{1-\alpha}^*$ the $1 - \alpha$ quantile of $\mathcal{N}(0, 1)$
- ▶ Given type I control, how to reduce type II error?
 - ▶ Take the smallest c
 - ▶ $\Rightarrow \mathcal{R} = \{T(X) > q_{1-\alpha}^*\}$
- ▶ \Leftrightarrow if the p -value $p(X) = \bar{\Phi}(T(X)) = 1 - \Phi(T(X))$ is $\leq \alpha$
- ▶ “Proof”: $\mathbb{P}_{H_0}(p(X) \leq \alpha) = \mathbb{P}_{H_0}(T(X) \geq q_{1-\alpha}^*) \leq \alpha$
- ▶ $p(X)$ is super-uniform under H_0 , $p(X) = \mathbb{P}$ of observing an event at least as extreme as the one observed under the null

Test of level α



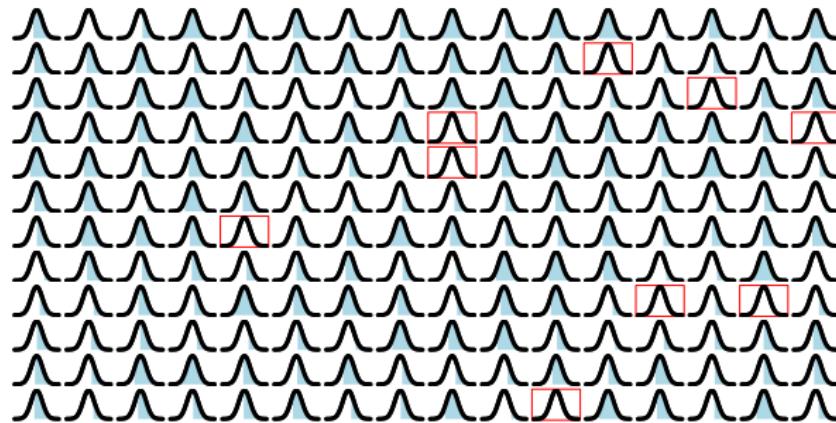
Multiple testing

- ▶ Now each X_i is a vector $(X_{i1}, \dots, X_{im}) \sim \mathcal{N}(\mu, \text{Id}_m)$ with $\mu = (\mu_1, \dots, \mu_m) \in \mathbb{R}_+^m$
- ▶ m null hypotheses $H_{0,j}$: " $\mu_j = 0$ " versus $H_{1,j}$: " $\mu_j > 0$ "
- ▶ Because of independence, at least one false positive with $\mathbb{P} = 1 - (1 - \alpha)^{m_0} \xrightarrow[m_0 \rightarrow \infty]{} 1$
- ▶ $\mathbb{E}[|\text{FP}|] = \alpha m_0$, $m_0 = |\{j : H_{0,j} \text{ is true}\}|$
- ▶ Example if $m = m_0 = 48$, $\alpha = 0.05$:



Multiple testing

- ▶ False positives explosion with m
- ▶ $m = m_0 = 192$, $\alpha = 0.05$:



Modern applications

- ▶ “Omic data”: genomic, proteomic... but also fMRI, exoplanet detection...
- ▶ $m = 10^4, 10^5, 10^6$
- ▶ Too many false positives without correction

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Formal setting

- ▶ Let $(\mathbb{X}, \mathcal{X}, \mathfrak{F})$ a statistical model and $(\Omega, \mathcal{A}, \mathbb{P})$ a probability space
- ▶ Hence $(\mathbb{X}, \mathcal{X})$ is a measurable space and \mathfrak{F} is a family of probability measures defined on \mathcal{X}
- ▶ Data is a measurable $X : (\Omega, \mathcal{A}) \rightarrow (\mathbb{X}, \mathcal{X})$ with $X \sim P \in \mathfrak{F}$
- ▶ Other notation frequently used: $\mathbb{P}_X = \mathcal{L}(X) = X_{\#\mathbb{P}} = P$
- ▶ P unknown \Rightarrow everything has to be valid $\forall P \in \mathfrak{F}$

Formal setting

- ▶ m null hypotheses $H_{0,i}$ and alternatives $H_{1,i}$ which are subsets of \mathfrak{F}
 - ▶ $H_{0,i} \cap H_{1,i} = \emptyset$
- ▶ $\mathcal{H}_0 = \mathcal{H}_0(P) = \{i : P \in H_{0,i}\}$: $i \in \mathcal{H}_0 \Leftrightarrow H_{0,i}$ is true
 - ▶ $\mathcal{H}_1(P) = \mathcal{H}_0(P)^c = \{i : P \in H_{1,i}\}$
- ▶ m p -values $p_i = p_i(X)$ such that $\mathcal{L}(p_i) \succeq \mathcal{U}([0, 1])$ if $i \in \mathcal{H}_0$
 - ▶ Each p_i provides an α level test :

$$\forall \alpha \in [0, 1], \forall P \in H_{0,i}, \forall X \sim P, \mathbb{P}(p_i \leq \alpha) \leq \alpha,$$

or, in short, $\mathbb{P}_{X \sim P \in H_{0,i}}(p_i \leq \alpha) \leq \alpha$

- ▶ 2 points of view: measurable application $p_i(\cdot) : \mathcal{X} \rightarrow [0, 1]$, then applied to X , or random variable $p_i(X)$
- ▶ For every subset of hypotheses S , let $V(S) = |S \cap \mathcal{H}_0|$ the # of false positives (FP) in S

Formal setting

- ▶ Formally, a rejection procedure R is a measurable function $(\mathcal{X}, \mathfrak{X}) \longrightarrow (\mathcal{P}(\llbracket 1, m \rrbracket), \mathcal{P}(\mathcal{P}(\llbracket 1, m \rrbracket)))$
- ▶ For a data point $X \sim P \in \mathfrak{F}$, the associated rejection set is $R(X)$ or R in short (\Rightarrow small ambiguity), the rejected hypotheses are the $H_{0,i}$ such that $i \in R(X)$
- ▶ “Classic” MT goal: construct a rejection procedure R with a statistical guarantee on $V(R) \Leftrightarrow$ control of an error rate related to # of FP

A toy example

In this formal setting

- ▶ $(\Omega, \mathcal{A}, \mathbb{P})$ a probability space
- ▶ $(\mathcal{X}, \mathfrak{X}) = (\mathbb{R}^m, \mathcal{B}(\mathbb{R}^m)) : X = (X_1, \dots, X_m)$
- ▶ $\mathcal{V}(1)$ the set of positive semidefinite matrices with 1's on the diagonal
- ▶ $\mathfrak{F} = \{\mathcal{N}(\boldsymbol{\mu}, \Sigma) : \forall j \in [\![1, m]\!], \mu_j \geq 0, \Sigma \in \mathcal{V}(1)\}$
- ▶ $H_{0,i} = \{\mathcal{N}(\boldsymbol{\mu}, \Sigma) : \mu_i = 0, \forall j \in [\![1, m]\!] \setminus \{i\}, \mu_j \geq 0, \Sigma \in \mathcal{V}(1)\}$
- ▶ $H_{1,i} = \{\mathcal{N}(\boldsymbol{\mu}, \Sigma) : \mu_i > 0, \forall j \in [\![1, m]\!] \setminus \{i\}, \mu_j \geq 0, \Sigma \in \mathcal{V}(1)\}$
- ▶ $p_i(X) = \bar{\Phi}(X_i) = 1 - \Phi(X_i)$

Generic construction of p -values

Following the idea of “the probability of an event at least as extreme as”

- ▶ Assume we have at hand m test statistics $T_1, \dots, T_m : \mathcal{X} \longrightarrow \mathbb{R}$
- ▶ for all $i \in [1, m]$, we can let
 - ▶ $\hat{p}_i(X) = \sup_{P \in H_{0,i}} \mathbb{P}_{Z \sim P, Z \perp X}(T_i(Z) \geq T_i(X)|X) = \sup_{P \in H_{0,i}} P(T_i^{-1}([T_i(X), \infty[)) = \sup_{P \in H_{0,i}} (T_i)_{\#P}([T_i(X), \infty[]),$ or
 - ▶ $\bar{p}_i(X) = \sup_{P \in H_{0,i}} \mathbb{P}_{Z \sim P, Z \perp X}(T_i(Z) \leq T_i(X)|X) = \sup_{P \in H_{0,i}} P(T_i^{-1}(]-\infty, T_i(X)])) = \sup_{P \in H_{0,i}} (T_i)_{\#P}(]-\infty, T_i(X)])),$ or
 - ▶ $\check{p}_i(X) = 2 \min(\hat{p}_i(X), \bar{p}_i(X))$
- ▶ Classical constructions for unilateral and bilateral tests, equivalent to UMP or UMP unbiased tests from Neyman-Pearson and Lehmann's theory for the appropriate choice of test statistics.
- ▶ Knowledge of $P \in H_{0,i}$, is required to compute \hat{p}_i , \bar{p}_i or \check{p}_i

Generic construction of p -values

Following the idea of “the probability of an event at least as extreme as”

Theorem

\hat{p}_i , \bar{p}_i , \check{p}_i all are appropriate p -values, that is, they are super-uniform under the null:

Denote by u the c.d.f. of $\mathcal{U}([0, 1])$: $u(x) = 0 \vee (x \wedge 1)$. Let $Q \in H_{0,i}$, $X \sim Q$, then

$$\forall x \in \mathbb{R}, \mathbb{P}(\hat{p}_i(X) \leq x) \leq u(x), \quad (1)$$

$$\forall x \in \mathbb{R}, \mathbb{P}(\bar{p}_i(X) \leq x) \leq u(x), \quad (2)$$

$$\forall x \in \mathbb{R}, \mathbb{P}(\check{p}_i(X) \leq x) \leq u(x). \quad (3)$$

Generic construction of p -values

Proof

- ▶ Only for (1), (2) and (3) left as an exercise
- ▶ $\hat{p}_i(X) \in [0, 1]$ a.s. so we only need to check (1) for $x \in [0, 1[$.
- ▶ (1) for $x \in]0, 1[$ implies (1) for $x = 0$ by right-continuity of the c.d.f
- ▶ Let $x \in]0, 1[$

$$\begin{aligned}\mathbb{P}(\hat{p}_i(X) \leq x) &= \mathbb{P}\left(\sup_{P \in H_{0,i}} P(T_i^{-1}([T_i(X), \infty[)) \leq x\right) \\ &= \mathbb{P}\left(\bigcap_{P \in H_{0,i}} \{P(T_i^{-1}([T_i(X), \infty[)) \leq x\}\right) \\ &\leq \mathbb{P}\left(Q(T_i^{-1}([T_i(X), \infty[)) \leq x\right)\end{aligned}$$

Generic construction of p -values

Proof

- ▶ Let F_i the c.d.f. of $T_i(X)$ and F_i^- its left-limit:

$$F_i^-(x) = \lim_{\substack{\varepsilon \rightarrow 0 \\ \varepsilon > 0}} F_i(x - \varepsilon) = \mathbb{P}(T_i(X) < x)$$

- ▶

$$\begin{aligned}\mathbb{P}\left(Q(T_i^{-1}([T_i(X), \infty[)) \leq x\right) &= \mathbb{P}\left(1 - Q(T_i^{-1}(]-\infty, T_i(X])) \leq x\right) \\ &= \mathbb{P}\left(1 - x \leq F_i^-(T_i(X))\right) \\ &= \mathbb{P}\left(T_i(X) \in (F_i^-)^{-1}([1-x, 1])\right)\end{aligned}$$

- ▶ F_i^- is nondecreasing with limits 0 in $-\infty$ and 1 in ∞ so $(F_i^-)^{-1}([1-x, 1])$ is an interval: $]a, \infty[$ or $[a, \infty[$ for some a .

Generic construction of p -values

Proof

- Case 1: $a \in (F_i^-)^{-1}([1-x, 1])$ then

$$\begin{aligned}\mathbb{P}\left(Q(T_i^{-1}([T_i(X), \infty[)) \leq x\right) &= \mathbb{P}(T_i(X) \geq a) \\ &= 1 - F_i^-(a) \\ &\leq 1 - (1-x) \\ &= x.\end{aligned}$$

- Case 2:

$$\begin{aligned}\mathbb{P}\left(Q(T_i^{-1}([T_i(X), \infty[)) \leq x\right) &= \mathbb{P}(T_i(X) > a) \\ &= 1 - F_i(a)\end{aligned}$$

Generic construction of p -values

Proof

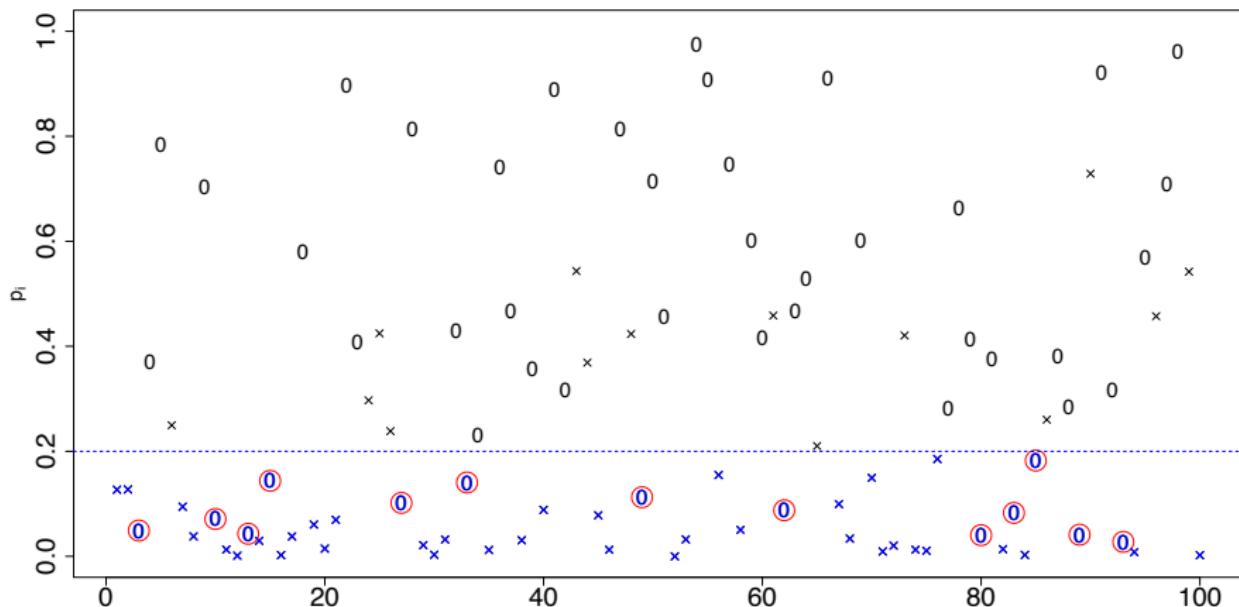
- ▶ $F_i(a)$ is the right-limit of F_i^- in a : $F_i(a) = \lim_{\substack{\varepsilon \rightarrow 0 \\ \varepsilon > 0}} F_i^-(a + \varepsilon)$
- ▶ Note that $a + \varepsilon \in (F_i^-)^{-1}([1 - x, 1])$ hence $F_i^-(a + \varepsilon) \geq 1 - x$
- ▶ $\varepsilon \rightarrow 0$: $F_i(a) \geq 1 - x$, which concludes case 2 and the proof

□

Rejection set

Thresholding

- ▶ Main idea: small p -values = signal (\mathcal{H}_1)
- ▶ In the remainder of this course, $R(X) = \{i : p_i(X) \leq \hat{t}(X)\} = R(\hat{t})$ in short, with $\hat{t} = \hat{t}(X) = \hat{t}(p_1(X), \dots, p_m(X))$ a random threshold



Thresholding

Sorting p -values

- ▶ Sorted p -values: $p_{(1)} \leq \dots \leq p_{(m)}$, $p_{(0)} = 0$ by convention
- ▶ $R(\hat{t}) = \{i : p_i \leq \hat{t}\} = \left\{ i : p_i \leq p_{(\hat{k})} \right\}$, $\hat{k} = \max\{k : p_{(k)} \leq \hat{t}\}$

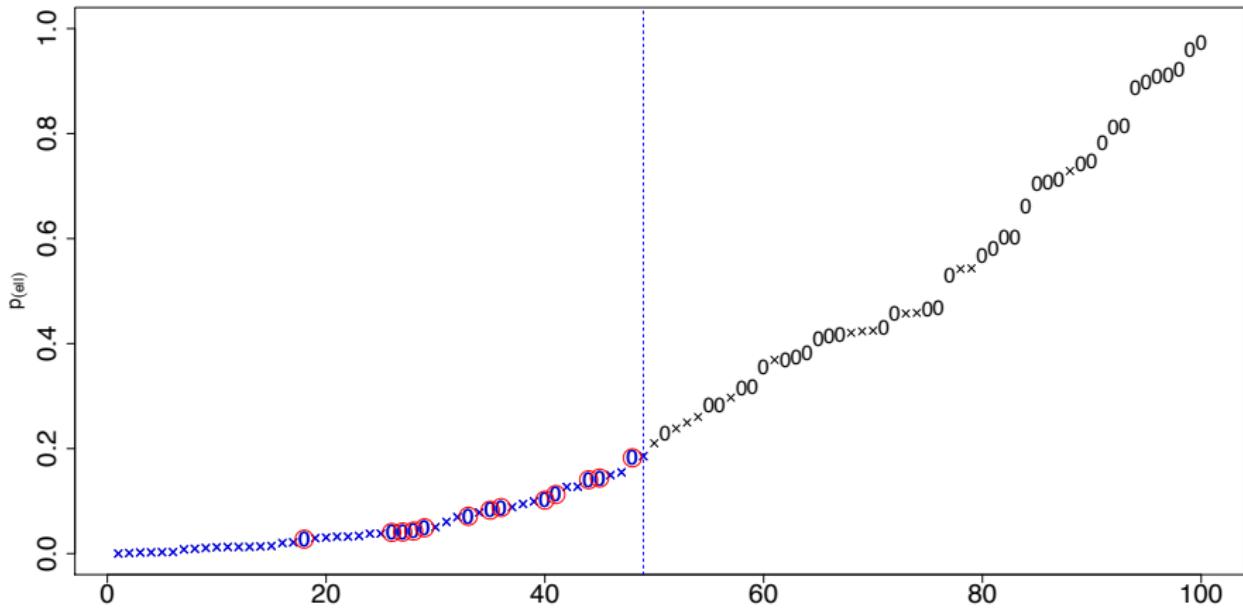


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Family-Wise Error Rate (FWER)

- ▶ Probability to make at least one false positive

$$\text{FWER}(R) = \mathbb{P}(V(R) > 0)$$

$$\text{FWER}(R(\hat{t})) = \mathbb{P}(\exists i, i \in \mathcal{H}_0 : p_i \leq \hat{t})$$

- ▶ The probability is taken with respect to $P \in \mathfrak{F}$

- ▶ Philosophy : we don't want any false positive

- ▶ Choose \hat{t}_α such that $\text{FWER}(R(\hat{t}_\alpha)) \leq \alpha$? ($\forall P \in \mathfrak{F}$)

Bonferroni method

- Bonferroni method: $\hat{t}_\alpha^{\text{Bonf}} = \frac{\alpha}{m}$ and $R^{\text{Bonf}} = R\left(\hat{t}_\alpha^{\text{Bonf}}\right)$ [Bonferroni (1936)]

Theorem

For all $P \in \mathfrak{F}$,

$$\text{FWER}\left(R^{\text{Bonf}}\right) \leq \alpha$$

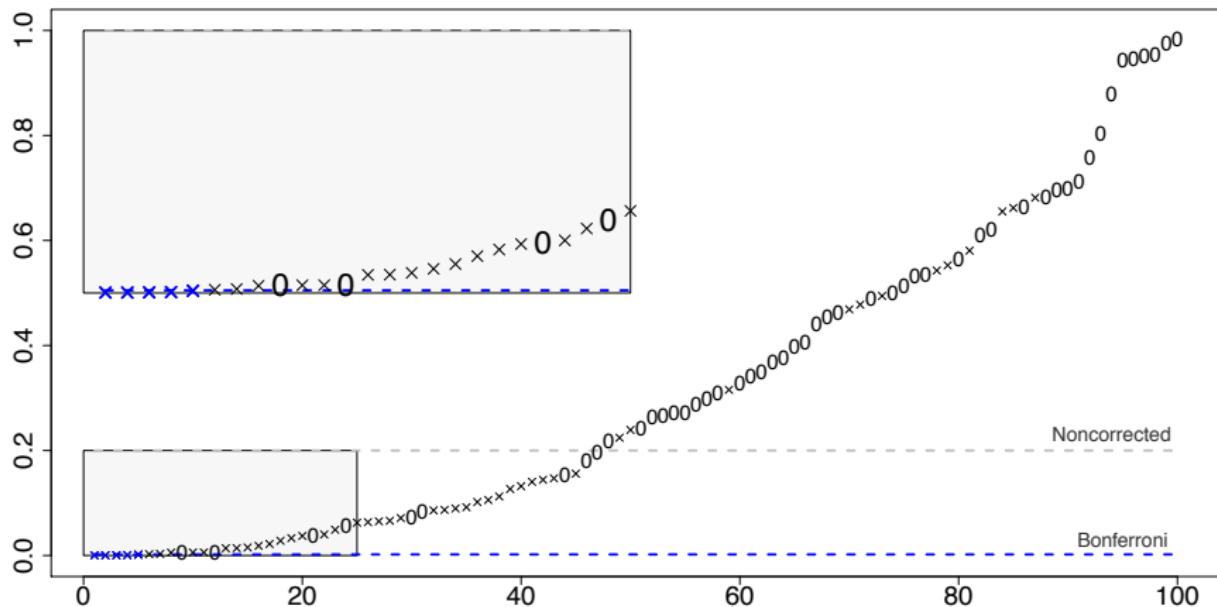
- Proof by union bound:

$$\begin{aligned}\text{FWER}\left(R^{\text{Bonf}}\right) &= \mathbb{P}\left(\exists i, i \in \mathcal{H}_0 : p_i \leq \hat{t}_\alpha^{\text{Bonf}}\right) \\ &= \mathbb{P}\left(\bigcup_{i \in \mathcal{H}_0} \left\{p_i \leq \frac{\alpha}{m}\right\}\right) \leq \sum_{i \in \mathcal{H}_0} \mathbb{P}\left(p_i \leq \frac{\alpha}{m}\right) \\ &\leq \alpha \frac{m_0}{m} \leq \alpha \quad \square\end{aligned}$$

- Adjusted p -value p_i^{adj} : smallest level that rejects $H_{0,i}$. For Bonferroni, $p_i^{\text{adj}} = 1 \wedge mp_i$

Illustration of Bonferroni method

$$\alpha = 0.2, m = 100$$



k -Family-Wise Error Rate (k -FWER)

A variant

$$k\text{-FWER}(R) = \mathbb{P}(V(R) \geq k)$$

- ▶ The probability is taken with respect to $P \in \mathfrak{F}$
- ▶ k -Bonferroni method: $\hat{t}_\alpha^{k\text{-Bonf}} = \frac{\alpha k}{m}$, $R^{k\text{-Bonf}} = R(\hat{t}_\alpha^{k\text{-Bonf}})$

Theorem [Lehmann and Romano (2005)]

For all $P \in \mathfrak{F}$,

$$\text{FWER}(R^{k\text{-Bonf}}) \leq \alpha$$

k -Family-Wise Error Rate (k -FWER)

A variant

- ▶ Proof by Markov inequality:

$$\begin{aligned}\mathbb{P} \left(V \left(R^{k\text{-Bonf}} \right) \geq k \right) &\leq \frac{\mathbb{E} \left[V \left(R \left(\frac{\alpha k}{m} \right) \right) \right]}{k} \\ &= \frac{\sum_{i \in \mathcal{H}_0} \mathbb{E} \left[\mathbf{1}_{\{p_i \leq \frac{\alpha k}{m}\}} \right]}{k} \\ &\leq \frac{1}{k} \sum_{i \in \mathcal{H}_0} \frac{\alpha k}{m} \\ &\leq \alpha \frac{m_0}{m} \leq \alpha \quad \square\end{aligned}$$

False Discovery Rate (FDR)

FWER too stringent

Especially for some settings where:

- ▶ m is large
- ▶ we want a lot of detections,
- ▶ and we can allow some false positive to do so

False Discovery Proportion (FDP) and FDR

$$\text{FDP}(R) = \frac{V(R)}{|R| \vee 1} \text{ (random variable)}$$

$$\text{FDR}(R) = \mathbb{E} [\text{FDP}(R)] \text{ } (\in [0, 1])$$

- ▶ The expectation is taken with respect to $P \in \mathfrak{F}$
- ▶ Choose a \hat{t}_α such that $\text{FDR}(R(\hat{t}_\alpha)) \leq \alpha$?

False Discovery Rate (FDR)

Estimating the FDP to derive a procedure

$$\begin{aligned}\text{FDP}(R(t)) &= \frac{\sum_{i \in \mathcal{H}_0} \mathbb{1}_{\{p_i \leq t\}}}{|R(t)| \vee 1} \\ &= m \frac{\frac{1}{m} \sum_{i \in \mathcal{H}_0} \mathbb{1}_{\{p_i \leq t\}}}{|R(t)| \vee 1} \\ &\leq m \frac{\frac{1}{m_0} \sum_{i \in \mathcal{H}_0} \mathbb{1}_{\{p_i \leq t\}}}{|R(t)| \vee 1}\end{aligned}$$

- ▶ Main idea: if m_0 large, $\frac{1}{m_0} \sum_{i \in \mathcal{H}_0} \mathbb{1}_{\{p_i \leq t\}} \lesssim t$ by law of large numbers and super-uniformity
- ▶ $\Rightarrow \widehat{\text{FDP}}^{\text{BH}}(t) = \frac{mt}{|R(t)| \vee 1}$
- ▶ $\Rightarrow \hat{t}_\alpha^{\text{heur}} = \sup \left\{ t \in [0, 1] : \widehat{\text{FDP}}^{\text{BH}}(t) \leq \alpha \right\} = \sup \left\{ t \in [0, 1] : \frac{\alpha}{m} (|R(t)| \vee 1) \geq t \right\}$

Benjamini-Hochberg procedure (BH)

[Benjamini and Hochberg (1995)]

- ▶ Sorted p -values: $p_{(1)} \leq \dots \leq p_{(m)}$, $p_{(0)} = 0$ by convention
- ▶ Traditional definition : $\hat{k}^{\text{BH}} = \max \left\{ k \in [\![1, m]\!] : p_{(k)} \leq \alpha \frac{k}{m} \right\}$,
 $\hat{k}^{\text{BH}} = 0$ if set empty, $\hat{t}_{\alpha}^{\text{BH}} = \alpha \frac{\hat{k}^{\text{BH}}}{m}$
- ▶ Slightly equivalent modification:
 $\hat{k}^{\text{BH}} = \max \left\{ k \in [\![0, m]\!] : p_{(k)} \leq \alpha \frac{k+1}{m} \right\}$, $\hat{t}_{\alpha}^{\text{BH}} = \alpha \frac{\hat{k}^{\text{BH}}+1}{m}$,
 $R^{\text{BH}} = R \left(\hat{t}_{\alpha}^{\text{BH}} \right)$
- ▶ (really the same except $\hat{t}_{\alpha}^{\text{BH}} = \frac{\alpha}{m}$ if $\hat{k}^{\text{BH}} = 0$, gives the same R^{BH})
- ▶ Adjusted p -values : $p_{(i)}^{\text{adj}} = 1 \wedge \min_{j \geq i} \frac{mp_{(j)}}{j}$

Lemma

$$|R^{\text{BH}}| = \hat{k}^{\text{BH}} \text{ and } \hat{t}_{\alpha}^{\text{heur}} = \hat{t}_{\alpha}^{\text{BH}}$$

This lemma generalizes in more complex settings where it is useful, see
[Roquain and Wiel (2009)], [Durand (2019)], and the following

Illustration of BH method

$\alpha = 0.2, m = 100$

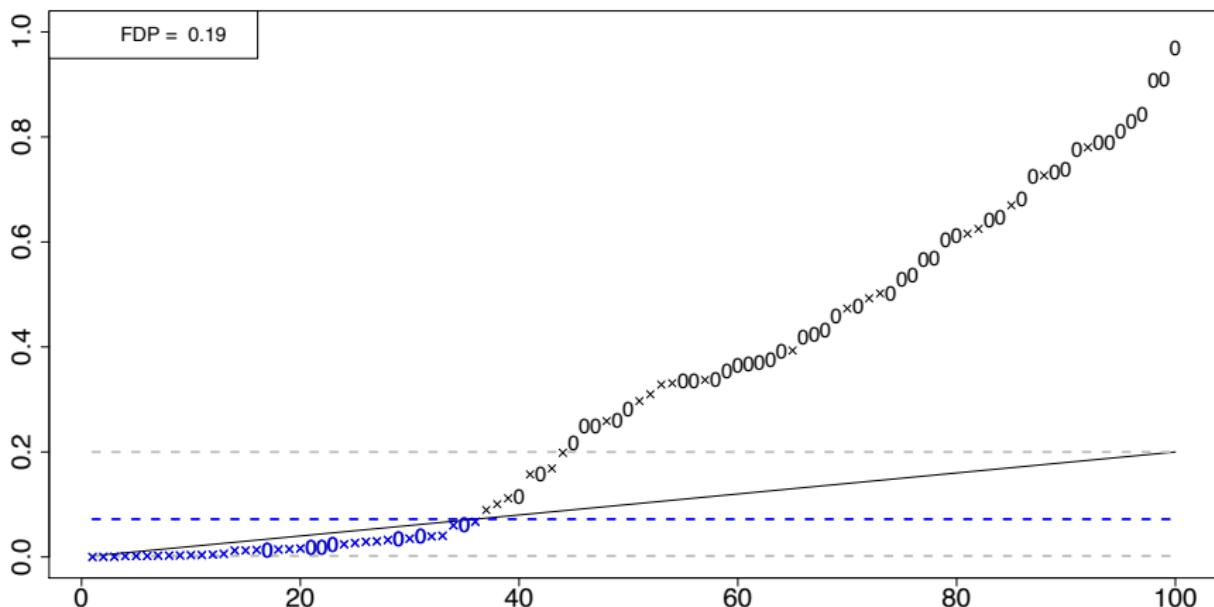
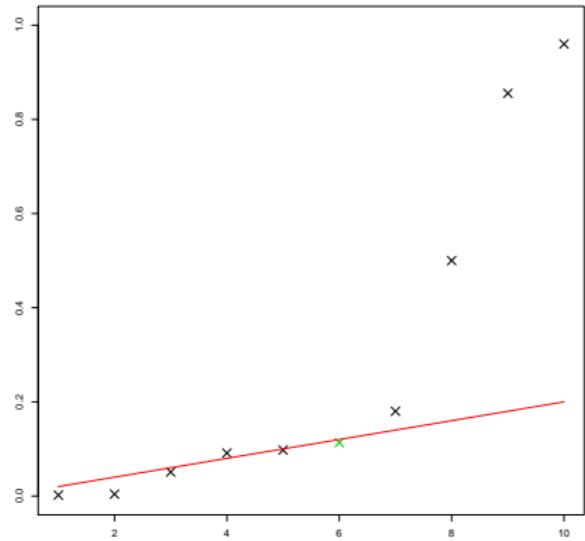
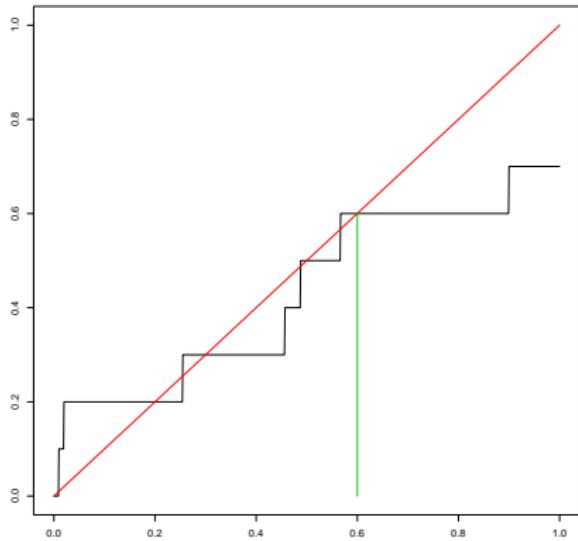


Illustration of BH method

$m = 10$



Benjamini-Hochberg procedure (BH)

Proof of the Lemma

- If $\hat{k}^{\text{BH}} \geq 1$,

$$p_{(\hat{k}^{\text{BH}})} \leq \alpha \frac{\hat{k}^{\text{BH}}}{m} \Rightarrow \forall i \in [\![1, \hat{k}^{\text{BH}}]\!], p_{(i)} \leq \alpha \frac{\hat{k}^{\text{BH}}}{m}$$
$$\Rightarrow \left| R\left(\hat{t}_\alpha^{\text{BH}}\right) \right| = \left| R\left(\alpha \frac{\hat{k}^{\text{BH}} \vee 1}{m}\right) \right| = \left| R\left(\alpha \frac{\hat{k}^{\text{BH}}}{m}\right) \right| \geq \hat{k}^{\text{BH}}$$

- Obvious if $\hat{k}^{\text{BH}} = 0$
- Reductio ad absurdum: if $\left| R\left(\hat{t}_\alpha^{\text{BH}}\right) \right| \geq \hat{k}^{\text{BH}} + 1$ then necessarily
 $p_{(\hat{k}^{\text{BH}}+1)} \leq \hat{t}_\alpha^{\text{BH}} = \alpha \frac{\hat{k}^{\text{BH}} \vee 1}{m} \leq \alpha \frac{(\hat{k}^{\text{BH}}+1) \vee 1}{m}$ which contradicts the definition of \hat{k}^{BH}

Benjamini-Hochberg procedure (BH)

Proof of the Lemma

- ▶ Supremum well-defined because non-empty set, $0 \in$ it
- ▶ Let $\widehat{G}(t) = \frac{\alpha}{m} (|R(t)| \vee 1)$: nondecreasing and $[0, 1] \rightarrow [0, 1]$
- ▶ Let $t_n \nearrow \hat{t}_\alpha^{heur}$, such that $\widehat{G}(t_n) \geq t_n$,

$$\widehat{G}\left(\hat{t}_\alpha^{heur}\right) \geq \widehat{G}(t_n) \geq t_n \xrightarrow{n \rightarrow \infty} \hat{t}_\alpha^{heur}$$

so \hat{t}_α^{heur} is a max

- ▶ So $\widehat{G}\left(\widehat{G}\left(\hat{t}_\alpha^{heur}\right)\right) \geq \widehat{G}\left(\hat{t}_\alpha^{heur}\right)$ so by def $\widehat{G}\left(\hat{t}_\alpha^{heur}\right) \leq \hat{t}_\alpha^{heur}$
- ▶ $\Rightarrow \hat{t}_\alpha^{heur} = \widehat{G}\left(\hat{t}_\alpha^{heur}\right)$

Benjamini-Hochberg procedure (BH)

Proof of the Lemma

- ▶ First note that $p_{(|R(t)|)} \leq t$ always
- ▶ $p_{(|R(\hat{t}_\alpha^{heur})|)} \leq \hat{t}_\alpha^{heur} = \hat{G}(\hat{t}_\alpha^{heur}) = \frac{\alpha}{m} (|R(\hat{t}_\alpha^{heur})| \vee 1)$
- ▶ $\Rightarrow |R(\hat{t}_\alpha^{heur})| \leq \hat{k}^{BH} \Rightarrow \hat{t}_\alpha^{heur} \leq \hat{t}_\alpha^{BH}$ by def of \hat{k}^{BH} and nondecreasing composition
- ▶ $\hat{G}(\hat{t}_\alpha^{BH}) = \frac{\alpha}{m} (|R(\hat{t}_\alpha^{BH})| \vee 1) = \frac{\alpha}{m} (\hat{k}^{BH} \vee 1) = \hat{t}_\alpha^{BH}$ by previous result
- ▶ $\Rightarrow \hat{t}_\alpha^{BH} \leq \hat{t}_\alpha^{heur}$ by def of \hat{t}_α^{heur}

□

Benjamini-Hochberg procedure (BH)

Proof of the adjusted p -value formula

$$\begin{aligned} p_{(i)} \leq \alpha \frac{\hat{k}^{\text{BH}}}{m} &\Leftrightarrow \hat{k}^{\text{BH}} \geq i \\ &\Leftrightarrow \exists j \geq i, p_{(j)} \leq \alpha \frac{j}{m} \\ &\Leftrightarrow \exists j \geq i, \frac{mp_{(j)}}{j} \leq \alpha \\ &\Leftrightarrow \min_{j \geq i} \frac{mp_{(j)}}{j} \leq \alpha \quad \square \end{aligned}$$

Benjamini-Hochberg procedure (BH)

- ▶ What about FDR control?

Theorem [Benjamini and Hochberg (1995)]

Assume that for all $P \in \mathfrak{F}$, the $(p_i)_{i \in \mathcal{H}_0}$ are independent, and they are independent from the $(p_i)_{i \in \mathcal{H}_1}$.

Then for all $P \in \mathfrak{F}$,

$$\text{FDR}\left(R^{\text{BH}}\right) \leq \alpha \frac{m_0}{m} \leq \alpha$$

Interlude

Step-up and step-down procedures

- Given a nondecreasing nonnegative sequence $\tau = (\tau_1, \dots, \tau_m)$, the respective step-up and step-down procedures associated with τ are:

$$\begin{aligned} R^{\text{SU}}(\tau) &= R(\tau_{\hat{k}^{\text{SU}}}) = \{i \in [1, m] : p_i \leq \tau_{\hat{k}^{\text{SU}}}\} \\ R^{\text{SD}}(\tau) &= R(\tau_{\hat{k}^{\text{SD}}}) = \{i \in [1, m] : p_i \leq \tau_{\hat{k}^{\text{SD}}}\} \end{aligned}$$

with

$$\begin{aligned} \hat{k}^{\text{SU}} &= \max \left\{ 0 \leq k \leq m : p_{(k)} \leq \tau_k \right\} \\ \hat{k}^{\text{SD}} &= \max \left\{ 0 \leq k \leq m : \forall k' \leq k, p_{(k')} \leq \tau_{k'} \right\} \end{aligned}$$

- Where we let $\tau_0 = \tau_1$ by convention
- So $\tau_k = \tau_{k \vee 1}$, $\forall 0 \leq k \leq m$
- Recall that $p_{(0)} = 0$ by convention too
- The τ_k are called the critical values
- The τ_k can be random as long as they stay nondecreasing nonnegative

Interlude

Step-up and step-down procedures

- ▶ With same proof as before:
 - ▶ $|R^{\text{SU}}(\tau)| = \hat{k}^{\text{SU}}$
 - ▶ $|R^{\text{SD}}(\tau)| = \hat{k}^{\text{SD}}$
- ▶ $R\left(\hat{t}_\alpha^{\text{Bonf}}\right) = R^{\text{SU}}(\tau) = R^{\text{SD}}(\tau)$ with $\tau_i = \frac{\alpha}{m}$
- ▶ $R\left(\hat{t}_\alpha^{k\text{-Bonf}}\right) = R^{\text{SU}}(\tau) = R^{\text{SD}}(\tau)$ with $\tau_i = \alpha \frac{k}{m}$
- ▶ $R\left(\hat{t}_\alpha^{\text{BH}}\right) = R^{\text{SU}}(\tau)$ with $\tau_i = \alpha \frac{i}{m}$
- ▶ Remark: for a fixed τ , $R^{\text{SU}}(\tau)$ is uniformly better than $R^{\text{SD}}(\tau)$, but sometimes SD allows FDR control for some larger τ than SU, see [Döhler, Durand, and Roquain (2018)] and the following

Benjamini-Hochberg procedure (BH)

Proof of the Theorem

- ▶ First lemma on SU procedures: let $i \in \llbracket 1, m \rrbracket$ and the SU procedure applied to all p -values except p_i , with
$$\tau^{-i} = (\tau_1^{-i}, \dots, \tau_{m-1}^{-i}) = (\tau_2, \dots, \tau_m)$$
- ▶ Let $p_{(1)}^{-i} \leq \dots \leq p_{(m-1)}^{-i}$ be the ordered p -values of this procedure
- ▶ Let $\hat{k}^{-i} = \max \left\{ k : p_{(k)}^{-i} \leq \tau_k^{-i} \right\}$ be the number of rejections of this procedure
- ▶ Then $\hat{k}^{-i} \geq \hat{k}^{\text{SU}} - 1$ and the three following assertions are equivalent:
 - (i) $p_i \leq \tau_{\hat{k}^{\text{SU}}}^{-i}$.
 - (ii) $p_i \leq \tau_{\hat{k}^{-i} + 1}^{-i}$.
 - (iii) $\hat{k}^{-i} = \hat{k}^{\text{SU}} - 1$.

Benjamini-Hochberg procedure (BH)

Proof of the first Lemma

- ▶ Assume $\hat{k}^{\text{SU}} \geq 2$, otherwise $\hat{k}^{-i} \geq \hat{k}^{\text{SU}} - 1$ is trivial
- ▶ Note that $p_{(\hat{k}^{\text{SU}}-1)}^{-i}$ is always equal to $p_{(\hat{k}^{\text{SU}}-1)}$ or $p_{(\hat{k}^{\text{SU}})}$, so $p_{(\hat{k}^{\text{SU}}-1)}^{-i} \leq \tau_{\hat{k}^{\text{SU}}} = \tau_{\hat{k}^{\text{SU}}-1}^{-i}$ and $\hat{k}^{-i} \geq \hat{k}^{\text{SU}} - 1$, by def of \hat{k}^{-i}
- ▶ (i) \Rightarrow (ii) τ nondecreasing and $\hat{k}^{\text{SU}} \leq \hat{k}^{-i} + 1$
- ▶ (ii) \Rightarrow (iii) By def of \hat{k}^{-i} , $p_{(1)}^{-i}, \dots, p_{(\hat{k}^{-i})}^{-i} \leq \tau_{\hat{k}^{-i}}^{-i} = \tau_{\hat{k}^{-i}+1}$. So if $p_i \leq \tau_{\hat{k}^{-i}+1}$, at least $\hat{k}^{-i} + 1$ p -values are $\leq \tau_{\hat{k}^{-i}+1}$, so $p_{(\hat{k}^{-i}+1)} \leq \tau_{\hat{k}^{-i}+1}$ and $\hat{k}^{\text{SU}} \geq \hat{k}^{-i} + 1$ by def of \hat{k}^{SU}
- ▶ (iii) \Rightarrow (i)
 - ▶ If $\hat{k}^{-i} = \hat{k}^{\text{SU}} - 1$ then $\tau_{\hat{k}^{\text{SU}}} = \tau_{\hat{k}^{-i}}^{-i}$
 - ▶ $p_{(\hat{k}^{-i}+1)}^{-i} > \tau_{(\hat{k}^{-i}+1)}^{-i} \geq \tau_{(\hat{k}^{-i})}^{-i} = \tau_{\hat{k}^{\text{SU}}}, \dots, p_{(m-1)}^{-i} > \tau_{\hat{k}^{\text{SU}}}$
 - ▶ $\Rightarrow m - 1 - \hat{k}^{-i} = m - \hat{k}^{\text{SU}}$ p -values that are not p_i are $> \tau_{\hat{k}^{\text{SU}}}$, there must be $m - \hat{k}^{\text{SU}}$ in total that are $> \tau_{\hat{k}^{\text{SU}}}$, hence $p_i \leq \tau_{\hat{k}^{\text{SU}}}$

□

Benjamini-Hochberg procedure (BH)

Proof of the Theorem

- ▶ Second lemma on SU procedures:

$$\{p_i \leq \tau_{\hat{k}^{\text{SU}}}, \hat{k}^{\text{SU}} = k\} = \{p_i \leq \tau_k, \hat{k}^{-i} = k - 1\}$$

- ▶ Decorrelates p_i and the rest of the p -values! Allows to use the independence assumption favorably

- ▶ Proof:

$$\begin{aligned} p_i \leq \tau_{\hat{k}^{\text{SU}}}, \hat{k}^{\text{SU}} = k &\iff p_i \leq \tau_{\hat{k}^{\text{SU}}}, \hat{k}^{-i} = \hat{k}^{\text{SU}} - 1, \hat{k}^{\text{SU}} = k & (i) \Rightarrow (iii) \\ &\iff p_i \leq \tau_{\hat{k}^{\text{SU}}}, \hat{k}^{-i} = k - 1 & (i) \Rightarrow (iii) \\ &\iff p_i \leq \tau_{\hat{k}^{-i} + 1}, \hat{k}^{-i} = k - 1 & (i) \Leftrightarrow (ii) \\ &\iff p_i \leq \tau_k, \hat{k}^{-i} = k - 1. \end{aligned}$$



Benjamini-Hochberg procedure (BH)

- ▶ Let $X \sim P \in \mathfrak{F}$
- ▶ For $i \in \mathcal{H}_0$ let \hat{k}^{-i} as in the Lemmas with $\tau = \left(\frac{\alpha k}{m} \right)_{k \in [1, m]}$

$$\begin{aligned}\text{FDR}\left(R^{\text{BH}}\right) &= \mathbb{E} \left[\frac{\sum_{i \in \mathcal{H}_0} \mathbb{1}_{\left\{ p_i \leq \alpha \frac{\hat{k}^{\text{BH}}}{m} \right\}}}{\hat{k}^{\text{BH}} \vee 1} \right] \\ &= \mathbb{E} \left[\sum_{k=1}^m \frac{1}{k} \sum_{i \in \mathcal{H}_0} \mathbb{1}_{\left\{ p_i \leq \alpha \frac{\hat{k}^{\text{BH}}}{m} \right\}} \mathbb{1}_{\left\{ \hat{k}^{\text{BH}} = k \right\}} \right] \\ &= \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \mathbb{P} \left(p_i \leq \alpha \frac{\hat{k}^{\text{BH}}}{m}, \hat{k}^{\text{BH}} = k \right) \\ &= \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \mathbb{P} \left(p_i \leq \alpha \frac{k}{m}, \hat{k}^{-i} = k - 1 \right) \\ &= \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \mathbb{P} \left(p_i \leq \alpha \frac{k}{m} \right) \mathbb{P} \left(\hat{k}^{-i} = k - 1 \right)\end{aligned}$$

Benjamini-Hochberg procedure (BH)

Proof of the Theorem

$$\begin{aligned}\text{FDR}\left(R^{\text{BH}}\right) &\leq \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \alpha \frac{k}{m} \mathbb{P}\left(\hat{k}^{-i} = k - 1\right) \\ &= \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \mathbb{P}\left(\hat{k}^{-i} = k - 1\right) \\ &= \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} 1 \\ &= \alpha \frac{m_0}{m} \quad \square\end{aligned}$$

- ▶ Note that the only inequality is an equality if $p_i \sim \mathcal{U}([0, 1])$ for all $i \in \mathcal{H}_0 \Rightarrow$ a stronger result when uniformity

Benjamini-Hochberg procedure (BH)

Can we do better than the independent case?

Some dependence conditions [Benjamini and Yekutieli (2001)][Blanchard and Roquain (2008)]

- ▶ $D \subseteq [0, 1]^m$ is nondecreasing if $(x_1, \dots, x_m) \in D$ and $x_i \leq y_i \forall i \in \llbracket 1, m \rrbracket$ imply $(y_1, \dots, y_m) \in D$
- ▶ Positive Regression Dependent on each one from a Subset (PRDS) : let $S \subseteq \llbracket 1, m \rrbracket$ the subset,

$$\forall D \subseteq [0, 1]^m \nearrow, \forall i \in S, \exists f_{i,D} \nearrow, \mathbb{P}(\boldsymbol{p} \in D | p_i) = f_{i,D}(p_i) \text{ a.s.}$$

- ▶ weak Positive Regression Dependent on each one from a Subset (wPRDS) : let $S \subseteq \llbracket 1, m \rrbracket$ the subset,

$$\forall D \subseteq [0, 1]^m \nearrow, \forall i \in S, g_{i,D} : u \mapsto \mathbb{P}(\boldsymbol{p} \in D | p_i \leq u)$$

is nondecreasing on $\{u \in [0, 1] : \mathbb{P}(p_i \leq u) > 0\}$

wPRDS is indeed weaker than PRDS

Proposition [Blanchard and Roquain (2008)]

If the p -values are PRDS on S , they are wPRDS on S .

- ▶ Fix D and $i \in S$ once and for all
- ▶ Notation: $\forall B \in \mathcal{A}, \mathbb{P}(B) > 0$, $\mathbb{P}_B : A \mapsto \mathbb{P}(A|B) = \frac{\mathbb{P}(A \cap B)}{\mathbb{P}(B)}$ and $\mathbb{P}_u = \mathbb{P}_{\{p_i \leq u\}}$, $\forall u \in [0, 1] : \mathbb{P}(p_i \leq u) > 0$
- ▶ Likewise, \mathbb{E}_B and \mathbb{E}_u
- ▶ 2 lemmas:
 - ▶ $\mathbb{P}_B \ll \mathbb{P}$ and $\frac{d\mathbb{P}_B}{d\mathbb{P}} : \omega \mapsto \frac{\mathbb{1}_B(\omega)}{\mathbb{P}(B)}$
 - ▶ $\mathbb{P}_u(p \in D|p_i) = \mathbb{P}(p \in D|p_i) = f_{i,D}(p_i)$ a.s.
 - ▶ (The second one is also true if conditioning on $B \in \sigma(p_i)$ instead of $\{p_i \leq u\}$)

wPRDS is indeed weaker than PRDS

Proof of first Lemma

$$\begin{aligned}\mathbb{P}_B(A) &= \frac{\mathbb{P}(A \cap B)}{\mathbb{P}(B)} \\ &= \int \frac{\mathbb{1}_{A \cap B}(\omega)}{\mathbb{P}(B)} d\mathbb{P}(\omega) \\ &= \int \mathbb{1}_A(\omega) \frac{\mathbb{1}_B(\omega)}{\mathbb{P}(B)} d\mathbb{P}(\omega) \quad \square\end{aligned}$$

wPRDS is indeed weaker than PRDS

Proof of second Lemma

- $\mathbb{P}_u(\mathbf{p} \in D | p_i) = \mathbb{E}_u [\mathbb{1}_{\{\mathbf{p} \in D\}} | p_i]$ and $\mathbb{P}(\mathbf{p} \in D | p_i) = \mathbb{E} [\mathbb{1}_{\{\mathbf{p} \in D\}} | p_i]$
- Let X $\sigma(p_i)$ -measurable

$$\begin{aligned}\mathbb{E}_u [X \mathbb{1}_{\{\mathbf{p} \in D\}}] &= \int X(\omega) \mathbb{1}_{\{\mathbf{p} \in D\}}(\omega) d\mathbb{P}_u(\omega) \\&= \int X(\omega) \mathbb{1}_{\{\mathbf{p} \in D\}}(\omega) \frac{\mathbb{1}_{\{p_i \leq u\}}(\omega)}{\mathbb{P}(p_i \leq u)} d\mathbb{P}(\omega) \\&= \mathbb{E} \left[X \frac{\mathbb{1}_{\{p_i \leq u\}}}{\mathbb{P}(p_i \leq u)} \mathbb{1}_{\{\mathbf{p} \in D\}} \right] \\&= \mathbb{E} \left[X \frac{\mathbb{1}_{\{p_i \leq u\}}}{\mathbb{P}(p_i \leq u)} f_{i,D}(p_i) \right] \left(X \frac{\mathbb{1}_{\{p_i \leq u\}}}{\mathbb{P}(p_i \leq u)} \text{ } \sigma(p_i)\text{-measurable} \right) \\&= \int X(\omega) f_{i,D}(p_i(\omega)) \frac{\mathbb{1}_{\{p_i \leq u\}}(\omega)}{\mathbb{P}(p_i \leq u)} d\mathbb{P}(\omega) \\&= \int X(\omega) f_{i,D}(p_i(\omega)) d\mathbb{P}_u(\omega) \\&= \mathbb{E}_u [X f_{i,D}(p_i)] \quad \square\end{aligned}$$

wPRDS is indeed weaker than PRDS

Proof of the proposition

- ▶ Let $u < u'$ with $\mathbb{P}(p_i \leq u) > 0$

$$g_{i,D}(u') = \mathbb{P}_{u'}(\mathbf{p} \in D)$$

$$= \mathbb{E}_{u'} \left[\mathbb{1}_{\{\mathbf{p} \in D\}} \right]$$

$$= \mathbb{E}_{u'} \left[\mathbb{E}_{u'} \left[\mathbb{1}_{\{\mathbf{p} \in D\}} \mid p_i \right] \right]$$

$$= \mathbb{E}_{u'} [\mathbb{P}_{u'}(\mathbf{p} \in D | p_i)]$$

$$= \mathbb{E}_{u'} [f_{i,D}(p_i)]$$

$$= \int f_{i,D}(p_i(\omega)) \frac{\mathbb{1}_{\{p_i \leq u'\}}(\omega)}{\mathbb{P}(p_i \leq u')} d\mathbb{P}(\omega)$$

$$= \int f_{i,D}(p_i(\omega)) \frac{\mathbb{1}_{\{p_i \leq u\}}(\omega)}{\mathbb{P}(p_i \leq u')} d\mathbb{P}(\omega) + \int f_{i,D}(p_i(\omega)) \frac{\mathbb{1}_{\{u < p_i \leq u'\}}(\omega)}{\mathbb{P}(p_i \leq u')} d\mathbb{P}(\omega)$$

wPRDS is indeed weaker than PRDS

Proof of the proposition

- Let $\gamma = \mathbb{P}_{u'}(p_i \leq u) = \frac{\mathbb{P}(p_i \leq u)}{\mathbb{P}(p_i \leq u')} \in]0, 1]$

$$\begin{aligned} \int f_{i,D}(p_i(\omega)) \frac{\mathbb{1}_{\{p_i \leq u\}}(\omega)}{\mathbb{P}(p_i \leq u')} d\mathbb{P}(\omega) &= \gamma \int f_{i,D}(p_i(\omega)) \frac{\mathbb{1}_{\{p_i \leq u\}}(\omega)}{\mathbb{P}(p_i \leq u)} d\mathbb{P}(\omega) \\ &= \gamma g_{i,D}(u) \end{aligned}$$

- If $\gamma = 1 \Leftrightarrow \mathbb{P}(u < p_i \leq u') = 0$ then $g_{i,D}(u') = g_{i,D}(u)$
- Else,

$$\begin{aligned} \int f_{i,D}(p_i(\omega)) \frac{\mathbb{1}_{\{u < p_i \leq u'\}}(\omega)}{\mathbb{P}(p_i \leq u')} d\mathbb{P}(\omega) &= \frac{\mathbb{P}(u < p_i \leq u')}{\mathbb{P}(p_i \leq u')} \int f_{i,D}(p_i(\omega)) \frac{\mathbb{1}_{\{u < p_i \leq u'\}}(\omega)}{\mathbb{P}(u < p_i \leq u')} d\mathbb{P}(\omega) \\ &= (1 - \gamma) \int f_{i,D}(p_i(\omega)) \frac{\mathbb{1}_{\{u < p_i \leq u'\}}(\omega)}{\mathbb{P}(u < p_i \leq u')} d\mathbb{P}(\omega) \\ &= (1 - \gamma) \mathbb{E}_{\{u < p_i \leq u'\}} [f_{i,D}(p_i)] \end{aligned}$$

wPRDS is indeed weaker than PRDS

Proof of the proposition

- ▶ $g_{i,D}(u') = \gamma g_{i,D}(u) + (1 - \gamma) \mathbb{E}_{\{u < p_i \leq u'\}} [f_{i,D}(p_i)]$
- ▶ $f_{i,D} \nearrow$ so:
 $\mathbb{E}_{\{u < p_i \leq u'\}} [f_{i,D}(p_i)] \geq f_{i,D}(u) \geq \mathbb{E}_{\{p_i \leq u\}} [f_{i,D}(p_i)] = g_{i,D}(u)$ □

What is wPRDS?

Proposition [Giraud (2021)]

Assume that for all $P \in \mathfrak{F}$, the $(p_i)_{i \in \mathcal{H}_0}$ are independent, and they are independent from the $(p_i)_{i \in \mathcal{H}_1}$.

Then, for all $P \in \mathfrak{F}$, the (p_i) are wPRDS with \mathcal{H}_0 as the subset.

- ▶ Other examples in [Benjamini and Yekutieli (2001)], [Roquain (2015)], [Giraud (2021)]
 - ▶ Like one-sided Gaussian p -values with $\Sigma_{ij} \geq 0 \forall 1 \leq i, j \leq m$
 - ▶ Or with $\Sigma = \rho \mathbf{1}_m \mathbf{1}_m^\top + (1 - \rho) \text{Id}_m, \rho \in \left[-\frac{1}{m-1}, 1\right]$

What is wPRDS?

Proof of the Proposition

- Fix $P \in \mathfrak{F}$, D nondecreasing and $i \in \mathcal{H}_0$
- Key point: p_i is independent from $(p_1, \dots, p_{i-1}, p_{i+1}, \dots, p_m)$ so for appropriate u :

$$\begin{aligned}\mathbb{P}(\boldsymbol{p} \in D | p_i \leq u) &= \frac{\mathbb{P}(\boldsymbol{p} \in D \text{ and } p_i \leq u)}{\mathbb{P}(p_i \leq u)} = \frac{\mathbb{E}[\mathbb{1}_{\{\boldsymbol{p} \in D\}} \mathbb{1}_{\{p_i \leq u\}}]}{\mathbb{P}(p_i \leq u)} \\ &= \int \mathbb{1}_{(x_1, \dots, x_{i-1}, x_i, x_{i+1}, \dots, x_m) \in D} \frac{\mathbb{1}_{x_i \leq u}}{\mathbb{P}(p_i \leq u)} d\mathbb{P}_{\boldsymbol{p}}(x_1, \dots, x_{i-1}, x_i, x_{i+1}, \dots, x_m)\end{aligned}$$

(transfer formula)

$$= \int \mathbb{1}_{(x_1, \dots, x_{i-1}, x_i, x_{i+1}, \dots, x_m) \in D} \frac{\mathbb{1}_{x_i \leq u}}{\mathbb{P}(p_i \leq u)} d\mathbb{P}_{p_i}(x_i) d\mathbb{P}_{\boldsymbol{p}_{-i}}(x_1, \dots, x_{i-1}, x_{i+1}, \dots, x_m)$$

(key observation)

$$= \int \mathbb{P}((x_1, \dots, x_{i-1}, p_i, x_{i+1}, \dots, x_m) \in D | p_i \leq u) d\mathbb{P}_{\boldsymbol{p}_{-i}}(x_1, \dots, x_{i-1}, x_{i+1}, \dots, x_m)$$

(Fubini) with $\mathbb{P}_{\boldsymbol{p}}$ the law of \boldsymbol{p} , $\mathbb{P}_{p_i} = \mathcal{L}(p_i)$ the law of p_i and $\mathbb{P}_{\boldsymbol{p}_{-i}}$ the law of $\boldsymbol{p}_{-i} = (p_1, \dots, p_{i-1}, p_{i+1}, \dots, p_m)$

What is wPRDS?

Proof of the Proposition

- ▶ \Rightarrow only need to show that
 $u \mapsto \mathbb{P}((x_1, \dots, x_{i-1}, p_i, x_{i+1}, \dots, x_m) \in D | p_i \leq u)$ nondecreasing for
any fixed $(x_1, \dots, x_{i-1}, x_{i+1}, \dots, x_m)$
- ▶ $= \mathbb{E}_u [g(p_i)]$ with $g : x_i \mapsto \mathbb{1}_{\{(x_1, \dots, x_{i-1}, x_i, x_{i+1}, \dots, x_m) \in D\}}$ nondecreasing
because D is
- ▶ same proof as before for proving that $u \mapsto \mathbb{E}_u [f_{i,D}(p_i)]$ was
nondecreasing

□

Benjamini-Hochberg procedure (BH)

Can we do better than the independent case?

Theorem [Benjamini and Yekutieli (2001)]

Assume that for all $P \in \mathfrak{F}$, the (p_i) are wPRDS with \mathcal{H}_0 as the subset.
Then for all $P \in \mathfrak{F}$,

$$\text{FDR}\left(R^{\text{BH}}\right) \leq \alpha \frac{m_0}{m} \leq \alpha$$

- ▶ Previous Theorem is not useless because of:
 - ▶ the equality case
 - ▶ the proof ideas (and Lemmas) that are reused in more complex procedures [Roquain and Wiel (2009)], [Döhler, Durand, and Roquain (2018)]

Benjamini-Hochberg procedure (BH)

Proof of the Theorem

- As before,

$$\begin{aligned}\text{FDR}\left(R^{\text{BH}}\right) &= \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \mathbb{P}\left(p_i \leq \alpha \frac{\hat{k}^{\text{BH}}}{m}, \hat{k}^{\text{BH}} = k\right) \\ &= \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \mathbb{P}\left(p_i \leq \alpha \frac{k}{m}, \hat{k}^{\text{BH}} = k\right) \\ &= \sum_{i \in \mathcal{H}_0} \sum_{k=k_i}^m \frac{1}{k} \mathbb{P}_{\alpha \frac{k}{m}}\left(\hat{k}^{\text{BH}} = k\right) \mathbb{P}\left(p_i \leq \alpha \frac{k}{m}\right) \\ &\leq \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} \sum_{k=k_i}^m \mathbb{P}_{\alpha \frac{k}{m}}\left(\hat{k}^{\text{BH}} = k\right)\end{aligned}$$

with $k_i = \min \left\{ k \in [\![1, m]\!]: \mathbb{P}\left(p_i \leq \alpha \frac{k}{m}\right) > 0 \right\}$, for all $i \in \mathcal{H}_0$ ($k_i = +\infty$ and empty sum = 0 if empty set)

Benjamini-Hochberg procedure (BH)

Proof of the Theorem

$$\begin{aligned}\text{FDR}\left(R^{\text{BH}}\right) &\leq \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} \sum_{k=k_i}^m \left(\mathbb{P}_{\alpha \frac{k}{m}} \left(\hat{k}^{\text{BH}} \leq k \right) - \mathbb{P}_{\alpha \frac{k}{m}} \left(\hat{k}^{\text{BH}} \leq k-1 \right) \right) \\ &\leq \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} \sum_{k=k_i}^m \left(\mathbb{P}_{\alpha \frac{k+1}{m}} \left(\hat{k}^{\text{BH}} \leq k \right) - \mathbb{P}_{\alpha \frac{k}{m}} \left(\hat{k}^{\text{BH}} \leq k-1 \right) \right) \\ &\leq \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} \mathbb{P}_{\alpha \frac{m+1}{m}} \left(\hat{k}^{\text{BH}} \leq m \right) \\ &\leq \alpha \frac{m_0}{m} \leq \alpha\end{aligned}$$

by wPRDS: $\forall k \in \mathbb{N}, \{\hat{k}^{\text{BH}} \leq k\} = \{\boldsymbol{p} \in D\}$ with D the preimage of $]-\infty, k]$ under the function that maps \boldsymbol{p} to \hat{k}^{BH} which is coordinate-wise nonincreasing, hence D is nondecreasing □

Step-up procedures

Can we go even beyond, to any dependency?

Theorem [Giraud (2021)]

Let $\tau = (\tau_1, \dots, \tau_m)$ a nondecreasing nonnegative sequence and consider the step-up procedure associated with τ .

Then for all $P \in \mathfrak{F}$,

$$\text{FDR} \left(R^{\text{SU}}(\tau) \right) \leq m_0 \sum_{j \geq 1} \frac{\tau_{j \wedge m}}{j(j+1)}$$

Step-up procedures

Proof of the Theorem

- As before,

$$\begin{aligned}\text{FDR} \left(R^{\text{SU}}(\tau) \right) &= \mathbb{E} \left[\frac{\sum_{i \in \mathcal{H}_0} \mathbb{1}_{\{p_i \leq \tau_{k^{\text{SU}}}^{\text{SU}}\}}}{\hat{k}^{\text{SU}} \vee 1} \right] \\ &= \sum_{i \in \mathcal{H}_0} \mathbb{E} \left[\mathbb{1}_{\{p_i \leq \tau_{k^{\text{SU}}}^{\text{SU}}\}} \frac{1}{\hat{k}^{\text{SU}} \vee 1} \right]\end{aligned}$$

- For $k \geq 1$,
 $\frac{1}{k} = \frac{1}{k} - \frac{1}{k+1} + \frac{1}{k+1} - \frac{1}{k+2} + \cdots = \sum_{j \geq k} \frac{1}{j(j+1)} = \sum_{j \geq 1} \frac{\mathbb{1}_{j \geq k}}{j(j+1)}$ so

$$\text{FDR} \left(R^{\text{SU}}(\tau) \right) = \sum_{i \in \mathcal{H}_0} \mathbb{E} \left[\mathbb{1}_{\{p_i \leq \tau_{k^{\text{SU}}}^{\text{SU}}\}} \sum_{j \geq 1} \frac{\mathbb{1}_{j \geq \hat{k}^{\text{SU}} \geq 1}}{j(j+1)} \right]$$

Step-up procedures

Proof of the Theorem

- By Fubini,

$$\begin{aligned}\text{FDR} \left(R^{\text{SU}}(\tau) \right) &= \sum_{i \in \mathcal{H}_0} \sum_{j \geq 1} \mathbb{E} \left[\mathbb{1}_{\{p_i \leq \tau_{\hat{k}^{\text{SU}}}^j\}} \frac{\mathbb{1}_{j \geq \hat{k}^{\text{SU}} \geq 1}}{j(j+1)} \right] \\ &\leq \sum_{i \in \mathcal{H}_0} \sum_{j \geq 1} \mathbb{E} \left[\mathbb{1}_{\{p_i \leq \tau_{j \wedge m}\}} \frac{\mathbb{1}_{j \geq \hat{k}^{\text{SU}} \geq 1}}{j(j+1)} \right] \\ &\leq \sum_{i \in \mathcal{H}_0} \sum_{j \geq 1} \frac{1}{j(j+1)} \mathbb{E} \left[\mathbb{1}_{\{p_i \leq \tau_{j \wedge m}\}} \right] \\ &\leq \sum_{i \in \mathcal{H}_0} \sum_{j \geq 1} \frac{\tau_{j \wedge m}}{j(j+1)} = m_0 \sum_{j \geq 1} \frac{\tau_{j \wedge m}}{j(j+1)} \quad \square\end{aligned}$$

Benjamini-Yekutieli procedure (BY)

FDR control under any dependency

- The Benjamini-Yekutieli procedure (BY) is the step-up procedure using $\tau_k = \frac{\alpha k}{mH_m}$, $H_m = \sum_{j=1}^m \frac{1}{j}$: uniformly worst than BH
- $R^{BY} = R^{SU} \left(\left(\frac{\alpha k}{mH_m} \right)_{k \in [1, m]} \right)$
- Adjusted p -values : $p_{(i)}^{adj} = 1 \wedge \min_{j \geq i} \frac{mH_m p_{(j)}}{j}$

Corollary [Benjamini and Yekutieli (2001)]

For all $P \in \mathfrak{F}$,

$$\text{FDR}(R^{BY}) \leq \alpha \frac{m_0}{m} \leq \alpha$$

$$\begin{aligned} m_0 \sum_{j \geq 1} \frac{\tau_{j \wedge m}}{j(j+1)} &= \frac{\alpha m_0}{m H_m} \left(\sum_{j=1}^{m-1} \frac{1}{j+1} + m \sum_{j=m}^{\infty} \frac{1}{j(j+1)} \right) \\ &= \frac{\alpha m_0}{m H_m} \left(\sum_{j=2}^m \frac{1}{j} + m \frac{1}{m} \right) = \frac{\alpha m_0}{m H_m} H_m \quad \square \end{aligned}$$

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Adaptivity to π_0

- ▶ $\pi_0 = \frac{m_0}{m}$
- ▶ Previous guarantees hold with “oracle” versions of the procedures using $m_0 = |\mathcal{H}_0|$ instead of m (\Leftrightarrow using $\frac{\alpha}{\pi_0}$ instead of α)
- ▶ Ex: “oracle” Bonferroni: $\mathbb{P}(\exists i, i \in \mathcal{H}_0 : p_i \leq \frac{\alpha}{m_0}) \leq \alpha$
- ▶ Ex: “oracle BH”, SU with $\tau_k = \frac{\alpha k}{m_0}$
- ▶ ⇒ Core idea: estimate m_0 or π_0 and somehow plug \hat{m}_0 or $\hat{\pi}_0$ in the procedure

Holm-Bonferroni procedure (HB)

[Holm (1979)]

- ▶ Core idea: if $p_{(1)} \leq \frac{\alpha}{m}$, $(1) \in \mathcal{H}_1$, $m_0 \leq m - 1$, and we could re-apply Bonferroni but with $m - 1$ instead of m
- ▶ Repeat this sequentially until stop
- ▶ This formalizes as a SD procedure with $\tau_k = \frac{\alpha}{m-k+1}$
- ▶ $R^{\text{HB}} = R^{\text{SD}} \left(\left(\frac{\alpha}{m-k+1} \right)_{k \in \llbracket 1, m \rrbracket} \right) = R \left(\frac{\alpha}{m-\hat{k}^{\text{HB}}+1} \right)$
- ▶ $\hat{k}^{\text{HB}} = \max \left\{ k \in \llbracket 0, m \rrbracket : \forall k' \leq k, p_{(k')} \leq \frac{\alpha}{m-k'+1} \right\}$
- ▶ Implicit estimation of m_0 by $\hat{m}_0 = m \wedge (m - \hat{k}^{\text{HB}} + 1)$
- ▶ Adjusted p -values : $p_{(i)}^{\text{adj}} = 1 \wedge \max_{j \leq i} (m - j + 1) p_{(j)}$
- ▶ Uniformly rejects more than Bonferroni

Holm-Bonferroni procedure (HB)

FWER control under any dependency

Theorem [Holm (1979)]

For all $P \in \mathfrak{F}$,

$$\text{FWER}(R^{\text{HB}}) \leq \alpha$$

- ▶ \Rightarrow HB has same guarantees than Bonferroni (and is almost as easy, computationally) \Rightarrow Bonferroni should never be used [Aickin and Gensler (1996)]

Holm-Bonferroni procedure (HB)

Proof of the Theorem

- ▶ As discussed before, $\text{FWER} \left(R \left(\frac{\alpha}{m_0} \right) \right) \leq \alpha$ so
$$\mathbb{P} \left(\left| R \left(\frac{\alpha}{m_0} \right) \cap \mathcal{H}_0 \right| = 0 \right) \geq 1 - \alpha$$
- ▶ Assume that $\left| R \left(\frac{\alpha}{m_0} \right) \cap \mathcal{H}_0 \right| = 0$ holds ($\Leftrightarrow R \left(\frac{\alpha}{m_0} \right) \subseteq \mathcal{H}_1$)
- ▶ If $\hat{k}^{\text{HB}} = 0$ then $V \left(R^{\text{HB}} \right) = 0$, so assume that $\hat{k}^{\text{HB}} \geq 1$
- ▶ By recursion, $\forall k \leq \hat{k}^{\text{HB}}$, $m_0 \leq m - k + 1$, $k = 1$ obvious, assume it is true for $k < \hat{k}^{\text{HB}}$

Holm-Bonferroni procedure (HB)

Proof of the Theorem

- ▶ For all $k' \leq k$ we have:

$$p(k') \leq p(k) \leq \frac{\alpha}{m - k + 1} \leq \frac{\alpha}{m_0},$$

- ▶ So $\left| R\left(\frac{\alpha}{m_0}\right) \right| \geq k$ so $|\mathcal{H}_1| \geq k$ so $m_0 = |\mathcal{H}_0| \leq m - k$ which ends the recursion
- ▶ So $\left| R\left(\frac{\alpha}{m_0}\right) \cap \mathcal{H}_0 \right| = 0 \Rightarrow R^{\text{HB}} \subseteq R\left(\frac{\alpha}{m_0}\right) \subseteq \mathcal{H}_1 \Rightarrow \left| R^{\text{HB}} \cap \mathcal{H}_0 \right| = 0$
- ▶ $\Rightarrow \text{FWER}\left(R^{\text{HB}}\right) \leq \text{FWER}\left(R\left(\frac{\alpha}{m_0}\right)\right) \leq \alpha$ □

Holm-Bonferroni procedure (HB)

Need for step-down

- ▶ What about the step-up procedure with same critical values?
- ▶ $m = 2$, $\mathcal{H}_0 = \llbracket 1, m \rrbracket$:
$$\text{FWER} \left(R^{SU} \left(\left(\frac{\alpha}{2}, \alpha \right) \right) \right) = \mathbb{P} \left(p_{(1)} \leq \frac{\alpha}{2} \text{ or } p_{(2)} \leq \alpha \right)$$
- ▶ $p_1 = p \sim \mathcal{U}([0, 1])$ and $p_2 = 1 - p$: extreme negative correlation
- ▶ $\text{FWER} \left(R^{SU} \left(\left(\frac{\alpha}{2}, \alpha \right) \right) \right) = \mathbb{P} \left(p_{(1)} \leq \frac{\alpha}{2} \text{ or } 1 - \alpha \leq p_{(1)} \right)$
- ▶ $\mathcal{L} \left(p_{(1)} \right) = \mathcal{U} \left(\left[0, \frac{1}{2} \right] \right)$: $\forall x \in \left[0, \frac{1}{2} \right]$,

$$\begin{aligned}\mathbb{P} \left(p_{(1)} \leq x \right) &= \mathbb{P} \left(\left(p \leq x \text{ and } p \leq \frac{1}{2} \right) \text{ or } \left(1 - p \leq x \text{ and } p \geq \frac{1}{2} \right) \right) \\ &= \mathbb{P} \left(p \leq x \wedge \frac{1}{2} \right) + \mathbb{P} \left(p \geq (1 - x) \vee \frac{1}{2} \right) \\ &= \mathbb{P} (p \leq x) + \mathbb{P} (p \geq 1 - x) \\ &= \mathbb{P} (p \leq x) + \mathbb{P} (p \geq 1 - x) = 2x\end{aligned}$$

Holm-Bonferroni procedure (HB)

Need for step-down

- ▶ If $\frac{\alpha}{2} \leq 1 - \alpha \Leftrightarrow \alpha \leq \frac{2}{3}$, $\text{FWER}\left(R^{SU}\left((\frac{\alpha}{2}, \alpha)\right)\right) = \mathbb{P}\left(p_{(1)} \leq \frac{\alpha}{2}\right) + \mathbb{P}\left(1 - \alpha \leq p_{(1)}\right) = \alpha + \mathbb{P}\left(1 - \alpha \leq p_{(1)}\right)$
- ▶ $\mathbb{P}\left(1 - \alpha \leq p_{(1)}\right) = 0$ if $\alpha \leq \frac{1}{2}$,
 $= 1 - \mathbb{P}\left(1 - \alpha \geq p_{(1)}\right) = 1 - 2(1 - \alpha) = 2\alpha - 1$ if $\alpha \geq \frac{1}{2}$
- ▶ If $\alpha \geq \frac{2}{3}$, $\text{FWER}\left(R^{SU}\left((\frac{\alpha}{2}, \alpha)\right)\right) = 1$

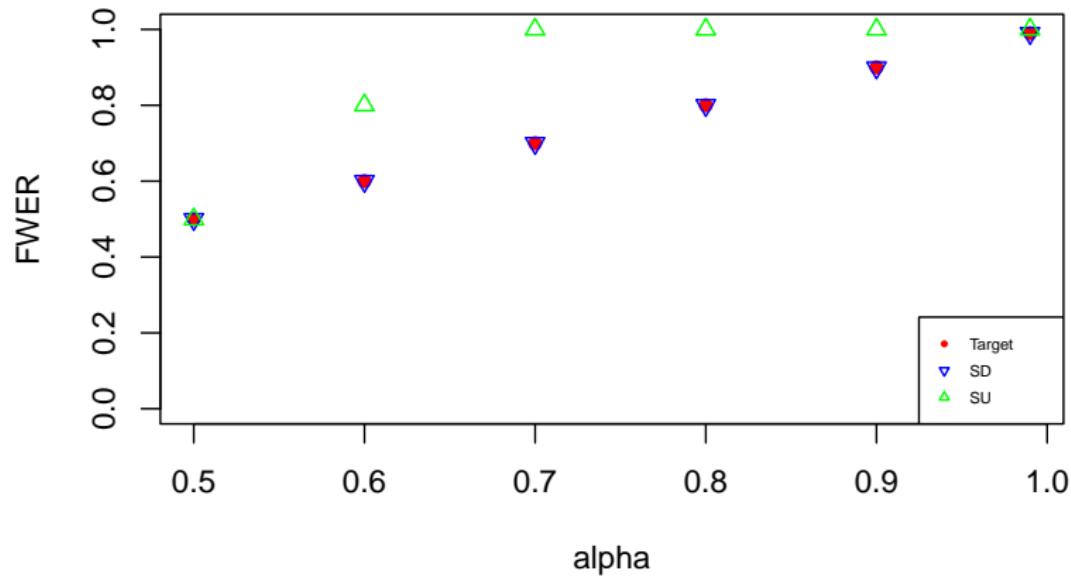
$$\Rightarrow \text{FWER}\left(R^{SU}\left(\left(\frac{\alpha}{2}, \alpha\right)\right)\right) = \begin{cases} \alpha & \text{if } \alpha \in \left[0, \frac{1}{2}\right] \\ 3\alpha - 1 & \text{if } \alpha \in \left[\frac{1}{2}, \frac{2}{3}\right] \\ 1 & \text{if } \alpha \in \left[\frac{2}{3}, 1\right] \end{cases}$$

- ▶ Remark: for this model, FWER is saturated for Bonf and HB:
 $\text{FWER}\left(R^{\text{Bonf}}\right) = \text{FWER}\left(R^{\text{HB}}\right) = \mathbb{P}\left(p_{(1)} \leq \frac{\alpha}{2}\right) = \alpha$

Holm-Bonferroni procedure (HB)

$2 \cdot 10^5$ replications

Target level vs estimated FWER of SU and SD Holm



Storey-BH

Adaptive FDR control

- ▶ [Storey, Taylor, and Siegmund (2004)]
- ▶ Fix $\lambda \in]0, 1[$, $\hat{m}_0 = \frac{\sum_{i=1}^m \mathbb{1}_{\{p_i > \lambda\}} + 1}{1 - \lambda} = \frac{m - |R(\lambda)| + 1}{1 - \lambda}$
- ▶ Idea : large p -values are mostly null, and nulls are super-uniform, so $\sum_{i=1}^m \mathbb{1}_{\{p_i > \lambda\}} \approx \sum_{i=1}^{m_0} \mathbb{1}_{\{p_i > \lambda\}} \gtrsim (1 - \lambda)m_0$
- ▶ “+1” for $\hat{m}_0 > 0$ and for technical reasons
- ▶ Storey-BH is the SU procedure with $\tau_k = \min \left(\alpha \frac{k}{\hat{m}_0}, \lambda \right)$, $k \geq 1$ (recall $\tau_0 = \tau_1$ so that $\tau_k = \tau_{k \vee 1}$)
- ▶ $\hat{k}^{\text{St-BH}} = \max \left\{ k \in [\![0, m]\!]: p_{(k)} \leq \min \left(\alpha \frac{k \vee 1}{\hat{m}_0}, \lambda \right) \right\}$
- ▶ $\hat{t}_\alpha^{\text{St-BH}} = \tau_{\hat{k}^{\text{St-BH}}} = \min \left(\alpha \frac{\hat{k}^{\text{St-BH}} \vee 1}{\hat{m}_0}, \lambda \right)$, $R^{\text{St-BH}} = R \left(\hat{t}_\alpha^{\text{St-BH}} \right)$
- ▶ $\min(\cdot, \lambda)$ above to avoid overfitting: you don't look at the same p -values for estimating m_0 and for rejecting hypotheses
- ▶ Up to this, Storey-BH is BH but with \hat{m}_0 instead of m

Storey-BH

- ▶ As before, a link with FDP estimation:
- ▶ $\widehat{\text{FDP}}^{\text{St-BH}}(t) = \frac{\hat{m}_0 t}{|R(t)| \vee 1}$ if $t \leq \lambda$, $= 1$ if $t > \lambda$
- ▶ $\hat{t}_\alpha^{\text{St-heur}} = \sup \left\{ t \in [0, 1] : \widehat{\text{FDP}}^{\text{St-BH}}(t) \leq \alpha \right\} = \sup \left\{ t \in [0, 1] : \widehat{G}_\lambda(t) \geq t \right\}$ with $\widehat{G}_\lambda(t) = \frac{\alpha}{\hat{m}_0} (|R(t)| \vee 1) \wedge \lambda$

Lemma

$$\hat{t}_\alpha^{\text{St-heur}} = \hat{t}_\alpha^{\text{St-BH}}$$

Storey-BH

Proof of the Lemma

- ▶ Similar to before, supremum well-defined, and $\widehat{G}_\lambda(t)$ nondecreasing and $[0, 1] \rightarrow [0, 1] \Rightarrow \hat{t}_\alpha^{St\text{-}heur}$ is a max and $\hat{t}_\alpha^{St\text{-}heur} = \widehat{G}_\lambda(\hat{t}_\alpha^{St\text{-}heur})$
- ▶ Remember that $p_{(|R(t)|)} \leq t$ and note that, here, $\widehat{G}_\lambda(t) = \tau_{|R(t)|}$, combine this:

$$p_{(|R(\hat{t}_\alpha^{St\text{-}heur})|)} \leq \hat{t}_\alpha^{St\text{-}heur} = \widehat{G}_\lambda(\hat{t}_\alpha^{St\text{-}heur}) = \tau_{|R(\hat{t}_\alpha^{St\text{-}heur})|}$$

$$\Rightarrow |R(\hat{t}_\alpha^{St\text{-}heur})| \leq \hat{k}^{St\text{-}BH}$$

$$\Rightarrow \hat{t}_\alpha^{St\text{-}heur} = \widehat{G}_\lambda(\hat{t}_\alpha^{St\text{-}heur}) = \tau_{|R(\hat{t}_\alpha^{St\text{-}heur})|} \leq \tau_{\hat{k}^{St\text{-}BH}}$$

Storey-BH

Proof of the Lemma

- ▶ Conversely, using that $|R(\tau_{\hat{k}^{\text{St-BH}}})| = \hat{k}^{\text{St-BH}}$ (property of SU),

$$\widehat{G}_\lambda(\tau_{\hat{k}^{\text{St-BH}}}) = \frac{\alpha}{\hat{m}_0} (|R(\tau_{\hat{k}^{\text{St-BH}}})| \vee 1) \wedge \lambda = \alpha \frac{\hat{k}^{\text{St-BH}} \vee 1}{\hat{m}_0} \wedge \lambda = \tau_{\hat{k}^{\text{St-BH}}}$$

- ▶ So $\tau_{\hat{k}^{\text{St-BH}}} \leq \hat{t}_\alpha^{\text{St-heur}}$ by definition of $\hat{t}_\alpha^{\text{St-heur}}$

□

Storey-BH

FDR control

Theorem [Storey, Taylor, and Siegmund (2004)]

Assume that for all $P \in \mathfrak{F}$, the $(p_i)_{i \in \mathcal{H}_0}$ are independent and $\sim \mathcal{U}([0, 1])$, and they are independent from the $(p_i)_{i \in \mathcal{H}_1}$.

Then for all $P \in \mathfrak{F}$,

$$\text{FDR}\left(R^{\text{St-BH}}\right) \leq \alpha(1 - \lambda^{m_0}) \leq \alpha$$

- ▶ Proof by martingale techniques: the stochastic process is important
- ▶ Need true uniformity under \mathcal{H}_0 !

Three Lemmas

- ▶ $V(R(t)) \sim \mathcal{B}(m_0, t)$ for all $t \in [0, 1]$
- ▶ The process $\left(\frac{V(R(t))}{t}\right)_{t \in]0,1]}$ is a reverse-time martingale w.r.t. the filtration $(\mathcal{F}_t)_{t \in]0,1]}$ with $\mathcal{F}_t = \sigma\left(\left(\mathbb{1}_{\{p_i \leq t'\}}\right)_{i \in [\![1, m]\!], t \leq t' \leq 1}\right)$, $t \in [0, 1]$
- ▶ $\hat{t}_\alpha^{\text{St-BH}}$ is a stopping time (in reverse) w.r.t. $(\mathcal{F}_t)_{t \in [0,1]}$

Storey-BH

Proof of the First Lemma

- ▶ $V(R(t)) = \sum_{i \in \mathcal{H}_0} \mathbb{1}_{\{p_i \leq t\}}$
- ▶ $\mathbb{1}_{\{p_i \leq t\}}, i \in \mathcal{H}_0$, are i.i.d. $\sim \mathcal{B}(t)$

□

Storey-BH

Proof of the Second Lemma

- We want to prove that for $0 < s \leq t$, $\mathbb{E} \left[\frac{V(R(s))}{s} \middle| \mathcal{F}_t \right] = \frac{V(R(t))}{t}$
- $\mathbb{E}[V(R(s))|\mathcal{F}_t] = \sum_{i \in \mathcal{H}_0} \mathbb{E} \left[\mathbf{1}_{\{p_i \leq s\}} \middle| \mathcal{F}_t \right]$ so proving $\frac{\mathbb{E} \left[\mathbf{1}_{\{p_i \leq s\}} \middle| \mathcal{F}_t \right]}{s} = \frac{\mathbf{1}_{\{p_i \leq t\}}}{t}$ for $i \in \mathcal{H}_0$ is sufficient
- By independence, for $i \in \mathcal{H}_0$,

$$\begin{aligned}\mathbb{E} \left[\mathbf{1}_{\{p_i \leq s\}} \middle| \mathcal{F}_t \right] &= \mathbb{E} \left[\mathbf{1}_{\{p_i \leq s\}} \middle| \sigma \left(\left(\mathbf{1}_{\{p_j \leq t'\}} \right)_{j \in [\![1, m]\!], t \leq t' \leq 1} \right) \right] \\ &= \mathbb{E} \left[\mathbf{1}_{\{p_i \leq s\}} \middle| \sigma \left(\left(\mathbf{1}_{\{p_i \leq t'\}} \right)_{t \leq t' \leq 1} \right) \right]\end{aligned}$$

- To have $\mathbb{E} \left[\frac{\mathbf{1}_{\{p_i \leq s\}}}{s} \middle| \mathcal{F}_t \right] = \frac{\mathbf{1}_{\{p_i \leq t\}}}{t}$ we need
 $\mathbb{E} \left[\mathbf{1}_A \frac{\mathbf{1}_{\{p_i \leq s\}}}{s} \right] = \mathbb{E} \left[\mathbf{1}_A \frac{\mathbf{1}_{\{p_i \leq t\}}}{t} \right]$ for all $A \in \sigma \left(\left(\mathbf{1}_{\{p_i \leq t'\}} \right)_{t \leq t' \leq 1} \right)$

Storey-BH

Proof of the Second Lemma

- ▶ Which is $\mathbb{P}_s(A) = \mathbb{P}_t(A)$ for all $A \in \sigma\left(\left(\mathbb{1}_{\{p_i \leq t'\}}\right)_{t \leq t' \leq 1}\right)$
- ▶ By the Sierpiński–Dynkin's π - λ theorem ("lemme des classes monotones"), for all A in a π -system that generates $\sigma\left(\left(\mathbb{1}_{\{p_i \leq t'\}}\right)_{t \leq t' \leq 1}\right)$ is sufficient

$$\begin{aligned}\sigma\left(\left(\mathbb{1}_{\{p_i \leq t'\}}\right)_{t \leq t' \leq 1}\right) &= \sigma\left(\bigcup_{t' \geq t} \sigma\left(\mathbb{1}_{\{p_i \leq t'\}}\right)\right) \\ &= \sigma\left(\bigcup_{t' \geq t} \mathbb{1}_{\{p_i \leq t'\}}^{-1}(\mathcal{B}(\mathbb{R}))\right)\end{aligned}$$

- ▶ $\mathbb{1}_{\{p_i \leq t'\}}^{-1}(\mathcal{B}(\mathbb{R})) = \{\emptyset, \{p_i \leq t'\}, \{p_i \leq t'\}^c, \Omega\}$

Storey-BH

Proof of the Second Lemma

- ▶ $\sigma \left(\left(\mathbb{1}_{\{p_i \leq t'\}} \right)_{t \leq t' \leq 1} \right) = \sigma (\{\{p_i \leq t'\}, t' \geq t\})$
- ▶ $\{\{p_i \leq t'\}, t' \geq t\}$ is a π -system:
 $\{p_i \leq t'\} \cap \{p_i \leq t''\} = \{p_i \leq t' \wedge t''\}$
- ▶ $\mathbb{P}_s (\{p_i \leq t'\}) = \mathbb{P}_s (\{p_i \leq s\}) = 1 = \mathbb{P}_t (\{p_i \leq t\}) = \mathbb{P}_t (\{p_i \leq t'\})$

□

Storey-BH

Proof of the Third Lemma, due to Romain Périer

- If $t > \lambda$, $\{\hat{t}_\alpha^{\text{St-BH}} \geq t\} = \emptyset \in \mathcal{F}_t$
- Let $t \leq \lambda$

$$\begin{aligned}\{\hat{t}_\alpha^{\text{St-BH}} \geq t\} &= \{\tau_{\hat{k}^{\text{St-BH}}} \geq t\} \\ &= \left\{ \alpha \frac{\hat{k}^{\text{St-BH}} \vee 1}{\hat{m}_0} \wedge \lambda \geq t \right\} \\ &= \left\{ \alpha \frac{\hat{k}^{\text{St-BH}} \vee 1}{\hat{m}_0} \geq t \right\} \text{ because } t \leq \lambda \\ &= \left\{ \hat{k}^{\text{St-BH}} \vee 1 \geq \frac{\hat{m}_0 t}{\alpha} \right\} = \left\{ \hat{k}^{\text{St-BH}} \vee 1 \geq \left\lceil \frac{\hat{m}_0 t}{\alpha} \right\rceil \right\} \\ &= \left\{ 1 \geq \left\lceil \frac{\hat{m}_0 t}{\alpha} \right\rceil \right\} \cup \left\{ \hat{k}^{\text{St-BH}} \geq \left\lceil \frac{\hat{m}_0 t}{\alpha} \right\rceil \right\}\end{aligned}$$

- with $\left\{ 1 \geq \left\lceil \frac{\hat{m}_0 t}{\alpha} \right\rceil \right\} \in \mathcal{F}_\lambda \subseteq \mathcal{F}_t$

Storey-BH

Proof of the Third Lemma, due to Romain Périer

- Let $\mathcal{M} = (1 - \lambda)^{-1} \llbracket 1, m + 1 \rrbracket$ the finite set \hat{m}_0 belongs to

$$\begin{aligned}\left\{ \hat{k}^{\text{St-BH}} \geq \left\lceil \frac{\hat{m}_0 t}{\alpha} \right\rceil \right\} &= \left\{ \exists k \geq \left\lceil \frac{\hat{m}_0 t}{\alpha} \right\rceil, p_{(k)} \leq \tau_k \right\} \\ &= \left\{ \exists k \geq \left\lceil \frac{\hat{m}_0 t}{\alpha} \right\rceil, \sum_{i=1}^m \mathbb{1}_{\{p_i \leq \tau_k\}} \geq k \right\} \\ &= \left\{ \exists k \geq \left\lceil \frac{\hat{m}_0 t}{\alpha} \right\rceil, \sum_{i=1}^m \mathbb{1}_{\left\{ p_i \leq \alpha \frac{k \vee 1}{\hat{m}_0} \wedge \lambda \right\}} \geq k \right\} \\ &= \bigcup_{m_0 \in \mathcal{M}} \{\hat{m}_0 = m_0\} \cap \left\{ \exists k \geq \left\lceil \frac{m_0 t}{\alpha} \right\rceil, \sum_{i=1}^m \mathbb{1}_{\left\{ p_i \leq \alpha \frac{k \vee 1}{m_0} \wedge \lambda \right\}} \geq k \right\} \\ &= \bigcup_{m_0 \in \mathcal{M}} \{\hat{m}_0 = m_0\} \cap \bigcup_{k \geq \left\lceil \frac{m_0 t}{\alpha} \right\rceil} \left\{ \sum_{i=1}^m \mathbb{1}_{\left\{ p_i \leq \alpha \frac{k \vee 1}{m_0} \wedge \lambda \right\}} \geq k \right\}\end{aligned}$$

Storey-BH

Proof of the Third Lemma, due to Romain Périer

- ▶ $\{\hat{m}_0 = m_0\} \in \mathcal{F}_\lambda \subseteq \mathcal{F}_t$ for all $m_0 \in \mathcal{M}$
- ▶ $\left\{ \sum_{i=1}^m \mathbb{1}_{\{p_i \leq \alpha \frac{k \vee 1}{m_0} \wedge \lambda\}} \geq k \right\} \in \mathcal{F}_{\alpha \frac{k \vee 1}{m_0} \wedge \lambda}$ for all $m_0 \in \mathcal{M}, k \geq \lceil \frac{m_0 t}{\alpha} \rceil$, but:

$$\begin{aligned}\alpha \frac{k \vee 1}{m_0} \wedge \lambda &\geq \alpha \frac{k}{m_0} \wedge \lambda \\ &\geq \frac{\alpha}{m_0} \left\lceil \frac{m_0 t}{\alpha} \right\rceil \wedge \lambda \\ &\geq \frac{\alpha}{m_0} \frac{m_0 t}{\alpha} \wedge \lambda \\ &\geq t \wedge \lambda = t\end{aligned}$$

- ▶ So $\mathcal{F}_{\alpha \frac{k \vee 1}{m_0} \wedge \lambda} \subseteq \mathcal{F}_t$ too

□

Storey-BH

Proof of the Theorem

- ▶ $\hat{t}_\alpha^{\text{St-BH}} = \widehat{G}_\lambda(\hat{t}_\alpha^{\text{St-BH}}) = \frac{\alpha}{\hat{m}_0} \left(|R(\hat{t}_\alpha^{\text{St-BH}})| \vee 1 \right) \wedge \lambda$
- ▶ If $\widehat{\text{FDP}}^{\text{St-BH}}(\lambda) \geq \alpha$, $\frac{\hat{m}_0 \lambda}{|R(\lambda)| \vee 1} \geq \alpha$ so $\hat{t}_\alpha^{\text{St-BH}} = \frac{\alpha}{\hat{m}_0} \left(|R(\hat{t}_\alpha^{\text{St-BH}})| \vee 1 \right)$
- ▶ And so $\text{FDP}\left(R\left(\hat{t}_\alpha^{\text{St-BH}}\right)\right) = \frac{V(R(\hat{t}_\alpha^{\text{St-BH}}))}{|R(\hat{t}_\alpha^{\text{St-BH}})| \vee 1} = \frac{\alpha V(R(\hat{t}_\alpha^{\text{St-BH}}))}{\hat{m}_0 \hat{t}_\alpha^{\text{St-BH}}} = \alpha \frac{1-\lambda}{m-|R(\lambda)|+1} \frac{V(R(\hat{t}_\alpha^{\text{St-BH}}))}{\hat{t}_\alpha^{\text{St-BH}}}$
- ▶ If $\widehat{\text{FDP}}^{\text{St-BH}}(\lambda) < \alpha$ then $\hat{t}_\alpha^{\text{St-BH}} = \lambda$ and $\frac{1}{|R(\lambda)| \vee 1} < \alpha \frac{1-\lambda}{m-|R(\lambda)|+1} \frac{1}{\lambda}$
- ▶ And so $\text{FDP}\left(R\left(\hat{t}_\alpha^{\text{St-BH}}\right)\right) = \text{FDP}(R(\lambda)) < \alpha \frac{1-\lambda}{m-|R(\lambda)|+1} \frac{V(R(\lambda))}{\lambda}$

Storey-BH

Proof of the Theorem

$$\begin{aligned}\text{FDR} \left(R \left(\hat{t}_\alpha^{\text{St-BH}} \right) \right) &= \mathbb{E} \left[\text{FDP} \left(R \left(\hat{t}_\alpha^{\text{St-BH}} \right) \right) \mathbb{1}_{\left\{ \widehat{\text{FDP}}^{\text{St-BH}}(\lambda) \geq \alpha \right\}} \right] \\ &\quad + \mathbb{E} \left[\text{FDP} \left(R \left(\hat{t}_\alpha^{\text{St-BH}} \right) \right) \mathbb{1}_{\left\{ \widehat{\text{FDP}}^{\text{St-BH}}(\lambda) < \alpha \right\}} \right] \\ &\leq \mathbb{E} \left[\alpha \frac{1 - \lambda}{m - |R(\lambda)| + 1} \frac{V \left(R \left(\hat{t}_\alpha^{\text{St-BH}} \right) \right)}{\hat{t}_\alpha^{\text{St-BH}}} \mathbb{1}_{\left\{ \widehat{\text{FDP}}^{\text{St-BH}}(\lambda) \geq \alpha \right\}} \right] \\ &\quad \mathbb{E} \left[\alpha \frac{1 - \lambda}{m - |R(\lambda)| + 1} \frac{V(R(\lambda))}{\lambda} \mathbb{1}_{\left\{ \widehat{\text{FDP}}^{\text{St-BH}}(\lambda) < \alpha \right\}} \right]\end{aligned}$$

Storey-BH

Proof of the Theorem

$$\begin{aligned} & \mathbb{E} \left[\alpha \frac{1 - \lambda}{m - |R(\lambda)| + 1} \frac{V(R(\hat{t}_\alpha^{\text{St-BH}}))}{\hat{t}_\alpha^{\text{St-BH}}} \mathbb{1}_{\{\widehat{\text{FDP}}^{\text{St-BH}}(\lambda) \geq \alpha\}} \right] \\ &= \mathbb{E} \left[\mathbb{E} \left[\alpha \frac{1 - \lambda}{m - |R(\lambda)| + 1} \frac{V(R(\hat{t}_\alpha^{\text{St-BH}}))}{\hat{t}_\alpha^{\text{St-BH}}} \mathbb{1}_{\{\widehat{\text{FDP}}^{\text{St-BH}}(\lambda) \geq \alpha\}} \middle| \mathcal{F}_\lambda \right] \right] \\ &= \mathbb{E} \left[\alpha \frac{1 - \lambda}{m - |R(\lambda)| + 1} \mathbb{E} \left[\frac{V(R(\hat{t}_\alpha^{\text{St-BH}}))}{\hat{t}_\alpha^{\text{St-BH}}} \middle| \mathcal{F}_\lambda \right] \mathbb{1}_{\{\widehat{\text{FDP}}^{\text{St-BH}}(\lambda) \geq \alpha\}} \right] \end{aligned}$$

Storey-BH

Proof of the Theorem

- ▶ By-product of optional stopping theorem: $\frac{V(R(t \vee \hat{t}_\alpha^{\text{St-BH}}))}{t \vee \hat{t}_\alpha^{\text{St-BH}}}$ is also a reverse-time martingale w.r.t. $(\mathcal{F}_t)_{t \in]0,1]}$
- ▶ Also note that $\lambda \geq \hat{t}_\alpha^{\text{St-BH}} \geq \tau_1 = \frac{\alpha}{\hat{m}_0} \wedge \lambda \geq \frac{\alpha(1-\lambda)}{m+1} \wedge \lambda$ a.s.

$$\begin{aligned}\mathbb{E} \left[\frac{V(R(\hat{t}_\alpha^{\text{St-BH}}))}{\hat{t}_\alpha^{\text{St-BH}}} \middle| \mathcal{F}_\lambda \right] &= \mathbb{E} \left[\frac{V(R((\frac{\alpha(1-\lambda)}{m+1} \wedge \lambda) \vee \hat{t}_\alpha^{\text{St-BH}}))}{(\frac{\alpha(1-\lambda)}{m+1} \wedge \lambda) \vee \hat{t}_\alpha^{\text{St-BH}}} \middle| \mathcal{F}_\lambda \right] \\ &= \frac{V(R(\lambda \vee \hat{t}_\alpha^{\text{St-BH}}))}{\lambda \vee \hat{t}_\alpha^{\text{St-BH}}} \\ &= \frac{V(R(\lambda))}{\lambda}\end{aligned}$$

Storey-BH

Proof of the Theorem

$$\begin{aligned}\text{FDR} \left(R \left(\hat{t}_\alpha^{\text{St-BH}} \right) \right) &\leq \alpha \mathbb{E} \left[\frac{1 - \lambda}{m - |R(\lambda)| + 1} \frac{V(R(\lambda))}{\lambda} \right] \\ &\leq \alpha \mathbb{E} \left[\frac{1 - \lambda}{m_0 - V(R(\lambda)) + 1} \frac{V(R(\lambda))}{\lambda} \right] \\ &\leq \alpha \sum_{k=1}^{m_0} \frac{1 - \lambda}{\lambda} \frac{k}{m_0 - k + 1} \binom{m_0}{k} \lambda^k (1 - \lambda)^{m_0 - k} \\ &\leq \alpha \sum_{k=1}^{m_0} \binom{m_0}{k-1} \lambda^{k-1} (1 - \lambda)^{m_0 - k + 1} \\ &\leq \alpha \sum_{k=0}^{m_0-1} \binom{m_0}{k} \lambda^k (1 - \lambda)^{m_0 - k} \\ &\leq \alpha (1 - \lambda^{m_0}) \leq \alpha \quad \square\end{aligned}$$

- ▶ Proof can be adapted to prove BH a 3rd time, but requires uniformity

Adaptivity to signal strength and location

Introduction to hypothesis weighting

- ▶ SU and SD procedures are implicitly adaptive to signal strength:
strong signal \Rightarrow small p_i 's \Rightarrow large $\hat{k}^{SU}/\hat{k}^{SD}$
- ▶ What if we have prior knowledge about the hypotheses likely to be (strong) signal?
- ▶ We can encode that into weights and plug them into the procedure:
 - ▶ Compare p_i to $w_i \tau_k$ instead of τ_k , $w_i \geq 0$, with a bounding condition on the w_i 's
 - ▶ If i likely to be (strong) signal: small w_i , which makes larger w_j 's affordable for other hypotheses
- ▶ Weights can be random

weighted-Benjamini-Hochberg procedure (wBH)

[Genovese, Roeder, and Wasserman (2006)]

- ▶ Let w_1, \dots, w_m nonnegative random variables and consider the weighted FDP estimator $\widehat{\text{FDP}}^{\text{wBH}}(t) = \frac{mt}{\sum_{i=1}^m \mathbb{1}_{\{p_i \leq w_i t\}} \vee 1}$
- ▶ Let $\hat{t}_\alpha^{\text{w-heur}} = \sup \left\{ t \in [0, 1] : \frac{\alpha}{m} \left(\sum_{i=1}^m \mathbb{1}_{\{p_i \leq w_i t\}} \vee 1 \right) \geq t \right\}$
- ▶ Alternatively, let

$$q_i = \begin{cases} 0 & \text{if } p_i = 0, w_i = 0 \\ 2 & \text{if } p_i \neq 0, w_i = 0 \\ \frac{p_i}{w_i} & \text{if } w_i \neq 0 \end{cases}$$

- ▶ Remarks:
 - ▶ $q_i \leq t$ if and only if $p_i \leq w_i t$
 - ▶ Not the same ordering for the q_i 's than the p_i 's: denote it $q_{(1)} \leq \dots \leq q_{(m)}$
 - ▶ The weighted p -values q_i 's are not valid p -values because not necessarily super-uniform under the null
 - ▶ All previous deterministic results on SU procedures hold nonetheless

weighted-Benjamini-Hochberg procedure (wBH)

- ▶ wBH can be defined as BH applied to the q_i 's:

$$\hat{k}^{\text{wBH}} = \max \left\{ k \in \llbracket 0, m \rrbracket, q_{(k)} \leq \alpha \frac{k \vee 1}{m} \right\}, \quad \hat{t}_\alpha^{\text{wBH}} = \alpha \frac{\hat{k}^{\text{wBH}} \vee 1}{m} \text{ and}$$
$$R^{\text{wBH}} = \left\{ i : q_i \leq \hat{t}_\alpha^{\text{wBH}} \right\} = \left\{ i : p_i \leq w_i \hat{t}_\alpha^{\text{wBH}} \right\}$$

- ▶ As before, $\hat{t}_\alpha^{\text{w-heur}} = \hat{t}_\alpha^{\text{wBH}}$, because

$$\hat{t}_\alpha^{\text{w-heur}} = \sup \left\{ t \in [0, 1] : \frac{\alpha}{m} \left(\sum_{i=1}^m \mathbb{1}_{\{q_i \leq t\}} \vee 1 \right) \geq t \right\}, \text{ same proof but with } q_i \text{ instead of } p_i$$

weighted-Benjamini-Hochberg procedure (wBH)

FDR control

Theorem [Genovese, Roeder, and Wasserman (2006)]

Assume that for all $P \in \mathfrak{F}$, the $(p_i)_{i \in \mathcal{H}_0}$ are independent, that they are independent from the $(p_i)_{i \in \mathcal{H}_1}$, that the $(w_i)_{i \in \mathcal{H}_0}$ are independent, that they are independent from the $(w_i)_{i \in \mathcal{H}_1}$, that (p_i) and (w_i) are independent, and finally that the w_i 's are integrable with $\sum_{i=1}^m \mathbb{E}[w_i] \leq m$. Then for all $P \in \mathfrak{F}$,

$$\text{FDR}\left(R^{\text{wBH}}\right) \leq \alpha \frac{\sum_{i \in \mathcal{H}_0} \mathbb{E}[w_i]}{m} \leq \alpha.$$

- ▶ Includes the case of deterministic (and possibly grouped) weights based on prior knowledge

Lemma

Under the same conditions, for all $i \in \mathcal{H}_0$, $\mathbb{P}(q_i \leq t) \leq t \mathbb{E}[w_i]$.

weighted-Benjamini-Hochberg procedure (wBH)

Proofs

$$\begin{aligned}\mathbb{P}(q_i \leq t) &= \mathbb{E}[\mathbb{P}(q_i \leq t | w_i)] \\ &= \mathbb{E}[\mathbb{P}(p_i \leq tw_i | w_i)] \\ &\leq \mathbb{E}[tw_i] \text{ by independence and super-uniformity} \\ &\leq t\mathbb{E}[w_i] \quad \square\end{aligned}$$

- ▶ For FDR control, same proof as BH for independent case, thanks to all deterministic Lemmas on SU procedures:

$$\begin{aligned}\text{FDR}\left(R^{\text{wBH}}\right) &= \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \mathbb{P}\left(q_i \leq \alpha \frac{k}{m}\right) \mathbb{P}\left(\hat{k}^{-i} = k - 1\right) \\ &\leq \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} \mathbb{E}[w_i] \sum_{k=1}^m \mathbb{P}\left(\hat{k}^{-i} = k - 1\right) \\ &\leq \alpha \frac{\sum_{i \in \mathcal{H}_0} \mathbb{E}[w_i]}{m} \leq \alpha \quad \square\end{aligned}$$

- ▶ Weights are independent of the data here, for adaptive weights see e.g. [Roquain and Wiel (2009)], [Durand (2019)]

Table of contents

1. From simple to multiple tests
2. Multiple testing framework
3. Classical error rates and methods
4. Adaptivity
5. The discrete heterogeneous problem
6. Towards exploratory analysis

An example of discrete test

Binomial test

- ▶ The simplest example: X_1, \dots, X_n i.i.d $\sim \mathcal{B}(p)$, $p \in [0, 1]$
- ▶ $X = \sum_{i=1}^n X_i$
- ▶ $\mathfrak{F} = \{\mathcal{B}(n, p), p \in [0, 1]\}$, discrete distributions
- ▶ Is the coin rigged? $\Leftrightarrow H_0 = \left\{ \mathcal{B}\left(n, \frac{1}{2}\right) \right\}$
- ▶ $\hat{p}_i(X), \bar{p}_i(X), \check{p}_i(X)$ also discrete, but $\check{p}_i(X)$ not the best suited for bilateral tests

Another example of discrete test

Fisher's exact test

- ▶ Testing association between an allele and a phenotype of interest

	Phenotype 1	Phenotype 2	Total
Allele A	$n_{1,A}$	$n_{2,A}$	n_A
Allele a	$n_{1,a}$	$n_{2,a}$	n_a
Total	n_1	n_2	N

- ▶ For large samples, χ^2 approximation:
$$\frac{\left(n_{1,A} - \frac{n_1 n_A}{N}\right)^2}{\frac{n_1 n_A}{N}} + \frac{\left(n_{1,a} - \frac{n_1 n_a}{N}\right)^2}{\frac{n_1 n_a}{N}} + \frac{\left(n_{2,A} - \frac{n_2 n_A}{N}\right)^2}{\frac{n_2 n_A}{N}} + \frac{\left(n_{2,a} - \frac{n_2 n_a}{N}\right)^2}{\frac{n_2 n_a}{N}}$$
 follows $\chi^2(1)$ distribution under H_0
- ▶ What if we want an exact test ?
- ▶ Under H_0 , conditionally to n_1 and n_A ,
 $n_{1,A} \sim \mathcal{H}(N, n_1, n_A) = \mathcal{H}(N, n_A, n_1)$, hypergeometric hence discrete
- ▶ $\hat{p}_i(X), \bar{p}_i(X), \check{p}_i(X)$ also discrete, but $\check{p}_i(X)$ not the best suited for bilateral tests

Generic construction of p -values with discreteness

Following the idea of “the probability of an event at least as extreme as”

- ▶ Assume we have at hand a test statistic $T_i : \mathcal{X} \rightarrow \mathbb{R}$ such that $\forall P \in H_{0,i}, \exists \mathcal{A}_{i,P}$ countable or finite such that $T_i(X) \in \mathcal{A}_{i,P}$ a.s.
- ▶ Then let

$$\begin{aligned}\check{p}_i(X) &= \sup_{P \in H_{0,i}} \sum_{\substack{k \in \mathcal{A}_{i,P} \\ \mathbb{P}_{Z \sim P}(T_i(Z)=k) \leq \mathbb{P}_{\substack{Z \sim P \\ Z \perp X}}(T_i(Z)=T_i(X)|X)}} \mathbb{P}_{\substack{Z \sim P \\ Z \perp X}}(T_i(Z)=k) \\ &= \sup_{P \in H_{0,i}} \mathbb{P}_{Z \sim P}(T_i(Z) \in \{k \in \mathcal{A}_{i,P} : (T_i)_{\#P}(\{k\}) \leq (T_i)_{\#P}(\{T_i(X)\})\}) \\ &= \sup_{P \in H_{0,i}} \sum_{\substack{k \in \mathcal{A}_{i,P} \\ (T_i)_{\#P}(\{k\}) \leq (T_i)_{\#P}(\{T_i(X)\})}} (T_i)_{\#P}(\{k\}) \\ &= \sup_{P \in H_{0,i}} (T_i)_{\#P}(\{k \in \mathcal{A}_{i,P} : (T_i)_{\#P}(\{k\}) \leq (T_i)_{\#P}(\{T_i(X)\})\})\end{aligned}$$

- ▶ $\check{p}_i = \mathbb{P}(\text{to realize a value of the support lesser or as common as } T_i(X))$

Generic construction of p -values with discreteness

Following the idea of “the probability of an event at least as extreme as”

Theorem

\check{p}_i is an appropriate p -value, that is, it is super-uniform under the null:

Let $Q \in H_{0,i}$, $X \sim Q$, then

$$\forall x \in \mathbb{R}, \mathbb{P}(\check{p}_i(X) \leq x) \leq u(x). \quad (4)$$

- ▶ This is actually more general than with discrete support given that discrete and $\subseteq \mathbb{R} \Rightarrow$ countable but not the reverse
- ▶ Proof:
- ▶ As before, $\check{p}_i(X) \geq \check{p}_{i,Q}(X) = \sum_{\substack{k \in \mathcal{A}_{i,Q} \\ (T_i)_{\#Q}(\{k\}) \leq (T_i)_{\#Q}(\{T_i(X)\})}} (T_i)_{\#Q}(\{k\})$
so proving $\check{p}_{i,Q}(X) \succeq \mathcal{U}([0, 1])$ is sufficient
- ▶ As before, $\check{p}_{i,Q}(X) \in [0, 1]$ a.s. and right-continuity of the c.d.f so we only need to check (4) for $x \in]0, 1[$

Generic construction of p -values with discreteness

Proof

- ▶ Note that

$$\check{p}_{i,Q}(X) \in \mathcal{S}_{i,Q} = \left\{ \sum_{\substack{k \in \mathcal{A}_{i,Q} \\ (\mathcal{T}_i)_{\#Q}(\{k\}) \leq (\mathcal{T}_i)_{\#Q}(\{\ell\})}} (\mathcal{T}_i)_{\#Q}(\{k\}) : \ell \in \mathcal{A}_{i,Q} \right\}$$

a.s., and $\mathcal{S}_{i,Q}$ is countable or finite

Generic construction of p -values with discreteness

Proof

- Also note that for $x \in \mathcal{S}_{i,Q}$, $x = \sum_{\substack{k \in \mathcal{A}_{i,Q} \\ (T_i)_{\#Q}(\{k\}) \leq (T_i)_{\#Q}(\{\ell\})}} (T_i)_{\#Q}(\{k\})$,

$\ell \in \mathcal{A}_{i,Q}$, the c.d.f. of $s_{i,Q}(X)$ in x is

$$\begin{aligned}\mathbb{P}(\check{p}_{i,Q}(X) \leq x) &= \mathbb{P}\left(\sum_{\substack{k \in \mathcal{A}_{i,Q} \\ (T_i)_{\#Q}(\{k\}) \leq (T_i)_{\#Q}(\{T_i(X)\})}} (T_i)_{\#Q}(\{k\}) \leq \sum_{\substack{k \in \mathcal{A}_{i,Q} \\ (T_i)_{\#Q}(\{k\}) \leq (T_i)_{\#Q}(\{\ell\})}} (T_i)_{\#Q}(\{k\})\right) \\ &= \mathbb{P}((T_i)_{\#Q}(\{T_i(X)\}) \leq (T_i)_{\#Q}(\{\ell\})) \\ &= \mathbb{P}(T_i(X) \in \{k \in \mathcal{A}_{i,Q} : (T_i)_{\#Q}(\{k\}) \leq (T_i)_{\#Q}(\{\ell\})\}) \\ &= (T_i)_{\#Q}(\{k \in \mathcal{A}_{i,Q} : (T_i)_{\#Q}(\{k\}) \leq (T_i)_{\#Q}(\{\ell\})\}) \\ &= \sum_{\substack{k \in \mathcal{A}_{i,Q} \\ (T_i)_{\#Q}(\{k\}) \leq (T_i)_{\#Q}(\{\ell\})}} (T_i)_{\#Q}(\{k\}) = x\end{aligned}$$

- ⇒ The c.d.f. of $\check{p}_{i,Q}(X)$ is the identity on the support of $\check{p}_{i,Q}(X)$

Generic construction of p -values with discreteness

Proof

- ▶ Let $x \in]0, 1[$, if $x < x'$ for all $x' \in \mathcal{S}_{i,Q}$ then $\mathbb{P}(\check{p}_{i,Q}(X) \leq x) = 0 \leq x$
- ▶ Else let $\underline{x} = \sup\{x' \in \mathcal{S}_{i,Q}, x' \leq x\}$ and note that
 $\mathbb{P}(\check{p}_{i,Q}(X) \leq x) = \mathbb{P}(\check{p}_{i,Q}(X) \leq \underline{x})$
- ▶ If $\underline{x} \in \mathcal{S}_{i,Q}$ (i.e. it's a max, e.g. if $\mathcal{A}_{i,Q}$ is finite), then
 $\mathbb{P}(\check{p}_{i,Q}(X) \leq \underline{x}) = \underline{x} \leq x$
- ▶ Else, $\mathbb{P}(\check{p}_{i,Q}(X) \leq \underline{x}) = \mathbb{P}(\check{p}_{i,Q}(X) < \underline{x}) = \lim_{\substack{t \rightarrow \underline{x} \\ t < \underline{x}}} \mathbb{P}(\check{p}_{i,Q}(X) < t)$ by left-continuity
- ▶ Let $t_n \in \{x' \in \mathcal{S}_{i,Q}, x' \leq x\}$, $t_n \rightarrow \underline{x}$,
 $\mathbb{P}(\check{p}_{i,Q}(X) < t_n) \leq \mathbb{P}(\check{p}_{i,Q}(X) \leq t_n) = t_n \leq x$

□

Generic construction of p -values with discreteness

Corollary

If, for all $P \in H_{0,i}$, $(T_i)_{\#P}$ does not depend on P , and if $\mathcal{A}_i = \mathcal{A}_{i,P}$ is finite, then $\mathcal{S}_i = \mathcal{S}_{i,P}$ is finite too and we can order its elements

$x_1 < \dots < x_N = 1$ for some N and describe the c.d.f. of $\check{p}_i(X)$ really simply:

$$\forall P \in H_{0,i}, X \sim P, \forall x \in \mathbb{R},$$

$$\mathbb{P}(\check{p}_i(X) \leq x) = \begin{cases} 0 & \text{if } x < x_1 \\ x_n & \text{if } x_n \leq x < x_{n+1}, n < N \\ 1 & \text{if } x \geq 1 \end{cases} \quad (5)$$

- ▶ Denote k_1, \dots, k_D the distinct elements of \mathcal{A}_i and order $(T_i)_{\#P}(\{k.\})_{(1)} \leq \dots \leq (T_i)_{\#P}(\{k.\})_{(D)}$
- ▶ Assuming all are $\neq 0$ (so take the smallest \mathcal{A}_i possible) and no ties, then $N = D$ and $x_n = \sum_{\nu=1}^n (T_i)_{\#P}(\{k.\})_{(\nu)}$, in particular $\mathbb{P}(\check{p}_i(X) = x_n) = (T_i)_{\#P}(\{k.\})_{(n)}$
- ▶ $x_N = (T_i)_{\#P}(\mathcal{A}_i) = 1$, always
- ▶ If ties, $N < D$

Generic construction of p -values with discreteness

Remark

- If, for all $P \in H_{0,i}$, $\mathcal{A}_i = \mathcal{A}_{i,P}$ does not depend on P (here, $(T_i)_{\#P}$ can) and is finite, then the set of possible values for $\hat{p}_i(X)$, $\bar{p}_i(X)$, $\check{p}_i(X)$, $\check{\check{p}}_i(X)$ are also finite and do not depend on P

$$\begin{aligned} & \hat{p}_i(X) \in \left\{ \sup_{P \in H_{0,i}} \sum_{\substack{k \in \mathcal{A}_i \\ k \geq \ell}} (T_i)_{\#P}(\{k\}) : \ell \in \mathcal{A}_i \right\} = \\ & \quad \left\{ \sup_{P \in H_{0,i}} (T_i)_{\#P}([\ell, \infty]) : \ell \in \mathcal{A}_i \right\} \text{ a.s.} \\ & \check{p}_i(X) \in \left\{ \sup_{P \in H_{0,i}} \sum_{\substack{k \in \mathcal{A}_i \\ (T_i)_{\#P}(\{k\}) \leq (T_i)_{\#P}(\{\ell\})}} (T_i)_{\#P}(\{k\}) : \ell \in \mathcal{A}_i \right\} \text{ a.s.} \end{aligned}$$

Generic construction of p -values with discreteness

Back to Fisher's test

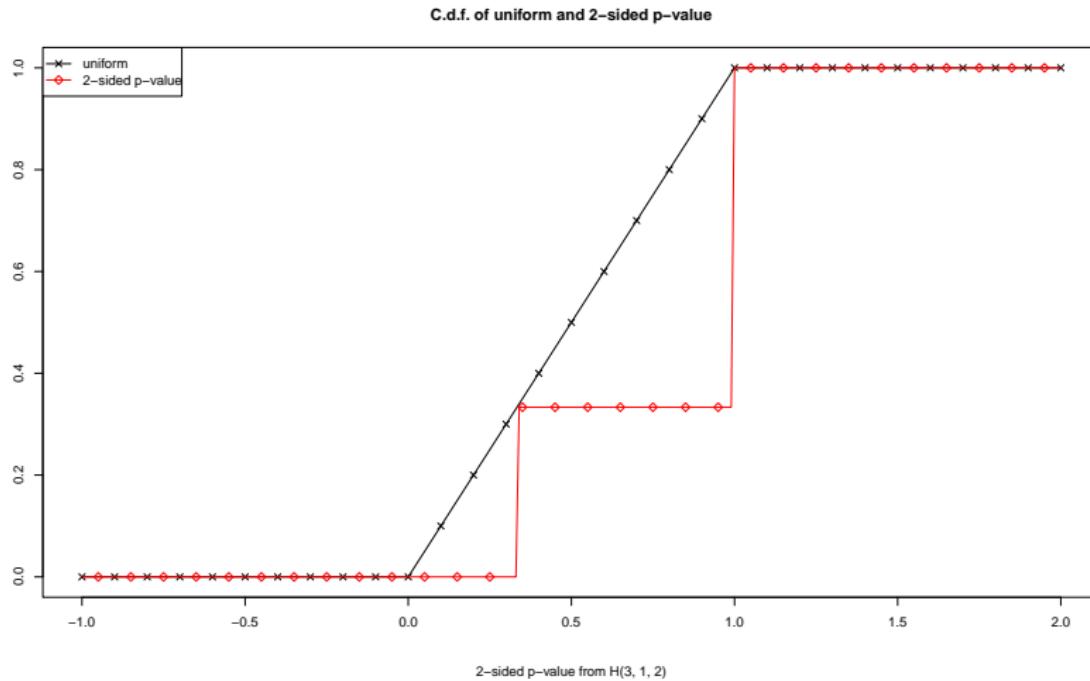
	Phenotype 1	Phenotype 2	Total
Allele A	0	1	$n_A = 1$
Allele a	2	0	$n_a = 2$
Total	$n_1 = 2$	$n_2 = 1$	$N = 3$

- ▶ Conditionnally to $n_A = 1, n_1 = 2$, without association,
 $n_{1,A} \sim \mathcal{H}(3, 1, 2) = P_0$
- ▶ $P_0(\{0\}) = \frac{\binom{2}{0}\binom{1}{1}}{\binom{3}{1}} = \frac{1}{3}$, $P_0(\{1\}) = \frac{\binom{2}{1}\binom{1}{0}}{\binom{3}{1}} = \frac{2}{3}$
- ▶ Then $\check{p}_i(n_{1,A}) = 2 \min(P_0(]-\infty, n_{1,A}]), P_0([n_{1,A}, \infty[)) = \frac{2}{3}\mathbb{1}_{\{n_{1,A}=0\}} + \frac{4}{3}\mathbb{1}_{\{n_{1,A}=1\}}$
- ▶ Whereas
$$\check{p}_i(n_{1,A}) = \sum_{\substack{k \in \{0,1\} \\ P_0(\{k\}) \leq P_0(\{n_{1,A}\})}} P_0(\{k\}) = \frac{1}{3}\mathbb{1}_{\{n_{1,A}=0\}} + \frac{2}{3}\mathbb{1}_{\{n_{1,A}=1\}}$$
- ▶ Clearly $\check{p}_i(n_{1,A})$ is less conservative than $\check{p}_i(n_{1,A})$, furthermore $\check{p}_i(X)$ can be > 1 (as soon as X has an atom of $\mathbb{P} > \frac{1}{2}$, and opening one interval makes it invalid)

Generic construction of p -values with discreteness

Back to Fisher's test

- C.d.f. of $\check{p}_i(n_{1,A})$ under H_0 , that is if $n_{1,A} \sim \mathcal{H}(3, 1, 2)$:



The issue with discrete p -values

Strict super-uniformity

$$\forall P \in H_{0,i}, X \sim P, \mathbb{P}(p_i(X) \leq x) \leq u(x) \text{ and } \exists x, \mathbb{P}(p_i(X) \leq x) < u(x)$$

i.e. under the null, our p -values are larger than uniforms

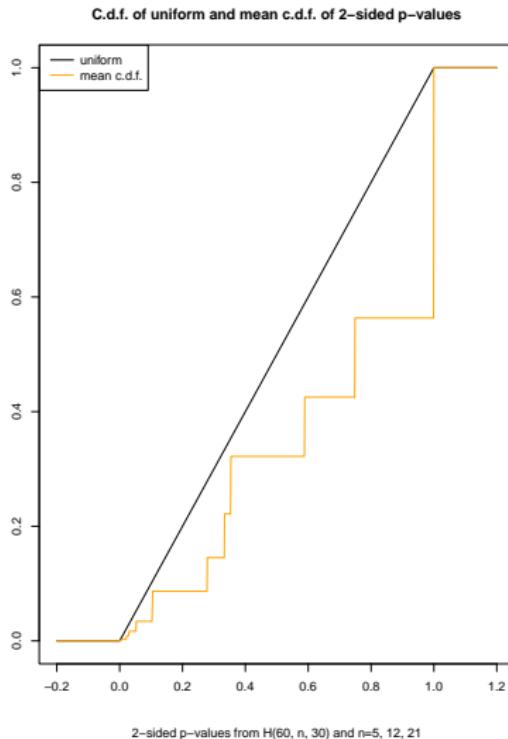
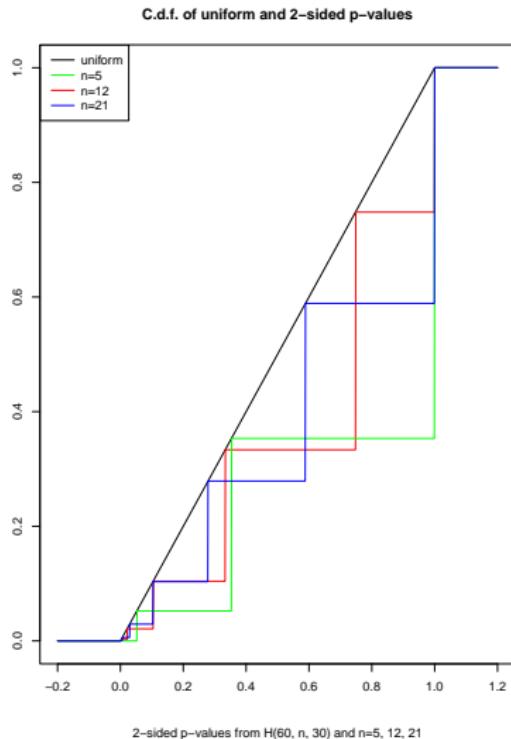
Problem

Usual MT procedures designed for uniform p -values (seen as the worst case)

- ▶ As discrete p -values are larger than uniforms, classic thresholds are too low, too conservative \implies loss of power
- ▶ Goal: use the knowledge of the discrete c.d.f. under the null to improve power

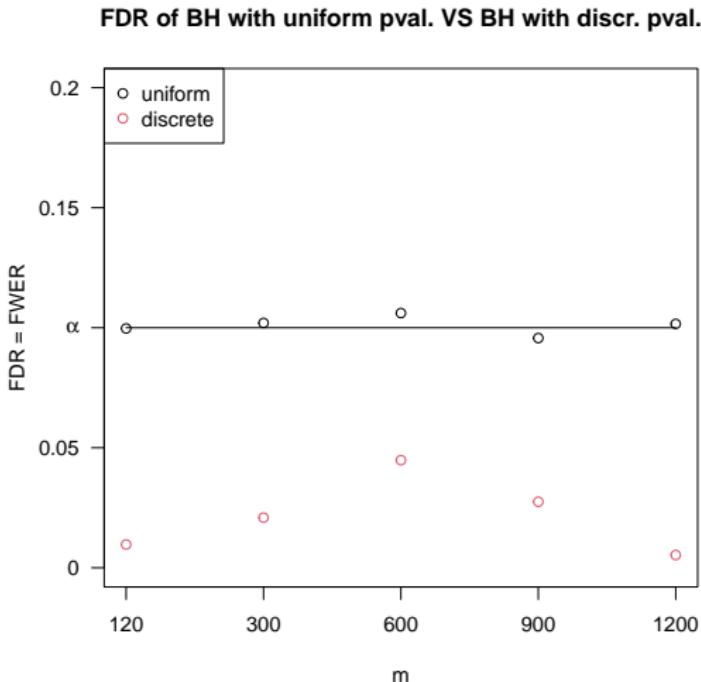
The issue with discrete p -values

- C.d.f. plots of 2-sided p -values associated with $\mathcal{H}(60, 5, 30)$, $\mathcal{H}(60, 12, 30)$ and $\mathcal{H}(60, 21, 30)$



The issue with discrete p -values

- BH under full null, $m/3$ 2-sided p -values derived from $\mathcal{H}(60, 5, 30)$,
 $m/3$ from $\mathcal{H}(60, 12, 30)$, $m/3$ from $\mathcal{H}(60, 21, 30)$
- MC estimation of the FDR with 10^4 replications



Assumption for the remainder of the section

- ▶ \exists a finite set \mathcal{S}_i such that $\forall P \in H_{0,i}, X \sim P, \mathbb{P}(p_i(X) \in \mathcal{S}_i) = 1$
- ▶ See previous remark for a sufficient condition and construction
- ▶ Also let $\underline{s}_i = \min \mathcal{S}_i$

Tarone-Bonferroni procedures

Increasing power for discrete tests [Tarone (1990)]

- ▶ A simple idea: if $\underline{s}_i > \alpha$, $H_{0,i}$ can never be wrongly rejected so might not count it when adjusting for multiplicity
- ▶ Let $R_1 = \{i \in [\![1, m]\!] : \underline{s}_i \leq \alpha\}$, $m(1) = |R_1|$, $\hat{t}_\alpha^{\text{TB}} = \frac{\alpha}{m(1)}$ and $R^{\text{TB}} = R(\hat{t}_\alpha^{\text{TB}})$
- ▶ $\hat{t}_\alpha^{\text{TB}} \geq \hat{t}_\alpha^{\text{Bonf}}$: less conservative than Bonferroni
- ▶ $\text{FWER}(R^{\text{TB}}) = \sum_{i \in \mathcal{H}_0} \mathbb{P}\left(p_i \leq \frac{\alpha}{m(1)}\right) = \sum_{i \in \mathcal{H}_0 \cap R_1} \mathbb{P}\left(p_i \leq \frac{\alpha}{m(1)}\right) \leq \alpha \frac{|\mathcal{H}_0 \cap R_1|}{m(1)} \leq \alpha$ □
- ▶ We can do better : $\forall k \in [\![1, m]\!]$, let $R_k = \{i \in [\![1, m]\!] : \underline{s}_i \leq \frac{\alpha}{k}\}$, $m(k) = |R_k|$, actually $\text{FWER}(R^{\text{TB}})$ is bounded by $\alpha \frac{|\mathcal{H}_0 \cap R_{m(1)}|}{m(1)}$ which is even smaller \Rightarrow “fixed point” research

Tarone-Bonferroni procedures

Increasing power for discrete tests

- ▶ Let $K^* = \min \{k \in \llbracket 1, m \rrbracket : m(k) \leq k\}$, non-empty set because $m(m(1)) \leq m(1)$, $\hat{t}_\alpha^{\text{TB-ref}} = \frac{\alpha}{K^*}$ and $R^{\text{TB-ref}} = R(\hat{t}_\alpha^{\text{TB-ref}})$
- ▶ For any fixed k ,

$$\forall P \in \mathfrak{F}, \mathbb{P} \left(\exists i \in \mathcal{H}_0 : p_i \leq \frac{\alpha}{k} \right) \leq \sum_{i \in \mathcal{H}_0 \cap R_k} \mathbb{P} \left(p_i \leq \frac{\alpha}{k} \right) \leq \alpha \frac{m(k)}{k},$$

which shows that $\text{FWER}(R^{\text{TB}}), \text{FWER}(R^{\text{TB-ref}}) \leq \alpha$ □

- ▶ K^* is the optimal choice, TB-refined is even less conservative

FDR control with discrete p -values

Heyse procedure

- ▶ Recall the previous plot of the mean c.d.f. of the discrete p -values
- ▶ ⇒ idea: “invert” this mean c.d.f. at $\alpha \frac{k}{m}$ and apply a SU procedure [Heyse (2011)]
- ▶ Let $F_i : t \mapsto \sup_{P \in H_{0,i}} \mathbb{P}_{X \sim P} (p_i(X) \leq t)$: worst-case c.d.f., and $\bar{F}(t) = \frac{1}{m} \sum_{i=1}^m F_i(t)$
- ▶ Let $\mathcal{S} = \bigcup_{i=1}^m \mathcal{S}_i$, $\tau_k = \max \left\{ t \in \mathcal{S} : \bar{F}(t) \leq \alpha \frac{k}{m} \right\}$
- ▶ $R^{\text{Heyse}} = R^{\text{SU}}(\tau)$
- ▶ BH is also the SU procedure with $\xi_k = \max \left\{ t \in \mathcal{S} : t \leq \alpha \frac{k}{m} \right\}$ (effective critical values), $\bar{F}(\xi_k) \leq \xi_k \leq \alpha \frac{k}{m}$ so $\tau_k \geq \xi_k$: Heyse less conservative than BH, only with heterogeneity though: if $F_i = F_j = \bar{F}$ and the assumption $F_i(t) = t$, $\forall t \in \mathcal{S}_i = \mathcal{S}$ then $\bar{F}(t) = t$ for all $t \in \mathcal{S}$ and $\tau_k = \xi_k$
- ▶ Problem: R^{Heyse} doesn't control the FDR! [Döhler, Durand, and Roquain (2018)]

FDR control with discrete p -values

- ▶ Heyse *almost* works though, it works up to a small rescaling factor
- ▶ Let $\tau_m = \max \left\{ t \in \mathcal{S} : \frac{1}{m} \sum_{i=1}^m \frac{F_i(t)}{1-F_i(t)} \leq \alpha \right\}$
- ▶ For $k < m$, let $\tau_k = \max \left\{ t \in \mathcal{S} : t \leq \tau_m, \sum_{i=1}^m \frac{F_i(t)}{1-F_i(\tau_m)} \leq \alpha k \right\}$
- ▶ Let $R^{\text{HSU}} = R^{\text{SU}}(\tau)$
- ▶ Can be more conservative than BH but not that much, and in practice isn't

Theorem [Döhler, Durand, and Roquain (2018)]

Assume that for all $P \in \mathfrak{F}$, the $(p_i)_{i \in \mathcal{H}_0}$ are independent, and they are independent from the $(p_i)_{i \in \mathcal{H}_1}$.

Then for all $P \in \mathfrak{F}$,

$$\text{FDR}\left(R^{\text{HSU}}\right) \leq \alpha$$

FDR control with discrete p -values

- ▶ We can do even better by implicit adaptivity to m_0 :
- ▶ Let τ_m the same
- ▶ For $k < m$, let $\tau_k = \max \left\{ t \in \mathcal{S} : t \leq \tau_m, \left(\left(\frac{F_i(t)}{1 - F_i(\tau_m)} \right)_{(1)} + \cdots + \left(\frac{F_i(t)}{1 - F_i(\tau_m)} \right)_{(m-k+1)} \right) \leq \alpha k \right\}$
- ▶ Idea: if k “good” rejections, $m_0 \leq m - k + 1$ so only control needed for the worst case with $m - k + 1$ kept null hypotheses
- ▶ Let $R^{\text{AHSU}} = R^{\text{SU}}(\tau)$
- ▶ Less conservative than HSU because of larger critical values

Theorem [Döhler, Durand, and Roquain (2018)]

Assume that for all $P \in \mathfrak{F}$, the $(p_i)_{i \in \mathcal{H}_0}$ are independent, and they are independent from the $(p_i)_{i \in \mathcal{H}_1}$.

Then for all $P \in \mathfrak{F}$,

$$\text{FDR}(R^{\text{AHSU}}) \leq \alpha$$

FDR control with discrete p -values

- Both FDR controls come from the same bound

Theorem [Döhler, Durand, and Roquain (2018)]

Assume that for all $P \in \mathfrak{F}$, the $(p_i)_{i \in \mathcal{H}_0}$ are independent, and they are independent from the $(p_i)_{i \in \mathcal{H}_1}$. Let any critical value sequence τ with $F_i(\tau_m) < 1$ for all $i \in [\![1, m]\!]$.

Then for all $P \in \mathfrak{F}$,

$$\text{FDR}\left(R^{\text{SU}}(\tau)\right) \leq \max_{1 \leq k \leq m} \max_{\substack{A \subseteq [\![1, m]\!] \\ |A|=m-k+1}} \frac{1}{k} \sum_{i \in A} \frac{F_i(\tau_k)}{1 - F_i(\tau_m)}$$

FDR control with discrete p -values

Proof of the Theorem

- ▶ Recall the Lemma on SU procedures:
 $\{p_i \leq \tau_{\hat{k}^{\text{SU}}}, \hat{k}^{\text{SU}} = k\} = \{p_i \leq \tau_k, \hat{k}^{-i} = k - 1\}$
- ▶ Another one: let $(\sigma_1, \dots, \sigma_m) = (\tau_2, \dots, \tau_m, \tau_m)$ and
 $\hat{k}^\# = \max\{k : p_{(k)} \leq \sigma_k\} = |R^{\text{SU}}(\sigma)|$. Then $p_i > \tau_m \Rightarrow \hat{k}^{-i} = \hat{k}^\#$
- ▶ Proof: $p_{(\hat{k}^{-i})} \leq p_{(\hat{k}^{-i})}^{-i} \leq \tau_{\hat{k}^{-i}}^{-i} = \sigma_{\hat{k}^{-i}} \text{ so } \hat{k}^{-i} \leq \hat{k}^\#, \text{ always}$
- ▶ Let $p_i = p_{(k_i)}$, note that $p_{(k)}^{-i} = p_{(k)}$ for all $k < k_i$ and $p_{(k)}^{-i} = p_{(k+1)}$ for all $m - 1 \geq k \geq k_i$
- ▶ $p_i > \tau_m$ entails $p_{(k_i)} = p_i > \tau_m \geq \sigma_{\hat{k}^\#} \geq p_{(\hat{k}^\#)}$ so $k_i > \hat{k}^\#$ (also entails $m > \hat{k}^\#$) so $p_{(\hat{k}^\#)}^{-i} = p_{(\hat{k}^\#)}$
- ▶ Finally $p_{(\hat{k}^\#)}^{-i} = p_{(\hat{k}^\#)} \leq \sigma_{\hat{k}^\#} = \tau_{\hat{k}^\#}^{-i}$ and $\hat{k}^\# \leq \hat{k}^{-i}$ □

FDR control with discrete p -values

Proof of the Theorem

- ▶ Starts like the proof of BH:

$$\begin{aligned}\text{FDR} \left(R^{\text{SU}}(\tau) \right) &= \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \mathbb{P}(p_i \leq \tau_k) \mathbb{P}(\hat{k}^{-i} = k - 1) \\ &\leq \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} F_i(\tau_k) \mathbb{P}(\hat{k}^{-i} = k - 1) \\ &\leq \sum_{i \in \mathcal{H}_0} \mathbb{E} \left[\frac{F_i(\tau_{\hat{k}^{-i}+1})}{\hat{k}^{-i} + 1} \right]\end{aligned}$$

FDR control with discrete p -values

Proof of the Theorem

- Hide 1: $1 - F_i(\tau_m) \leq 1 - \mathbb{P}(p_i \leq \tau_m)$ so

$$\begin{aligned} 1 &\leq \frac{\mathbb{P}(p_i > \tau_m)}{1 - F_i(\tau_m)} \\ &= \mathbb{E} \left[\frac{\mathbb{1}_{\{p_i > \tau_m\}}}{1 - F_i(\tau_m)} \right] \\ &= \mathbb{E} \left[\frac{\mathbb{1}_{\{p_i > \tau_m\}}}{1 - F_i(\tau_m)} \middle| \hat{k}^{-i} \right] \text{ by independence} \end{aligned}$$

FDR control with discrete p -values

Proof of the Theorem

► Hence

$$\begin{aligned}\text{FDR}\left(R^{\text{SU}}(\tau)\right) &\leq \sum_{i \in \mathcal{H}_0} \mathbb{E} \left[\frac{F_i(\tau_{\hat{k}^{-i}+1})}{\hat{k}^{-i} + 1} \times 1 \right] \\ &\leq \sum_{i \in \mathcal{H}_0} \mathbb{E} \left[\frac{F_i(\tau_{\hat{k}^{-i}+1})}{\hat{k}^{-i} + 1} \times \mathbb{E} \left[\frac{\mathbb{1}_{\{p_i > \tau_m\}}}{1 - F_i(\tau_m)} \middle| \hat{k}^{-i} \right] \right] \\ &= \sum_{i \in \mathcal{H}_0} \mathbb{E} \left[\frac{F_i(\tau_{\hat{k}^{-i}+1})}{\hat{k}^{-i} + 1} \frac{\mathbb{1}_{\{p_i > \tau_m\}}}{1 - F_i(\tau_m)} \right] \\ &\leq \sum_{i \in \mathcal{H}_0} \mathbb{E} \left[\frac{F_i(\tau_{\hat{k}^\#+1})}{1 - F_i(\tau_m)} \frac{\mathbb{1}_{\{p_i > \tau_m\}}}{\hat{k}^\# + 1} \mathbb{1}_{\{\hat{k}^\# < m\}} \right] \text{ by the new Lemma}\end{aligned}$$

FDR control with discrete p -values

Proof of the Theorem

► Hence

$$\begin{aligned} \text{FDR}\left(R^{\text{SU}}(\tau)\right) &\leq \sum_{i \in \mathcal{H}_0} \mathbb{E} \left[\frac{F_i(\tau_{\hat{k}^\#+1})}{1 - F_i(\tau_m)} \frac{\mathbb{1}_{\{p_i > \sigma_{\hat{k}^\#}\}}}{\hat{k}^\# + 1} \mathbb{1}_{\{\hat{k}^\# < m\}} \right] \text{ because } \tau_m \geq \sigma_{\hat{k}^\#} \\ &\leq \mathbb{E} \left[\sum_{i \in \mathcal{H}_0} \frac{F_i(\tau_{\hat{k}^\#+1})}{1 - F_i(\tau_m)} \frac{\mathbb{1}_{\{p_i > \sigma_{\hat{k}^\#}\}}}{\hat{k}^\# + 1} \mathbb{1}_{\{\hat{k}^\# < m\}} \right] \end{aligned}$$

► $A = \{i : p_i > \sigma_{\hat{k}^\#}\} = [\![1, m]\!] \setminus R^{\text{SU}}(\sigma)$ so $|A| = m - \hat{k}^\#$ by property of SU

$$\begin{aligned} \text{FDR}\left(R^{\text{SU}}(\tau)\right) &\leq \mathbb{E} \left[\max_{\substack{A \subseteq [\![1, m]\!] \\ |A|=m-\hat{k}^\#}} \sum_{i \in \mathcal{H}_0 \cap A} \frac{F_i(\tau_{\hat{k}^\#+1})}{1 - F_i(\tau_m)} \frac{1}{\hat{k}^\# + 1} \mathbb{1}_{\{\hat{k}^\# < m\}} \right] \\ &\leq \max_{0 \leq k \leq m-1} \max_{\substack{A \subseteq [\![1, m]\!] \\ |A|=m-k}} \sum_{i \in \mathcal{H}_0 \cap A} \frac{F_i(\tau_{k+1})}{1 - F_i(\tau_m)} \frac{1}{k + 1} \quad \square \end{aligned}$$

FDR control with discrete p -values

- ▶ Analog Lemmas for FDR bound and procedures SD
- ▶ HSD: SD with $\tau_k = \max \left\{ t \in \mathcal{S} : \sum_{i=1}^m \frac{F_i(t)}{1-F_i(t)} \leq \alpha k \right\}$
- ▶ AHSD: SD with $\tau_k = \max \left\{ t \in \mathcal{S} : \left(\left(\frac{F_i(t)}{1-F_i(t)} \right)_{(1)} + \cdots + \left(\frac{F_i(t)}{1-F_i(t)} \right)_{(m-k+1)} \right) \leq \alpha k \right\}$
- ▶ Higher critical values than HSU and AHSU, but SD: no one generally better than the other

Theorem [Döhler, Durand, and Roquain (2018)]

Assume that for all $P \in \mathfrak{F}$, the $(p_i)_{i \in \mathcal{H}_0}$ are independent, and they are independent from the $(p_i)_{i \in \mathcal{H}_1}$. Let any critical value sequence τ with $F_i(\tau_m) < 1$ for all $i \in [\![1, m]\!]$.

Then for all $P \in \mathfrak{F}$,

$$\text{FDR} \left(R^{\text{SD}}(\tau) \right) \leq \max_{1 \leq k \leq m} \max_{\substack{A \subseteq [\![1, m]\!] \\ |A|=m-k+1}} \frac{1}{k} \sum_{i \in A} \frac{F_i(\tau_k)}{1 - F_i(\tau_k)}$$

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Exploratory analysis in multiple testing

Exploratory analysis: searching interesting hypotheses that will be cautiously investigated after.

Desired properties [Goeman and Solari (2011)]:

- ▶ Mildness: allows some false positives
- ▶ Flexibility: the procedure does not prescribe, but advise
- ▶ Post hoc: take decisions on the procedure after seeing the data

[Goeman and Solari (2011)]

This **reverses the traditional roles** of the user and procedure in multiple testing. Rather than [...] to let the user choose the quality criterion, and to let the procedure return the collection of rejected hypotheses, the **user chooses the collection of rejected hypotheses freely**, and the multiple testing procedure returns the **associated quality criterion**.

FWER is somewhat flexible, FDR is somewhat mild

Post hoc and replication crisis

Post hoc done wrong: *p*-hacking

- ▶ Pre-selecting variables that seem significant, exclude others
- ▶ Theoretical results no longer hold because the selection step is random
- ▶ Example: selecting the 1000 smallest *p*-values in a genetic study with 10^6 variants

- ▶ *p*-hacking may be one of the causes of the replication crisis (many published results non reproducible)
- ▶ ⇒ need for exploratory analysis MT procedures with the above properties
- ▶ Larger field: selective inference

Post hoc inference

a.k.a. simultaneous inference

Confidence bounds on any set of selected variables

A confidence bound is a (random: depends on X) function \hat{V} such that

$$\forall P \in \mathfrak{F}, \forall \alpha \in]0, 1[, \mathbb{P} \left(\forall S \subset [1, m], V(S) \leq \hat{V}(S) \right) \geq 1 - \alpha$$

- ▶ Hence for any selected $\hat{S} = \hat{S}(X)$, $\mathbb{P} \left(V(\hat{S}) \leq \hat{V}(\hat{S}) \right) \geq 1 - \alpha$ holds
- ▶ Also FDP control: $\mathbb{P} \left(\forall S \subset [1, m], \text{FDP}(S) \leq \frac{\hat{V}(S)}{|S|^{1/2}} \right) \geq 1 - \alpha$, hence (far) better than FDR control
- ▶ Originates from [\[Genovese and Wasserman \(2006\)\]](#), [\[Meinshausen \(2006\)\]](#)
- ▶ A guarantee over any selected set instead of a rejected set, advise some \hat{S} instead of prescribe one R : the MT paradigm is reversed

Post hoc inference

Some first, trivial bounds

- ▶ $\hat{V}(S) = |S|$
- ▶ Let a procedure R controlling the FWER, then $\hat{V}(S) = |S \setminus R|$ is a valid post hoc bound

$$\begin{aligned}\mathbb{P}(\exists S : |S \cap \mathcal{H}_0| > |S \setminus R|) &\leq \mathbb{P}(\exists S : |S \cap \mathcal{H}_0 \cap R^c| + |S \cap \mathcal{H}_0 \cap R| > |S \cap \mathcal{H}_0|) \\ &\leq \mathbb{P}(\exists S : |S \cap \mathcal{H}_0 \cap R| > 0) \\ &\leq \mathbb{P}(|\mathcal{H}_0 \cap R| > 0) \leq \alpha \quad \square\end{aligned}$$

- ▶ Let a procedure R controlling the k -FWER, then $\hat{V}(S) = |S \setminus R| + k - 1$ is a valid post hoc bound

$$\begin{aligned}\mathbb{P}(\exists S : |S \cap \mathcal{H}_0| > |S \setminus R| + k - 1) &\leq \mathbb{P}(\exists S : |S \cap \mathcal{H}_0 \cap R| > k - 1) \\ &\leq \mathbb{P}(|\mathcal{H}_0 \cap R| > k - 1) \leq \alpha \quad \square\end{aligned}$$

BNR technology

[Blanchard, Neuvial, and Roquain (2020)]

Key concept: reference family

- $\mathfrak{R} = (R_k, \zeta_k)_{k \in \mathcal{K}}$ with $R_k \subseteq [1, m]$, $\zeta_k \in [0, |R_k|]$ (everything can depend on X) such that the Joint Error Rate (JER):

$$\text{JER}(\mathfrak{R}) = \mathbb{P}(\exists k, |R_k \cap \mathcal{H}_0| > \zeta_k)$$

is controlled at level α for all $P \in \mathfrak{F}$

- Conversely, $\forall P \in \mathfrak{F}, \mathbb{P}_{X \sim P}(\forall k, |R_k \cap \mathcal{H}_0| \leq \zeta_k) \geq 1 - \alpha$
- Confidence bound only on the $K = |\mathcal{K}|$ members of \mathfrak{R}
- \implies Derivation of a global confidence bound by interpolation

BNR technology

[Blanchard, Neuvial, and Roquain (2020)]

- Idea: we get the following info on \mathcal{H}_0 :

$$\mathcal{H}_0 \in \mathcal{A}(\mathfrak{R}) = \{A \subseteq [\![1, m]\!], \forall k, |R_k \cap A| \leq \zeta_k\}$$

Two different bounds

- $V_{\mathfrak{R}}^*(S) = \max_{A \in \mathcal{A}(\mathfrak{R})} |S \cap A|$ optimal but hard to compute
- $\overline{V}_{\mathfrak{R}}(S) = \min_{k \in \mathcal{K}} (\zeta_k + |S \setminus R_k|) \wedge |S|$ easier to compute
- $\overline{V}_{\mathfrak{R}}$ is worse than $V_{\mathfrak{R}}^*$, proof: let $A \in \mathcal{A}(\mathfrak{R})$
- $|S \cap A| = |S \cap A \cap R_k| + |S \cap A \cap R_k^c| \leq |A \cap R_k| + |S \cap R_k^c| \leq \zeta_k + |S \setminus R_k|$
- True for all k : $|S \cap A| \leq \overline{V}_{\mathfrak{R}}(S)$, true for all A : $V_{\mathfrak{R}}^*(S) \leq \overline{V}_{\mathfrak{R}}(S)$ □

BNR technology

Proposition

Assume that the R_k 's are nested, that is $R_k \subseteq R_{k'}$ or $R_{k'} \subseteq R_k$ for $k, k' \in \mathcal{K}$. Then $V_{\mathfrak{R}}^*(S) = \overline{V}_{\mathfrak{R}}(S)$ for all $S \subseteq \llbracket 1, m \rrbracket$.

- ▶ In the following we identify \mathcal{K} and $\llbracket 1, K \rrbracket$ such that $R_k \subseteq R_{k'}$ for $k \leq k'$
- ▶ $\overline{V}_{\mathfrak{R}}(S) = \min_{k \leq K} (\zeta_k + |S \setminus R_k|) \wedge |S| = \min_{k \leq K} (\zeta_k + |S \setminus (R_k \cap S)|) \wedge |S| = \overline{V}_{\mathfrak{R} \wedge S}(S)$ with $\mathfrak{R} \wedge S = (R_k \cap S, \zeta_k)_{k \leq K}$
- ▶ Let $\tilde{\zeta}_k = \overline{V}_{\mathfrak{R} \wedge S}(R_k \cap S) = \min_{j \leq K} (\zeta_j + |(R_k \cap S) \setminus (R_j \cap S)|) \wedge |R_k \cap S|$ and consider $\tilde{\mathfrak{R}} = (R_k \cap S, \tilde{\zeta}_k)_{k \leq K}$
- ▶ By taking $j = k$, $\tilde{\zeta}_k \leq (\zeta_k + |(R_k \cap S) \setminus (R_k \cap S)|) \wedge |R_k \cap S| \leq \zeta_k$ so $\overline{V}_{\tilde{\mathfrak{R}}}(S) \leq \overline{V}_{\mathfrak{R} \wedge S}(S) = \overline{V}_{\mathfrak{R}}(S)$

BNR technology

Proof of the Proposition

- ▶ Useful set property : $|E \setminus G| \leq |E \setminus F| + |F \setminus G|$

$$\begin{aligned}\overline{V}_{\tilde{\mathfrak{R}}}(S) &= \min_{k \leq K} \left(\min_{j \leq K} (\zeta_j + |(R_k \cap S) \setminus (R_j \cap S)|) \wedge |R_k \cap S| + |S \setminus (R_k \cap S)| \right) \\ &= \min_{k \leq K} \left(\min_{j \leq K} (\zeta_j + |(R_k \cap S) \setminus (R_j \cap S)|) + |S \setminus (R_k \cap S)| \right) \wedge |S| \\ &= \min_{k \leq K} \min_{j \leq K} (\zeta_j + |(R_k \cap S) \setminus (R_j \cap S)| + |S \setminus (R_k \cap S)|) \wedge |S| \\ &\geq \min_{j \leq K} (\zeta_j + |S \setminus (R_j \cap S)|) \wedge |S| = \overline{V}_{\mathfrak{R}_{\wedge S}}(S) = \overline{V}_{\mathfrak{R}}(S)\end{aligned}$$

- ▶ So $\overline{V}_{\tilde{\mathfrak{R}}}(S) = \overline{V}_{\mathfrak{R}}(S)$ (self-consistency result)
- ▶ Remark: this intermediate result does not use the nestedness and is true in general

BNR technology

Proof of the Proposition

- ▶ Let's construct $A \subseteq S$, $A \in \mathcal{A}(\mathfrak{R})$ such that $|A| \geq \overline{V}_{\mathfrak{R}}(S)$, will imply $V_{\mathfrak{R}}^*(S) \geq \overline{V}_{\mathfrak{R}}(S)$
- ▶ By nestedness,

$$\begin{aligned}\tilde{\zeta}_k &= \min_{j \leq K} (\zeta_j + |(R_k \cap S) \setminus (R_j \cap S)|) \wedge |R_k \cap S| \\ &\leq \min_{j \leq K} (\zeta_j + |(R_{k+1} \cap S) \setminus (R_j \cap S)|) \wedge |R_{k+1} \cap S| \\ &= \tilde{\zeta}_{k+1}\end{aligned}$$

BNR technology

Proof of the Proposition

► Furthermore,

$$\begin{aligned}\tilde{\zeta}_{k+1} &= \min_{j \leq K} (\zeta_j + |(R_{k+1} \cap S) \setminus (R_j \cap S)|) \wedge |R_{k+1} \cap S| \\ &\leq \min_{j \leq K} (\zeta_j + |(R_{k+1} \cap S) \setminus (R_k \cap S)| + |(R_k \cap S) \setminus (R_j \cap S)|) \wedge |R_{k+1} \cap S| \\ &= (|(R_{k+1} \cap S) \setminus (R_k \cap S)| + \min_{j \leq K} (\zeta_j + |(R_k \cap S) \setminus (R_j \cap S)|)) \wedge |R_{k+1} \cap S| \\ &= |(R_{k+1} \cap S) \setminus (R_k \cap S)| + \min_{j \leq K} (\zeta_j + |(R_k \cap S) \setminus (R_j \cap S)|) \wedge |R_k \cap S| \\ (\text{nestedness: } |R_{k+1} \cap S| &= |(R_{k+1} \cap S) \setminus (R_k \cap S)| + |R_k \cap S|) \\ &= |(R_{k+1} \cap S) \setminus (R_k \cap S)| + \tilde{\zeta}_k\end{aligned}$$

► So $0 \leq \tilde{\zeta}_{k+1} - \tilde{\zeta}_k \leq |(R_{k+1} \cap S) \setminus (R_k \cap S)|$

BNR technology

Proof of the Proposition

- ▶ Let $B_k = \{\tilde{\zeta}_k - \tilde{\zeta}_{k-1}\}$ elements of $(R_k \cap S) \setminus (R_{k-1} \cap S)\}$, $1 \leq k \leq K$, with $R_0 = \emptyset$ and $\tilde{\zeta}_0 = 0$
- ▶ Let $A = \bigcup_{k=1}^K B_k \cup (S \setminus (R_K \cap S))$, disjoint union because of nestedness, $A \subseteq S$
- ▶ $|R_k \cap A| = \left| \bigcup_{\ell=1}^k B_\ell \right| = \sum_{\ell=1}^k |B_\ell| = \sum_{\ell=1}^k (\tilde{\zeta}_\ell - \tilde{\zeta}_{\ell-1}) = \tilde{\zeta}_k \leq \zeta_k$ so $A \in \mathcal{A}(\mathfrak{R})$
- ▶ $|A| = \sum_{\ell=1}^K |B_\ell| + |S \setminus (R_K \cap S)| = \tilde{\zeta}_K + |S \setminus (R_K \cap S)| = (\tilde{\zeta}_K + |S \setminus (R_K \cap S)|) \wedge |S|$ because $A \subseteq S$
- ▶ Finally $\overline{V}_{\mathfrak{R}}(S) = \overline{V}_{\tilde{\mathfrak{R}}}(S) \leq (\tilde{\zeta}_K + |S \setminus (R_K \cap S)|) \wedge |S| = |A|$ □

BNR technology

- ▶ How to construct effectively a reference family $(R_k, \zeta_k)_{k \in \mathcal{K}}$ with JER control?
- ▶ One approach: constrain $\zeta_k = k - 1$, $R_k = \{i \in [\![1, m]\!], p_i \leq t_k\}$, $k \in [\![1, m]\!]$, $t_k \nearrow$ and search for valid $(t_k)_{1 \leq k \leq m}$
- ▶ In this case, $R_k \subseteq R_{k+1}$: nestedness hence $\bar{V}_{\mathfrak{R}}$ optimal
- ▶ In this case, $\text{JER}(\mathfrak{R}) = \mathbb{P}(\exists k, |R_k \cap \mathcal{H}_0| \geq k)$: k -FWER but simultaneous over all k
- ▶ $(t_k)_{1 \leq k \leq m}$ can be constructed with probabilistic inequalities

Simes and Hommel inequalities

[Hommel (1983)], [Simes (1986)]

- ▶ Let U_1, \dots, U_{m_0} m_0 super-uniform random variables
- ▶ Then $\mathbb{P} \left(\exists i \leq m_0, U_{(i)} \leq \frac{\alpha i}{m_0 H_{m_0}} \right) \leq \alpha$ (Hommel inequality)
- ▶ If, furthermore, they are wPRDS on $\llbracket 1, m_0 \rrbracket$,
 $\mathbb{P} \left(\exists i \leq m_0, U_{(i)} \leq \frac{\alpha i}{m_0} \right) \leq \alpha$ (Simes inequality)

Simes and Hommel inequalities

Proofs

- ▶ Consider the model $\mathfrak{F}_U = \{\mathbb{P}_{U_1, \dots, U_{m_0}}\}$ with $H_{0,i} = \mathfrak{F}_U$ for all $i \in [1, m_0]$, the U_i 's are valid p -values
- ▶ Note that FWER = FDR when all null hypotheses are true, which is the case here

$$\begin{aligned}\mathbb{P}\left(\exists i \leq m_0, U_{(i)} \leq \frac{\alpha i}{m_0 H_{m_0}}\right) &= \text{FWER}(R^{\text{BY}}) \\ &= \text{FDR}(R^{\text{BY}}) \\ &\leq \alpha \quad \square\end{aligned}$$

- ▶ Same proof for Simes and wPRDS using the FDR control of BH □

BNR technology

- ▶ Consequence: $\forall P \in \mathfrak{F}$,

$\mathbb{P} \left(\exists i \leq m_0, p_{(i:\mathcal{H}_0)} \leq \frac{\alpha i}{m H_m} \right) \leq \mathbb{P} \left(\exists i \leq m_0, p_{(i:\mathcal{H}_0)} \leq \frac{\alpha i}{m_0 H_{m_0}} \right) \leq \alpha$ and
similarly with wPRDS on \mathcal{H}_0 , $\mathbb{P} \left(\exists i \leq m_0, p_{(i:\mathcal{H}_0)} \leq \frac{\alpha i}{m} \right) \leq \alpha$

- ▶ $t_k = \frac{\alpha k}{m H_m}$ induces JER control, and if wPRDS on \mathcal{H}_0 $\forall P \in \mathfrak{F}$,
 $t_k = \frac{\alpha k}{m}$ too
- ▶ Proof: let $c_m = H_m$ or 1 depending on the case (Hommel or Simes)

$$\begin{aligned}\exists k \leq K : |R_k \cap \mathcal{H}_0| \geq k &\Leftrightarrow \exists k \leq m_0 : \left| \left\{ i \in [\![1, m]\!] : p_i \leq \frac{\alpha k}{mc_m} \right\} \cap \mathcal{H}_0 \right| \geq k \\ &\Leftrightarrow \exists k \leq m_0 : \left| \left\{ i \in \mathcal{H}_0 : p_i \leq \frac{\alpha k}{mc_m} \right\} \right| \geq k \\ &\Leftrightarrow \exists k \leq m_0 : p_{(k:\mathcal{H}_0)} \leq \frac{\alpha k}{mc_m} \quad \square\end{aligned}$$

BNR technology

Theorem [Blanchard, Neuvial, and Roquain (2020)]

The bound $V_{\mathfrak{R}_{Hommel}}^* : S \mapsto \min_{1 \leq k \leq m} \left(k - 1 + \sum_{i \in S} \mathbb{1}_{\{p_i > \frac{\alpha k}{m H_m}\}} \right) \wedge |S|$ is a valid confidence bound, associated to the reference family $\mathfrak{R}_{Hommel} = \left(\left\{ i : p_i \leq \frac{\alpha k}{m H_m} \right\}, k - 1 \right)_{k \in \llbracket 1, m \rrbracket}$.

If, for all $P \in \mathfrak{F}$, the (p_i) are wPRDS with \mathcal{H}_0 as the subset, the bound $V_{\mathfrak{R}_{Simes}}^* : S \mapsto \min_{1 \leq k \leq m} \left(k - 1 + \sum_{i \in S} \mathbb{1}_{\{p_i > \frac{\alpha k}{m}\}} \right) \wedge |S|$ is a valid confidence bound, associated to the reference family $\mathfrak{R}_{Simes} = \left(\left\{ i : p_i \leq \frac{\alpha k}{m} \right\}, k - 1 \right)_{k \in \llbracket 1, m \rrbracket}$.

Closed testing

[Marcus, Peritz, and Gabriel (1976)]

- ▶ Designed for FWER control
- ▶ Form $H_{0,I} = \bigcap_{i \in I} H_{0,i}$ all intersection hypotheses
- ▶ Have a collection of α -level local intersection tests ϕ_I :
 $\forall P \in H_{0,I}, \mathbb{P}_{X \sim P}(\phi_I(X) = 1) \leq \alpha$
- ▶ Examples:
 - ▶ Bonferroni local test $\phi_I = 1$ if $\exists i \in I : p_i \leq \frac{\alpha}{|I|}$
 - ▶ Hommel local test $\phi_I = 1$ if $\exists i \in I : p_{(i:I)} \leq \frac{\alpha i}{|I| |H_{|I|}|}$
 - ▶ Simes local test $\phi_I = 1$ if $\exists i \in I : p_{(i:I)} \leq \frac{\alpha i}{|I|}$ (under wPRDS on \mathcal{H}_0)
 - ▶ Proofs: if $P \in H_{0,I}$, $P \in H_{0,i}$ for all $i \in I$ so $\mathcal{L}(p_i) \succeq \mathcal{U}([0, 1])$ for all $i \in I$

□

Closed testing

- ▶ Closed testing: iteratively test $H_{0,I}$ only if all $H_{0,J}$, $J \supsetneq I$, are rejected, then reject the individual hypotheses $H_{0,i}$ such that $H_{0,\{i\}}$ has been rejected: $R^{Closed} = \{i \in [1, m] : \forall I \subseteq [1, m] \text{ with } i \in I, \phi_I = 1\}$
- ▶ $\forall P \in \mathfrak{F}, \text{FWER}(R^{Closed}) \leq \alpha$
- ▶ $P \in H_{0,\mathcal{H}_0}$ (tautological), so

$$\begin{aligned}\text{FWER}(R^{Closed}) &= \mathbb{P}(\exists i \in \mathcal{H}_0 : \forall I \subseteq [1, m], i \in I, \phi_I = 1) \\ &\leq \mathbb{P}(\phi_{\mathcal{H}_0} = 1) \\ &\leq \alpha \quad \square\end{aligned}$$

- ▶ Remark: each intersection test at level α , no multiplicity adjustment to the number of intersection hypotheses tested (only $\phi_{\mathcal{H}_0}$ matters)

Closed testing

A fun result

Proposition

Assume that closed testing is conducted with the Bonferroni intersection test $\phi_I = \mathbb{1}_{\{\exists i \in I : p_i \leq \frac{\alpha}{|I|}\}}$. Then $R^{Closed} = R^{\text{HB}}$ a.s.

- ▶ First note that $\forall k \in [\![1, m]\!], \forall I$ such that $|I| = m - k + 1, \exists k' \leq k$ such that $p_{(k')} \in \{p_i : i \in I\}$, because if $p_i > p_{(k)}$ for all $i \in I$ then $|I| \leq m - k$
- ▶ If $p_i \leq \frac{\alpha}{m - \hat{k}^{\text{HB}} + 1}$ (implies $\hat{k}^{\text{HB}} \geq 1$), let I such that $i \in I$, we want $\phi_I = 1$. 2 cases.
- ▶ If $|I| \leq m - \hat{k}^{\text{HB}} + 1$ then $p_i \leq \frac{\alpha}{m - \hat{k}^{\text{HB}} + 1} \leq \frac{\alpha}{|I|}$ so $\phi_I = 1$
- ▶ If $|I| > m - \hat{k}^{\text{HB}} + 1$ (implies $\hat{k}^{\text{HB}} \geq 2$), $|I| = m - k + 1$ with $k \in [\![1, \hat{k}^{\text{HB}}]\!]$. Let $k' \leq k$ such that $p_{(k')} \in \{p_i : i \in I\}$. $k' \leq \hat{k}^{\text{HB}}$ so by definition of SD procedures $p_{(k')} \leq \frac{\alpha}{m - k' + 1} \leq \frac{\alpha}{m - k + 1} = \frac{\alpha}{|I|}$ so $\phi_I = 1$
- ▶ Hence $R^{\text{HB}} \subseteq R^{Closed}$

Closed testing

Proof of the Proposition

- ▶ Let $i \in R^{\text{Closed}}$: $\phi_I = 1$ for all I such that $i \in I$
- ▶ Let $\tilde{k} = \min \left\{ k \in [\![1, m]\!] : p_i \leq \frac{\alpha}{m-k+1} \right\}$, well-defined because $\phi_{\{i\}} = 1$ so $p_i \leq \alpha$
- ▶ Goal : show that $\tilde{k} \leq \hat{k}^{\text{HB}}$, will imply $i \in R^{\text{HB}}$
- ▶ By recursion, $p_{(k')} \leq \frac{\alpha}{m-k'+1}$ for all $k' \in [\![1, \tilde{k}]\!]$, imply $\tilde{k} \leq \hat{k}^{\text{HB}}$ by definition
- ▶ $k' = 1$: $\phi_{[\![1, m]\!]} = 1$ so $p_{(1)} \leq \frac{\alpha}{m}$
- ▶ Let $k' < \tilde{k}$, by definition of \tilde{k} , $p_i > \frac{\alpha}{m-k'+1} \geq p_{(k')} \geq \dots \geq p_{(1)}$
- ▶ So $i \in I = [\![1, m]\!] \setminus \{(1), \dots, (k')\}$ with $|I| = m - k'$. $i \in R^{\text{Closed}}$ so $\phi_I = 1$, hence $\exists j \in I : p_j \leq \frac{\alpha}{|I|} = \frac{\alpha}{m-(k'+1)+1}$ hence $p_{(k'+1)} = \min_{j \in I} p_i \leq \frac{\alpha}{m-(k'+1)+1}$

□

Closed testing for post hoc inference

[Goeman and Solari (2011)]

Main idea

The closed testing provides more information than just the individual rejections:

- ▶ Let \mathcal{X} the (random) set of all I such that we rejected $H_{0,I}$
- ▶ Simultaneous guarantee over all $H_{0,I}, I \in \mathcal{X}$:

$$\forall P \in \mathfrak{F}, \mathbb{P}(\exists I \in \mathcal{X}, P \in H_{0,I}) \leq \alpha$$

- ▶ Proof: as before, if $P \in H_{0,I}, I \subseteq \mathcal{H}_0$, so $\mathcal{H}_0 \in \mathcal{X}$, so $\phi_{\mathcal{H}_0} = 1$



Closed testing for post hoc inference

- ▶ A simple example where the closed testing is more informative than the resulting FWER procedure:
- ▶ $p_1 = \frac{2\alpha}{3}$, $p_2 = \frac{2\alpha}{3}$, $p_3 = 1$, and Simes intersection test
- ▶ $p_{(k)} \leq \alpha \frac{k}{3}$ for $k = 1$ and 2 so $H_{0,\{1,2,3\}}$ rejected
- ▶ $p_{(2)} \leq \alpha \frac{2}{2}$ so $H_{0,\{1,2\}}$ rejected
- ▶ But $p_{(1)} > \frac{\alpha}{2}$, $p_{(2)} > \frac{\alpha}{2}$ and $p_{(3)} > \alpha$ so $H_{0,\{1,3\}}$ and $H_{0,\{2,3\}}$ conserved
- ▶ Hence $H_{0,\{1\}}$, $H_{0,\{2\}}$ and $H_{0,\{3\}}$ all conserved and $R^{Closed} = \emptyset$, but we learned that there is signal in $H_{0,\{1,2,3\}}$ and $H_{0,\{1,2\}}$!

Closed testing for post hoc inference

Confidence bound derivation

- ▶ The proposed confidence bound is $V_{GS}(S) = \max_{\substack{J \subseteq S \\ J \notin \mathcal{X}}} |J|$
- ▶ Uses all information in \mathcal{X} , not just singletons
- ▶ First note that $V_{GS}(S) = \max_{J \notin \mathcal{X}} |S \cap J|$, \leq obvious, and if $J \notin \mathcal{X}$, $S \cap J \in \mathcal{X}$ would imply $J \in \mathcal{X}$ by closure, so $S \cap J \notin \mathcal{X}$ and \geq achieved
- ▶ $V_{GS}(S) = \max_{\substack{J \subseteq S \\ J \notin \mathcal{X}}} |J|$ is a valid confidence bound because

$$\begin{aligned}\mathbb{P}(\exists S, |S \cap \mathcal{H}_0| > V_{GS}(S)) &\leq \mathbb{P}\left(\exists S, |S \cap \mathcal{H}_0| > \max_{J \notin \mathcal{X}} |S \cap J|\right) \\ &\leq \mathbb{P}(\mathcal{H}_0 \in \mathcal{X}) \\ &\leq \mathbb{P}(\phi_{\mathcal{H}_0} = 1) \leq \alpha \quad \square\end{aligned}$$

Closed testing for post hoc inference

JER equivalence

Proposition

$\mathfrak{R} = (I, |I| - 1)_{I \in \mathcal{X}}$ controls the JER and $V_{GS}(S) = V_{\mathfrak{R}}^*(S)$.

$$\begin{aligned}\mathbb{P}(\exists I \in \mathcal{X} : |I \cap \mathcal{H}_0| > |I| - 1) &\leq \mathbb{P}(\exists I \in \mathcal{X} : |I \cap \mathcal{H}_0| = |I|) \\ &\leq \mathbb{P}(\exists I \in \mathcal{X} : I \subseteq \mathcal{H}_0) \\ &\leq \mathbb{P}(\mathcal{H}_0 \in \mathcal{X}) \text{ by closure} \\ &\leq \mathbb{P}(\phi_{\mathcal{H}_0} = 1) \leq \alpha\end{aligned}$$

- ▶ Recall $V_{GS}(S) = \max_{J \in \mathcal{X}^c} |S \cap J|$
- ▶ $\mathcal{A}(\mathfrak{R})^c = \{A : \exists I \in \mathcal{X}, |I \cap A| = |I|\} = \{A : \exists I \in \mathcal{X}, I \cap A = I\} = \{A : \exists I \in \mathcal{X}, I \subseteq A\} = \mathcal{X}$ by closure
- ▶ So $V_{GS}(S) = \max_{J \in \mathcal{A}(\mathfrak{R})} |S \cap J| = V_{\mathfrak{R}}^*(S)$ □

Closed testing for post hoc inference

JER equivalence

Proposition

Reciprocally, let \mathfrak{R} that controls the JER, then there exists a collection of intersection tests for which $V_{GS}(S) = V_{\mathfrak{R}}^*(S)$.

- ▶ Let $\phi_I = \mathbb{1}_{\{I \notin \mathcal{A}(\mathfrak{R})\}}$, valid test : let $P \in H_{0,I}$, so $I \subseteq \mathcal{H}_0$, then

$$\begin{aligned}\mathbb{P}(I \notin \mathcal{A}(\mathfrak{R})) &= \mathbb{P}(\exists k \in \mathcal{K} : |I \cap R_k| > \zeta_k) \\ &\leq \mathbb{P}(\exists k \in \mathcal{K} : |\mathcal{H}_0 \cap R_k| > \zeta_k) \leq \alpha\end{aligned}$$

- ▶ By definition, $\mathcal{A}(\mathfrak{R})$ = exactly the conserved intersection hypotheses, so trivially $\mathcal{A}(\mathfrak{R}) \subseteq \mathcal{X}^c$ and $V_{\mathfrak{R}}^*(S) \leq V_{GS}(S)$
- ▶ Conversely, if $J \in \mathcal{X}^c$, there is $B \in \mathcal{A}(\mathfrak{R})$ such that $J \subseteq B$ so $|S \cap J| \leq |S \cap B|$ and so $V_{GS}(S) \leq V_{\mathfrak{R}}^*(S)$

□

Back to BNR technology

[Durand et al. (2020)]

- ▶ How to construct effectively a reference family $(R_k, \zeta_k)_{k \in \mathcal{K}}$ with JER control?
- ▶ Another approach: constrain R_k to some deterministic regions (using prior knowledge like gene ontologies) and (super-)estimate $|R_k \cap \mathcal{H}_0|$ to get a ζ_k

Proposition

If the R_k form a partition of $\llbracket 1, m \rrbracket$, then $V_{\mathfrak{R}}^*(S) = \sum_{k \in \mathcal{K}} \zeta_k \wedge |S \cap R_k|$.

- ▶ Let any $A \in \mathcal{A}(\mathfrak{R})$, $|R_k \cap A| \leq \zeta_k$ so $|A \cap S| = \sum_{k \in \mathcal{K}} |A \cap S \cap R_k|$ with $|A \cap S \cap R_k| \leq |R_k \cap A| \leq \zeta_k$ and $|A \cap S \cap R_k| \leq |S \cap R_k|$ so by taking the max, $V_{\mathfrak{R}}^*(S) \leq \sum_{k \in \mathcal{K}} \zeta_k \wedge |S \cap R_k|$
- ▶ Construct $A = \bigcup_{k \in \mathcal{K}} \{\zeta_k \wedge |S \cap R_k| \text{ elements of } S \cap R_k\}$, $A \in \mathcal{A}(\mathfrak{R})$ so $\sum_{k \in \mathcal{K}} \zeta_k \wedge |S \cap R_k| = |A| \leq V_{\mathfrak{R}}^*(S)$ □

Back to BNR technology

ζ_k computation

Theorem

Assume that for all $P \in \mathfrak{F}$, the $(p_i)_{i \in \mathcal{H}_0}$ are independent, and they are independent from the $(p_i)_{i \in \mathcal{H}_1}$.

Assume that \mathcal{K} and the R_k are deterministic. Let $C_\lambda = \sqrt{\frac{1}{2} \log \left(\frac{1}{\lambda} \right)}$ for all $\lambda \in]0, 1[$. Let

$$\zeta_k = |R_k| \wedge \min_{t \in [0, 1[} \left[\frac{C_{\frac{\alpha}{K}}}{2(1-t)} + \left(\frac{C_{\frac{\alpha}{K}}^2}{4(1-t)^2} + \frac{\sum_{i \in R_k} \mathbb{1}_{\{p_i > t\}}}{1-t} \right)^{1/2} \right]^2$$

Then, if $\frac{\alpha}{K} < \frac{1}{2}$, \mathfrak{R} controls the JER at level α .

Back to BNR technology

ζ_k computation

- ▶ In practice,

$$\zeta_k = |R_k| \wedge \min_{0 \leq \ell \leq |R_k|} \left[\frac{C_{\frac{\alpha}{K}}}{2(1-p_{(\ell:R_k)})} + \left(\frac{C_{\frac{\alpha}{K}}^2}{4(1-p_{(\ell:R_k)})^2} + \frac{s-\ell}{1-p_{(\ell:R_k)}} \right)^{1/2} \right]^2$$

- ▶ Entry cost: $\zeta_k \geq \left\lfloor C_{\frac{\alpha}{K}}^2 \right\rfloor = \left\lfloor \log \left(\frac{K}{\alpha} \right) \right\rfloor \geq 1$ as soon as $\alpha \leq e^{-2}K$: impossible to detect regions made of pure signal
- ▶ $\frac{\alpha}{K}$: union bound correction w.r.t. the number of regions
- ▶ Dependency on α and K are only through a log

Back to BNR technology

Proof of the Theorem

- ▶ Dvoretzky-Kiefer-Wolfowitz-Massart inequality [Massart (1990)]: let any $S \subseteq \llbracket 1, m \rrbracket$, $S_0 = S \cap \mathcal{H}_0$ $\nu = |S_0|$ and U_1, \dots, U_m i.i.d. r.v. with $\mathbb{P}_{U_1} = \mathcal{U}([0, 1])$. For all $\varepsilon \geq \sqrt{\frac{1}{2\nu} \log 2}$,

$$\begin{aligned}\mathbb{P} \left(\sup_{t \in \mathbb{R}} \left(\frac{1}{\nu} \sum_{i \in S_0} \mathbb{1}_{\{U_i \leq t\}} - u(t) \right) > \varepsilon \right) &= \mathbb{P} \left(\sup_{t \in [0, 1[} \left(\frac{1}{\nu} \sum_{i \in S_0} \mathbb{1}_{\{U_i \leq t\}} - t \right) > \varepsilon \right) \\ &\leq e^{-2\nu\varepsilon^2}\end{aligned}$$

- ▶ Let any $\lambda < \frac{1}{2}$ and $\varepsilon = \sqrt{\frac{1}{2\nu} \log \left(\frac{1}{\lambda} \right)} = \frac{1}{\sqrt{\nu}} C_\lambda$, $\varepsilon \geq \sqrt{\frac{1}{2\nu} \log 2}$

Back to BNR technology

Proof of the Theorem

- ▶ So, $\mathbb{P} \left(\sup_{t \in [0,1]} \left(\frac{1}{\nu} \sum_{i \in S_0} \mathbb{1}_{\{U_i \leq t\}} - t \right) > \varepsilon \right) \leq \lambda$
- ▶ $\mathbb{P} \left(\sup_{t \in [0,1]} \left(\frac{1}{\nu} \sum_{i \in S_0} \mathbb{1}_{\{U_i \leq t\}} - t \right) \leq \varepsilon \right) \geq 1 - \lambda$
- ▶ $\mathbb{P} \left(\inf_{t \in [0,1]} \left(t - \frac{1}{\nu} \sum_{i \in S_0} \mathbb{1}_{\{U_i \leq t\}} \right) \geq -\varepsilon \right) \geq 1 - \lambda$
- ▶ $\mathbb{P} \left(\forall t \in [0, 1[, t - \frac{1}{\nu} \sum_{i \in S_0} \mathbb{1}_{\{U_i \leq t\}} \geq -\varepsilon \right) \geq 1 - \lambda$
- ▶ $\mathbb{P} \left(\forall t \in [0, 1[, \left(1 - \frac{1}{\nu} \sum_{i \in S_0} \mathbb{1}_{\{U_i \leq t\}} \right) - (1-t) \geq -\varepsilon \right) \geq 1 - \lambda$
- ▶ $\mathbb{P} \left(\forall t \in [0, 1[, \frac{1}{\nu} \sum_{i \in S_0} \mathbb{1}_{\{U_i > t\}} - (1-t) \geq -\varepsilon \right) \geq 1 - \lambda$

Back to BNR technology

Proof of the Theorem

- With $\mathbb{P} \geq 1 - \lambda$, for all $t \in [0, 1[$,
 $\sum_{i \in S_0} \mathbb{1}_{\{U_i > t\}} - \nu(1-t) + \sqrt{\nu} C_\lambda \geq 0$, let $x = \sqrt{\nu}$ and solve this second degree polynom in x
- $\Delta = C_\lambda^2 + 4(1-t) \sum_{i \in S_0} \mathbb{1}_{\{U_i > t\}} > 0$, the polynom is ≥ 0 inside of its two real roots $\frac{C_\lambda \pm \sqrt{C_\lambda^2 + 4(1-t) \sum_{i \in S_0} \mathbb{1}_{\{U_i > t\}}}}{2(1-t)}$, one is ≤ 0 and the other ≥ 0 , and $x = \sqrt{\nu} \geq 0$, so

$$\begin{aligned}x &\leq \frac{C_\lambda + \sqrt{C_\lambda^2 + 4(1-t) \sum_{i \in S_0} \mathbb{1}_{\{U_i > t\}}}}{2(1-t)} \\&= \frac{C_\lambda}{2(1-t)} + \left(\frac{C_\lambda^2}{4(1-t)^2} + \frac{\sum_{i \in S_0} \mathbb{1}_{\{U_i > t\}}}{1-t} \right)^{1/2}\end{aligned}$$

Back to BNR technology

Proof of the Theorem

- With $\mathbb{P} \geq 1 - \lambda$, for all $t \in [0, 1[$,

$$\nu \leq \left(\frac{C_\lambda}{2(1-t)} + \left(\frac{C_\lambda^2}{4(1-t)^2} + \frac{\sum_{i \in S_0} \mathbb{1}_{\{U_i > t\}}}{1-t} \right)^{1/2} \right)^2$$

- Let $b_{it} = \mathbb{P}(p_i \leq t)$, for $i \in \mathcal{H}_0$, $b_{it} \leq t$ so $\mathbb{1}_{\{U_i > t\}} \leq \mathbb{1}_{\{U_i > b_{it}\}}$
- Then,

$$\mathbb{P} \left(\nu \leq \min_{t \in [0,1[} \left(\frac{C_\lambda}{2(1-t)} + \left(\frac{C_\lambda^2}{4(1-t)^2} + \frac{\sum_{i \in S_0} \mathbb{1}_{\{U_i > b_{it}\}}}{1-t} \right)^{1/2} \right)^2 \right) \geq 1 - \lambda$$

Back to BNR technology

Proof of the Theorem

► Lemma: $\left(\sum_{i \in S_0} \mathbb{1}_{\{U_i > b_{it}\}} \right)_{t \in [0,1[} \stackrel{\mathcal{L}}{=} \left(\sum_{i \in S_0} \mathbb{1}_{\{p_i > t\}} \right)_{t \in [0,1[}$

► So

$$\mathbb{P} \left(\nu \leq \min_{t \in [0,1[} \left(\frac{C_\lambda}{2(1-t)} + \left(\frac{C_\lambda^2}{4(1-t)^2} + \frac{\sum_{i \in S_0} \mathbb{1}_{\{p_i > t\}}}{1-t} \right)^{1/2} \right)^2 \right) \geq 1 - \lambda$$

► And finally

$$\mathbb{P} \left(|S \cap \mathcal{H}_0| \leq \min_{t \in [0,1[} \left(\frac{C_\lambda}{2(1-t)} + \left(\frac{C_\lambda^2}{4(1-t)^2} + \frac{\sum_{i \in S} \mathbb{1}_{\{p_i > t\}}}{1-t} \right)^{1/2} \right)^2 \right) \geq 1 - \lambda$$

► Apply this to $S = R_k$ and $\lambda = \frac{\alpha}{K}$, add the $\lfloor \cdot \rfloor$ and $|R_k| \wedge$ freely, and use a union bound to conclude



Back to BNR technology

Proof of the Lemma

- We show that the marginals finite-dimensional are equal, only with two marginals w.l.o.g.: let $t_1 < t_2 \in [0, 1[$
- We show $\left(\sum_{i \in S_0} \mathbb{1}_{\{U_i > b_{it_1}\}}, \sum_{i \in S_0} \mathbb{1}_{\{U_i > b_{it_2}\}} \right) \stackrel{\mathcal{L}}{=} \left(\sum_{i \in S_0} \mathbb{1}_{\{p_i > t_1\}}, \sum_{i \in S_0} \mathbb{1}_{\{p_i > t_2\}} \right)$ with the equality of the characteristic functions

$$\begin{aligned}\phi(s, u) &= \mathbb{E} \left[\exp \left(\imath s \sum_{i \in S_0} \mathbb{1}_{\{U_i > b_{it_1}\}} + \imath u \sum_{i \in S_0} \mathbb{1}_{\{U_i > b_{it_2}\}} \right) \right] \\ &= \prod_{i \in S_0} \mathbb{E} \left[\exp \left(\imath s \mathbb{1}_{\{U_i > b_{it_1}\}} + \imath u \mathbb{1}_{\{U_i > b_{it_2}\}} \right) \right]\end{aligned}$$

by independence

- Same for $\left(\sum_{i \in S_0} \mathbb{1}_{\{p_i > t_1\}}, \sum_{i \in S_0} \mathbb{1}_{\{p_i > t_2\}} \right)$: showing equality inside the product is enough

Back to BNR technology

Proof of the Lemma

- ▶ $(b_{it})_t$ nondecreasing so

$$\begin{aligned}\phi_i(s, u) &= \mathbb{E} \left[\exp \left(\imath s \mathbb{1}_{\{U_i > b_{it_1}\}} + \imath u \mathbb{1}_{\{U_i > b_{it_2}\}} \right) \right] \\ &= \mathbb{E} \left[\exp \left(\imath(s+u) \mathbb{1}_{\{U_i > b_{it_2}\}} + \imath s \mathbb{1}_{\{b_{it_2} \geq U_i > b_{it_1}\}} \right) \right] \\ &= \int_{[0,1]} e^{\imath(s+u)\mathbb{1}_{\{x > b_{it_2}\}} + \imath s \mathbb{1}_{\{b_{it_2} \geq x > b_{it_1}\}}} dx \\ &= \int_{]b_{it_2}, 1]} e^{\imath(s+u)} dx + \int_{]b_{it_1}, b_{it_2}]} e^{\imath s} dx + \int_{[0, b_{it_1}]} dx \\ &= e^{\imath(s+u)}(1 - b_{it_2}) + e^{\imath s}(b_{it_2} - b_{it_1}) + b_{it_1}\end{aligned}$$

Back to BNR technology

Proof of the Lemma

► Similarly,

$$\begin{aligned}\psi_i(s, u) &= \mathbb{E} \left[\exp \left(\imath s \mathbb{1}_{\{p_i > t_1\}} + \imath u \mathbb{1}_{\{p_i > t_2\}} \right) \right] \\ &= \mathbb{E} \left[\exp \left(\imath(s+u) \mathbb{1}_{\{p_i > t_2\}} + \imath s \mathbb{1}_{\{t_2 \geq p_i > t_1\}} \right) \right] \\ &= \int_{[0,1]} e^{\imath(s+u)\mathbb{1}_{\{x>t_2\}} + \imath s \mathbb{1}_{\{t_2 \geq x > t_1\}}} \mathbb{P}_{p_i}(dx) \\ &= \int_{]t_2,1]} e^{\imath(s+u)} \mathbb{P}_{p_i}(dx) + \int_{]t_1,t_2]} e^{\imath s} \mathbb{P}_{p_i}(dx) + \int_{[0,t_1]} \mathbb{P}_{p_i}(dx) \\ &= e^{\imath(s+u)} \mathbb{P}_{p_i}(]t_2, 1]) + e^{\imath s} \mathbb{P}_{p_i}(]t_1, t_2]) + \mathbb{P}_{p_i}([0, t_1]) \\ &= e^{\imath(s+u)} (1 - b_{it_2}) + e^{\imath s} (b_{it_2} - b_{it_1}) + b_{it_1} \quad \square\end{aligned}$$

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