Tests multiples et bornes post hoc pour des données hétérogènes

Soutenance de thèse

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Summary of contributions

- 2 published papers on previous works [Durand and Lessard (2016)], [Chatelain et al. (2018)]
- 1 paper in revision about optimal weighting arXiv:1710.01094
- 1 published paper about discrete tests [Döhler, Durand, and Roquain (2018)]
- 1 submitted paper about post hoc arXiv:1807.01470
- participation to 2 R packages: DiscreteFDR and sansSouci

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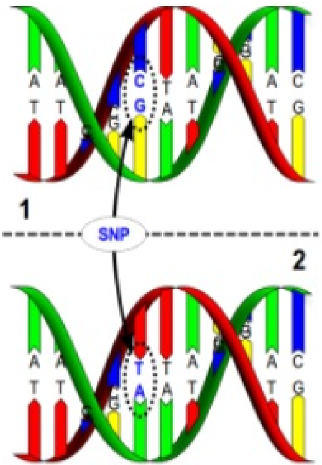
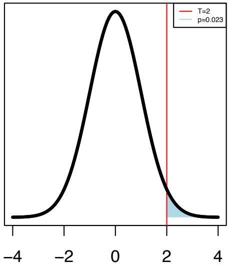
SNP association study

- A SNP = a location on the genome where there is variation
- Study the association of a SNP with a trait: case-control study
- Apply a **statistical test** to a measure $X \sim \mathcal{N}(\mu, 1)$
- Question: is $\mu = 0$ (no association) or > 0 ?



Single testing

- Null hypothesis H_0: "$\mu = 0$" versus alternative H_1: "$\mu > 0$"
- X in the tail of $\mathcal{N}(0,1) \Rightarrow$ unrealistic $\Rightarrow$ reject H_0
- $\Leftrightarrow$ Reject H_0 if the p-value $p(X) = \bar{\Phi}(X)$ is small ($\leq \alpha$)



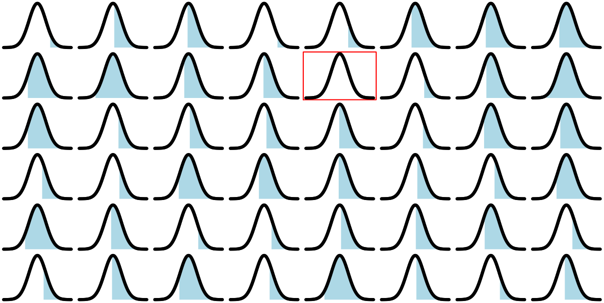
Probability to wrongly reject H_0

$$\mathbb{P}_{H_0}(p(X) \leq \alpha) \leq \alpha \text{ (uniformity under } H_0)$$

$\Longrightarrow$ false positive control

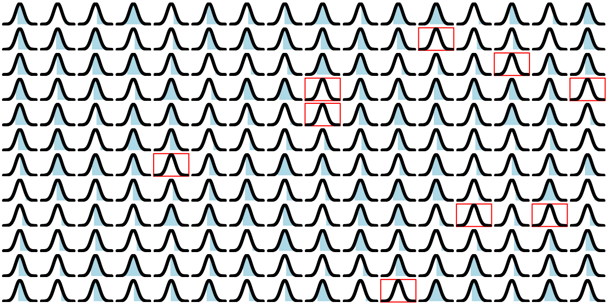
Multiple testing

- Now what if we test m SNPs at the same time?
- m null hypotheses $H_{0,i}$: "$\mu_i = 0$" versus $H_{1,i}$: "$\mu_i > 0$"
- Example if $m = 48$ and only noise (no signal):



Multiple testing

- $m = 192$, and only noise:



- $\mathbb{P}(\text{make at least one FP}) = 1 - (1-\alpha)^m \underset{m\to\infty}{\longrightarrow} 1$

Modern days applications

- $m = 10^4, 10^5, 10^6$
- Too many false positives if we keep using α as threshold

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Multiple testing procedures

- What we want: a rejection set R with a control on $V(R)$ the number of false positives in R

Bonferroni procedure

- Use α/m instead of α
- Then $\mathbb{P}(V(R) > 0) \leq \alpha$

This can be too stringent when:

- we want a lot of detections
- we allow some false positives

False Discovery Proportion (FDP) and False Discovery Rate (FDR)

$$\mathrm{FDP}(R) = \frac{V(R)}{|R| \vee 1} \quad ; \quad \mathrm{FDR}(R) = \mathbb{E}\left[\mathrm{FDP}(R)\right]$$

Benjamini-Hochberg (BH) procedure

[Benjamini and Hochberg (1995)][Benjamini and Yekutieli (2001)]

- Sort p-values: $p_{(1)} \leq \cdots \leq p_{(m)}$
- Let $\hat{k} = \max \left\{ k \in [\![1, m]\!] : p_{(k)} \leq \alpha \frac{k}{m} \right\}$ or 0 if empty set
- Reject $H_{0,i}$ if $p_i \leq \frac{\alpha \hat{k}}{m}$
- Theorem: FDR of BH $\leq \alpha$ under independence or PRDS

Useful other formulation

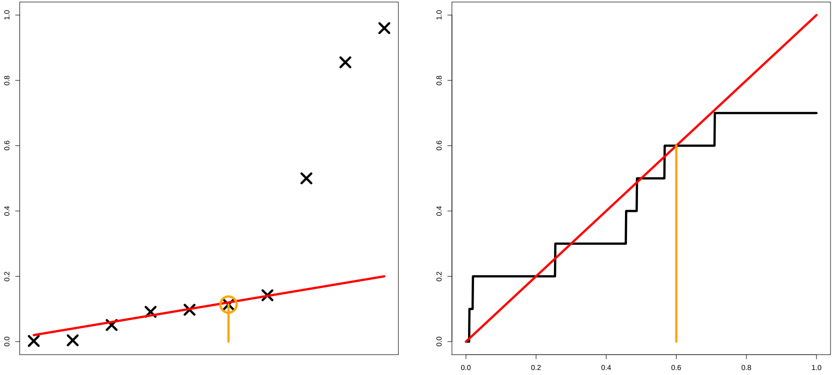
$\frac{\hat{k}}{m} = \max \left\{ u : \widehat{G}(u) \geq u \right\} = \mathcal{I}\left(\widehat{G}\right)$ where

$$\widehat{G} : u \mapsto m^{-1} \sum_{i=1}^{m} \mathbb{1}_{\{p_i \leq \alpha u\}}, u \in [0, 1]$$

- $\widehat{G}$ empirical c.d.f. of p-values (up to α)
- Useful for asymptotics ($m \to \infty$)

An illustration of $\mathcal{I}(\widehat{G})$

Last crossing point between $\widehat{G}$ and the identity function



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Heterogeneity

Example: GWAS study

- Multiple SNPs tested, with heterogeneous Minor Allele Frequency (MAF)
- Distinguish SNPs with low and large MAF because this changes the power of tests
- $\Longrightarrow$ form two groups of SNPs

Multiple other examples [Cai and Sun (2009)]

- Sociologic studies, fMRI...

Setting

- G groups of sizes m_g with true null proportion $\pi_{g,0}$
- $p_{g,i} \sim \mathcal{U}([0,1])$ under the null (noise); $p_{g,i} \sim F_g$ **strictly concave** under the alternative (signal)
- weak dependence [Storey, Taylor, and Siegmund (2004)] and technical assumptions

Quantities of interest

- we want FDR(R) control
- we study the optimality of the global **power**:

$$\mathrm{Pow}(R) = m^{-1}\mathbb{E}\left[|R| - V(R)\right]$$

Main tool

Attribute **weights** to each group [Holm (1979)],[Genovese, Roeder, and Wasserman (2006)],[Blanchard and Roquain (2008)]...

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Weighted BH (WBH)

Take some weights $(w_g)_{1\leq g\leq G}, w_g \geq 0$, apply BH to modified p-values $\tilde{p}_{g,i} = p_{g,i}/w_g$

Interpretation with the $\mathcal{I}$ functional

Define

$$\widehat{G}_w : u \mapsto m^{-1} \sum_{g=1}^{G} \sum_{i=1}^{m_g} \mathbb{1}_{\{p_{g,i} \leq \alpha u w_g\}}$$

and reject all $p_{g,i} \leq \alpha \hat{u} w_g$ with $\hat{u} = \mathcal{I}\left(\widehat{G}_w\right) = \max\left\{u : \widehat{G}_w(u) \geq u\right\}$.

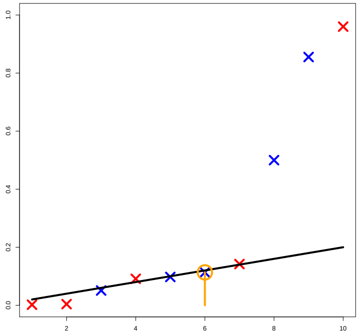
- A constraint is necessary for FDR control, for example:

$$w \in \mathcal{W} = \left\{w \geq 0, \sum_{g=1}^{G} m_g w_g \leq m\right\}$$

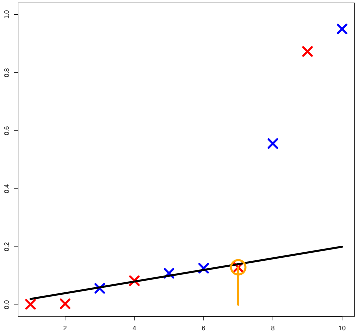
Unweighted vs Weighted BH procedure

Two groups with $w_1 + w_2 = 2$

- $w_1 = w_2 = 1$ (BH):



- $w_1 = 1.1,\ w_2 = 0.9$:



- Weights can increase detections $\Longrightarrow$ increase power ?

Multi-Weighting

[Roquain and van de Wiel (2009)]

- A generalization needed for the search for optimal power

Now weights are a function $u \mapsto W(u)$ for $u \in [0,1]$. If

$$\widehat{G}_W : u \mapsto m^{-1} \sum_{g=1}^{G} \sum_{i=1}^{m_g} \mathbb{1}_{\{p_{g,i} \leq \alpha u W_g(u)\}} \text{ is nondecreasing,}$$

then $\mathrm{MWBH}(W) = \{(g,i) : p_{g,i} \leq \alpha \hat{u} W_g(\hat{u})\}$ with $\hat{u} = \mathcal{I}\left(\widehat{G}_W\right)$.

Optimal weighting

- Fix u and w and define $R_{u,w}$ which rejects all $p_{g,i} \leq \alpha u w_g$
- Maximize its power for all u on the weight space $\mathcal{W}$:

Optimal oracle weights [Roquain and van de Wiel (2009)]

$$W^*_{or}(u) = \arg\max_{w \in \mathcal{W}} \mathrm{Pow}\left(R_{u,w}\right)$$

Theorem [Roquain and van de Wiel (2009)]

Existence and uniqueness of W^*_{or} if regularity assumptions on F_g and $\pi_{g,0} = \pi_0$.
Moreover, MWBH$\left(W^*_{or}\right)$ has asymptotical:

- FDR control at level $\pi_0\alpha$
- Power optimality among all WBH procedures

Issues and consequences

1. F_g's are unknown in practice ! So is W^*_{or}
2. The assumption $\pi_{g,0} = \pi_0$ removes some heterogeneity
3. $\sum_g m_g w_g \leq m \Longrightarrow \pi_0\alpha$-FDR control $\Longrightarrow$ conservativeness

Goal

- Estimate the oracle optimal weights
- enlarge $\mathcal{W}$ in a way that incorporates $\pi_{g,0}$ estimators
- keep asymptotical results on FDR control and power optimality

$\Longrightarrow$ Adaptive Data-Driven Optimal Weighting (ADDOW)

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π_0 estimation

- Each $\pi_{g,0}$ is estimated with $\hat{\pi}_{g,0}$
- $\widehat{\mathcal{W}} = \left\{ w : \sum_g m_g \hat{\pi}_{g,0} w_g \leq m \right\}$ allows larger weights than $\mathcal{W}$!
- Asymptotics: $\hat{\pi}_{g,0} \xrightarrow[m \to \infty]{\mathbb{P}} \tilde{\pi}_{g,0} \geq \pi_{g,0} \Longrightarrow$ over-estimation (e.g. Storey)

Multiplicative Estimation (ME) case

There exists $C \geq 1$ such that $\tilde{\pi}_{g,0} = C \pi_{g,0}$ $\forall g$

- Includes the consistent case $\tilde{\pi}_{g,0} = \pi_{g,0}$ $\forall g$ $(C = 1)$
- Includes the case where $\hat{\pi}_{g,0} = 1$ and $\pi_{g,0} = \pi_0$ $\forall g$ $(C = 1/\pi_0)$

Definition of ADDOW

$$\text{ADDOW} = \text{MWBH}\left(\widehat{W}^*\right)$$

where

$$\forall u,\ \widehat{W}^*(u) = \arg\max_{w \in \widehat{\mathcal{W}}} \widehat{G}_w(u)$$

$\Longrightarrow$ $\widehat{W}^*$ maximizes the *number of rejections*

Key idea

Under (ME), maximizing the rejections is the same as maximizing the power

Remark : if $\hat{\pi}_{g,0} = 1\ \forall g$, ADDOW=IHW [Ignatiadis et al. (2016)]

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Asymptotic FDR control

Theorem

$$\lim_{m\to\infty} \text{FDR}(\text{ADDOW}) \leq \alpha$$

Moreover if $\alpha \leq \tilde{\pi}_0$ and (ME):

$$\lim_{m\to\infty} \text{FDR}(\text{ADDOW}) = \frac{\alpha}{C}$$

By-product

If $\pi_{g,0} = \pi_0 \; \forall g$,

$$\lim_{m\to\infty} \text{FDR}(\text{IHW}) = \pi_0\alpha.$$

Proofs inspired by [Roquain and van de Wiel (2009)], [Hu, Zhao, and Zhou (2010)] and [Zhao and Zhang (2014)].

Power optimality

Theorem

If (ME),

$$\lim_{m\to\infty} \operatorname{Pow}(\text{ADDOW}) \geq \limsup_{m\to\infty} \operatorname{Pow}\left(\text{MWBH}\left(\widehat{W}\right)\right)$$

for any weight function sequence such that $\widehat{W}(u) \in \widehat{\mathcal{W}}$.

By-product

If $\pi_{g,0} = \pi_0 \ \forall g$,

$$\lim_{m\to\infty} \operatorname{Pow}(\text{IHW}) \geq \limsup_{m\to\infty} \operatorname{Pow}\left(\text{MWBH}\left(\widehat{W}\right)\right)$$

for any weight function sequence such that $\sum_g m_g \widehat{W}_g(u) \leq m$.

Comparison with other methods

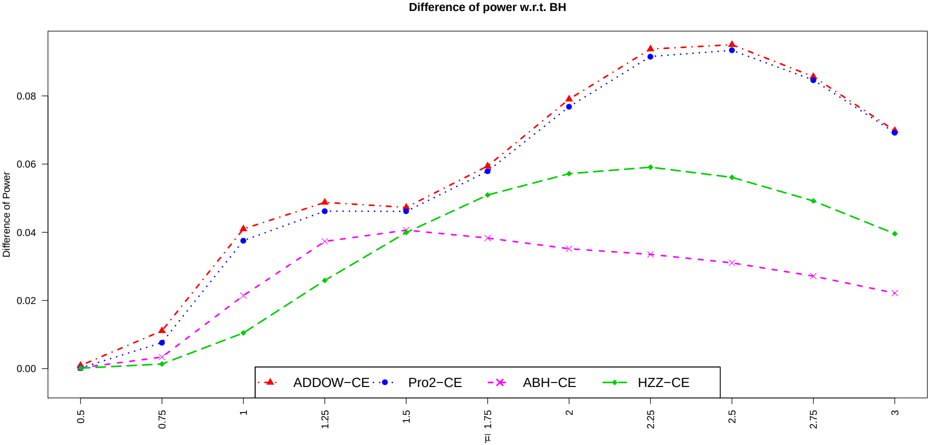
$\alpha = 0.05$, $\pi_{1,0} = 0.7$, $\pi_{2,0} = 0.8$, $m_1 = m_2 = 2000$, $\mu_1 = \bar{\mu}$ and $\mu_2 = 2\bar{\mu}$

4 methods compared with $\hat{\pi}_{g,0} = \pi_{g,0}$ (oracle) and varying signal parameter $\bar{\mu}$:

- ADDOW
- Pro2 [Zhao and Zhang (2014)]
- HZZ [Hu, Zhao, and Zhou (2010)]
- Adaptive BH

Comparison with other methods

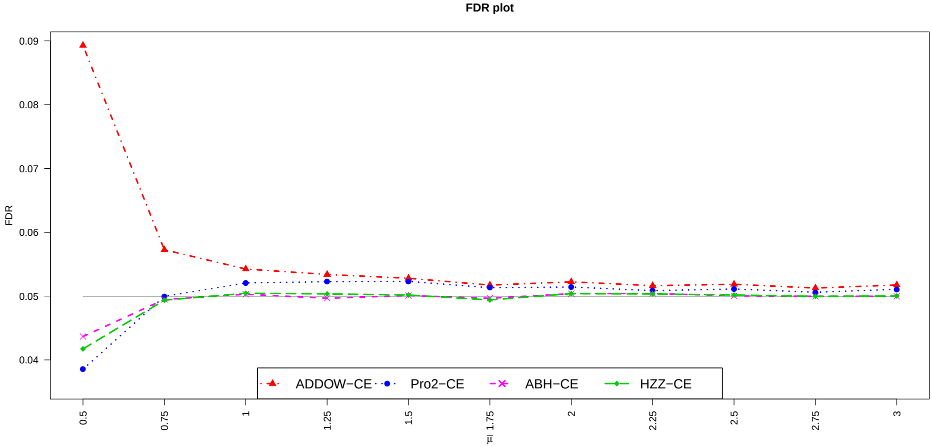
$\alpha = 0.05$, $\pi_{1,0} = 0.7$, $\pi_{2,0} = 0.8$, $m_1 = m_2 = 2000$, $\mu_1 = \bar{\mu}$ and $\mu_2 = 2\bar{\mu}$



- ADDOW > Pro2 > HZZ & ABH

Comparison with other methods

$\alpha = 0.05$, $\pi_{1,0} = 0.7$, $\pi_{2,0} = 0.8$, $m_1 = m_2 = 2000$, $\mu_1 = \bar{\mu}$ and $\mu_2 = 2\bar{\mu}$

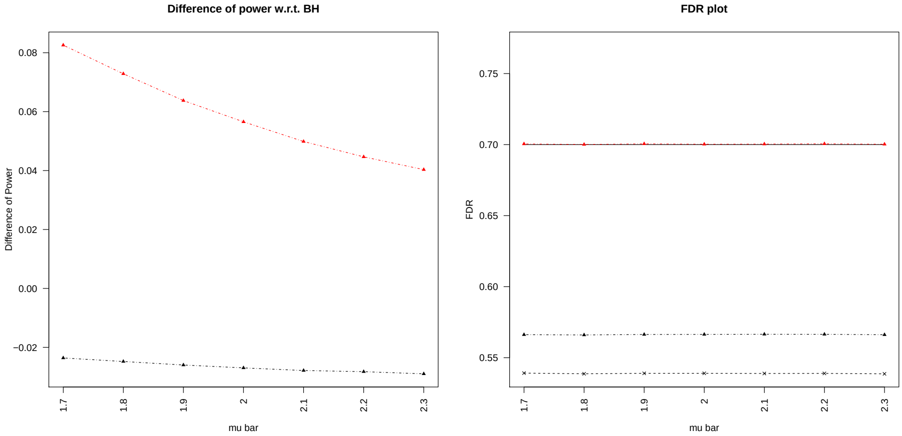


- Overfitting for ADDOW and Pro2

BH better than IHW?

$\alpha = 0.7$, $\pi_{1,0} = 0.05$, $\pi_{2,0} = 0.85$, $m_1 = 1000$, $m_2 = 9000$, $\mu_1 = 2$ and $\mu_2 = \bar{\mu}$

- ADDOW with oracle $\hat{\pi}_{g,0}$ vs IHW vs BH with heterogeneous $\pi_{g,0}$



- Remark: $m = 10^4$ here and no overfitting

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Outlook

- Optimal asymptotical properties but with restrictive dependence assumptions and finite sample overfitting
- Incorporate the dependence ?
- Use a better estimator of the rejections than $\widehat{G}_w$? LCM ?
- FDR bound in finite sample ? (done in [Ignatiadis and Huber (2017)] with folds and censoring)
- Convergence rates ? With more regularity assumptions on F_g ?

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Replication crisis

- Published results/experiments impossible to reproduce
- 70% fail rate (*Nature* poll)

A possible explanation: *p*-hacking [Wasserstein and Lazar (2016)]

- Pre-selecting variables that seem significant, exclude others from experiment
- Theoretical results no longer hold
- Results poorly interpretable and non reproductible

Toy example

- GWAS study with 10^6 genetic variants
- MTP over only the 10 smallest p-values
- Distribution of 10 smallest $\neq$ distribution of 10 p-values taken at random

Our general problem

Confidence bounds on any set of selected variables [Goeman and Solari (2011)]

A confidence (post hoc) bound is a (random) function $\widehat{V}$ such that

$$\mathbb{P}\left(\forall S \subset \mathbb{N}_m, V(S) \leq \widehat{V}(S)\right) \geq 1 - \alpha$$

- Hence for any selected $\widehat{S}$, $\mathbb{P}\left(V(\widehat{S}) \leq \widehat{V}(\widehat{S})\right) \geq 1 - \alpha$ holds
- Not a classic MTP: a guarantee over any selected set instead of a rejected set
- Originates from [Genovese and Wasserman (2006)],[Meinshausen (2006)]

BNR methodology

[Blanchard, Neuvial, and Roquain (2018)]

Key concept: reference family

- $\mathfrak{R} = (R_k, \zeta_k)$ (random) with Joint Error Rate (JER) control:

$$\mathbb{P}\left(\forall k, V(R_k) \leq \zeta_k\right) \geq 1 - \alpha$$

- Confidence bound only on the members of $\mathfrak{R}$
- $\Longrightarrow$ Derivation of a global confidence bound
- Flexible approach: we choose $\mathfrak{R}$

Two different interpolation bounds

- $V^*_{\mathfrak{R}}(S) = \max\left\{|S \cap A|, \forall k, |R_k \cap A| \leq \zeta_k\right\}$ difficult to compute
- $\overline{V}_{\mathfrak{R}}(S) = \min_k \left(\zeta_k + |S \setminus R_k|\right) \wedge |S|$ less sharp but easy to compute

Simes bound

[Goeman and Solari (2011)],[Blanchard, Neuvial, and Roquain (2018)]

Choice of $\mathfrak{R}$:

- Fix $\zeta_k = k - 1, \forall\, 1 \leq k \leq m$
- $R_k = \{i : p_i < \alpha k/m\}$

Simes bound formula

$$V^*_{\mathfrak{R}}(S) = \overline{V}_{\mathfrak{R}}(S) = \min_k \left(k - 1 + \sum_{i \in S} \mathbb{1}_{\{p_i \geq \alpha k/m\}}\right) \wedge |S|$$

Based on:

- Simes inequality and PRDS for JER control
- Nestedness of R_k's for $V^*_{\mathfrak{R}}(S) = \overline{V}_{\mathfrak{R}}(S)$

New approach

Opposite to Simes approach of BNR

1. Deterministic R_k's with a localized structure (e.g. chromosomes). Requires to compute $V^*_{\mathfrak{R}}$
2. Over-estimate $V(R_k)$ in each R_k with a simple method
   - Example with the DKWM inequality [Dvoretzky, Kiefer, and Wolfowitz (1956)],[Massart (1990)] (independence needed):
   - $\zeta_k =$
     $$|R_k| \wedge \min_{0\leq \ell \leq |R_k|} \left\lfloor \frac{C}{2(1-p_{(\ell)})} + \left(\frac{C^2}{4(1-p_{(\ell)})^2} + \frac{\sum_{i\in R_k} \mathbf{1}\{p_i > p_{(\ell)}\}}{1-p_{(\ell)}} \right)^{1/2} \right\rfloor^2,$$
     where $C = \sqrt{\frac{1}{2}\log\left(\frac{K}{\alpha}\right)}$ (union bound)
   - Other estimators possible

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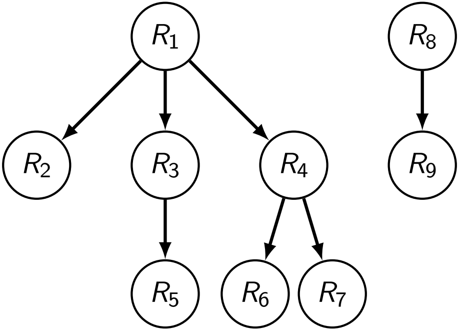
Choice of R_k: Forest structure

- $\forall k, k' \in \mathcal{K}, \;\; R_k \cap R_{k'} \in \{R_k, R_{k'}, \varnothing\}$
- Includes nested families or totally disjoint families



Main points

1. Accommodates to realistic localization structures
2. There is a simple algorithm to compute $V^*_{\mathfrak{R}}(S)$ with this structure

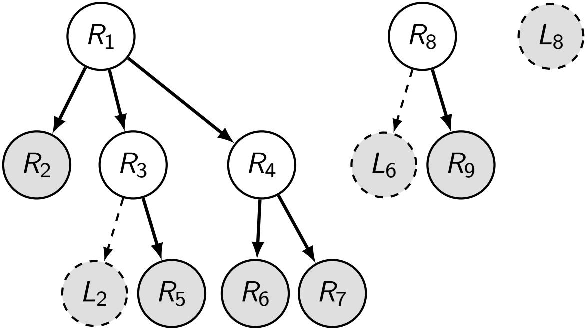
Properties of forest structures

Proposition

There is a partition $(L_n)_{1 \leq n \leq N}$ of $\mathbb{N}_m$ (the leaves) such that each R_k can be written as a union $\bigcup_{i \leq n \leq j} L_n$.

Proposition

Each forest structure can be completed to include all leaves.



New interpolation bounds

Recall: $\overline{V}_{\mathfrak{R}}(S) = \min_k \left(\zeta_k + |S \setminus R_k|\right) \wedge |S|$

Definition

For any $q \leq K$,

$$\widetilde{V}^q_{\mathfrak{R}}(S) = \min_{Q \subset \mathcal{K}, |Q| \leq q} \left(\sum_{k \in Q} \zeta_k \wedge |S \cap R_k| + \left| S \setminus \bigcup_{k \in Q} R_k \right| \right),$$

and

$$\widetilde{V}_{\mathfrak{R}}(S) = \widetilde{V}^K_{\mathfrak{R}}(S).$$

Property

$$V^*_{\mathfrak{R}}(S) \leq \widetilde{V}_{\mathfrak{R}}(S) \leq \widetilde{V}^{K-1}_{\mathfrak{R}}(S) \leq \cdots \leq \widetilde{V}^2_{\mathfrak{R}}(S) \leq \widetilde{V}^1_{\mathfrak{R}}(S) = \overline{V}_{\mathfrak{R}}(S)$$

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Main results

Theorem

For a reference family with a forest structure and $\ell =$ number of leaves,

$$V^*_{\mathfrak{R}}(S) = \widetilde{V}_{\mathfrak{R}}(S) = \widetilde{V}^{\ell}_{\mathfrak{R}}(S).$$

Lemma

There is a simple algorithm to compute $\widetilde{V}_{\mathfrak{R}}$ if $\mathfrak{R}$ is complete.

Lemma

Completing the family does not change $V^*_{\mathfrak{R}}$ and $\widetilde{V}_{\mathfrak{R}}$.

Corollary

There is a simple algorithm to compute $V^*_{\mathfrak{R}}(S)$ by:

1. Completing the family
2. Travel across the forest from the leaves

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Outlook

- Incorporation of local structure $\Longrightarrow$ better power
- DKWM inequality involves independence
- Other over-estimators of true nulls ? [Blanchard, Neuvial, and Roquain (2018)],[Hemerik and Goeman (2018)]
- Other families combining BNR approach and deterministic regions ?
  - $\mathfrak{R} = (R_{k,i_k}, \zeta_{k,i_k})_{\substack{k \in \mathcal{K} \\ 1 \leq i_k \leq |R_k|}}$

Conclusion

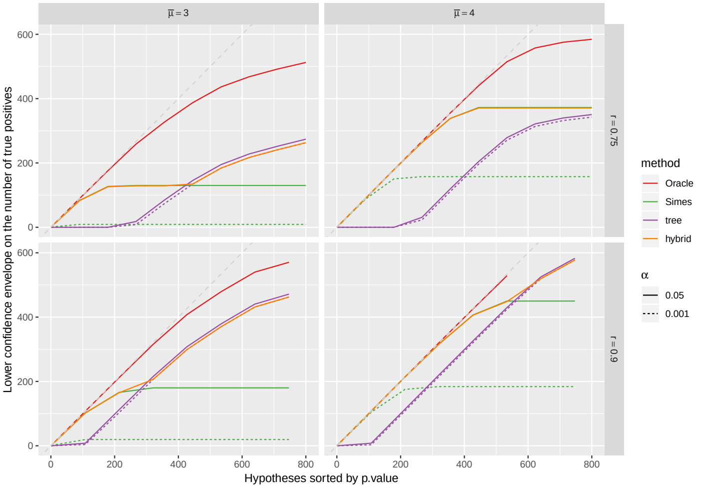
3 different ways to tackle heterogeneity in multiple testing:

- heterogeneity under the alternative with groups and weights
- heterogeneity under the discrete null
- localization heterogeneity with post hoc bounds

Next step: combine them all?

Hybrid bound

- $V^{\gamma}_{\text{hybrid}}(\alpha, S) = \min\left(V_{\text{Simes}}((1-\gamma)\alpha, S), V_{\text{tree}}(\gamma\alpha, S)\right)$
- $\gamma = 0.02$: favors Simes, convenient thanks to V_{tree} relation to α



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Multi-Weighting

A practical way to compute $\mathcal{I}\left(\widehat{G}_W\right)$

No need to compute $W(u)$ for each u !

$\forall k \in [\![1, m]\!]$, compute all $\frac{p_i}{W_i(\frac{k}{m})}$ and take q_k the k-th smallest.

Let $q_0 = 0$.

Then $\mathcal{I}\left(\widehat{G}_W\right) = m^{-1} \max\{k \in [\![0, m]\!] : q_k \leq \alpha \frac{k}{m}\}$.

About the computation of $\widehat{W}^*$

Key ideas

- Compute only $\widehat{W}^*(u)$ for $u = \frac{1}{m}, \frac{2}{m}, \dots, \frac{m-1}{m}, 1$
- Fixing u, $w \mapsto \widehat{G}_w(u)$ only jumps at the $\frac{p_{g,i}}{\alpha u} \Longrightarrow$ let $\widehat{W}_g^*(u) = \frac{p_{g,i_g}}{\alpha u}$ such that $\sum m_g \hat{\pi}_{g,0} \frac{p_{g,i_g}}{\alpha u} \leq m$ and $\sum_g i_g$ is maximal
- $\widehat{G}_w(u)$ nondecreasing in u AND w : try to reject 1 hyp, then 2, then 3... for $u = \frac{1}{m}$, when fail at k hyp, try to reject k hyp for $u = \frac{2}{m}$, ...

Proof ideas

- $\widehat{G}_{\widehat{W}^*}(\hat{u}) \xrightarrow{\mathbb{P}} G^{\infty}_{W^*}(u^*)$ by LLN and careful use of maximality
- Then $\hat{u} \xrightarrow{\mathbb{P}} u^*$ by continuity of $\mathcal{I}(\cdot)$
- Then $\widehat{W}^*(\hat{u}) \xrightarrow{\mathbb{P}} W^*(u^*)$ by reductio ad absurdum
- $\Longrightarrow \text{FDP} = \dfrac{m^{-1}\sum_g \sum_i \mathbb{1}_{\left\{p_{g,i} \le \alpha \hat{u} \widehat{W}^*_g(\hat{u}) \text{ and } H_{g,i} \text{ true}\right\}}}{\widehat{G}_{\widehat{W}^*}(\hat{u})} \xrightarrow{\mathbb{P}}$
  $\dfrac{\alpha \sum_g \pi_g \pi_{g,0} u^* W^*_g(u^*)}{u^*} = \alpha \sum_g \pi_g \pi_{g,0} W^*_g(u^*) \le \alpha$ (weight space choice)
- under (ME), maximize rejections $\Leftrightarrow$ maximize power because we can write $\sum_g \pi_g \pi_{g,0} U(\alpha u w_g) \le \frac{\alpha u}{C} \sum_g \pi_g \tilde{\pi}_{g,0} w_g \le \frac{\alpha u}{C} \Longrightarrow$ no dependence in w in $G^{\infty}_w - P^{\infty}_w$!

sADDOW$_\beta$

Stabilization for weak signal

- ADDOW overfits so FDR control lost with weak signal in finite sample
- We should prefer BH then
- $\Longrightarrow$ test if there is signal before choosing the procedure, like KS tests

Definition

$$\text{sADDOW}_\beta = \begin{cases} \text{ADDOW} & \text{if } \phi_\beta = \mathbb{1}_{\{Z_m > q_{\beta,m}\}} = 1 \\ \text{BH} & \text{if } \phi_\beta = \mathbb{1}_{\{Z_m > q_{\beta,m}\}} = 0 \end{cases}$$

with $Z_m = \sqrt{m}\sup_{u\in[0,1]}\left(\widehat{G}_{\widehat{W}^*}(u) - \alpha u\right)$ and $q_{\beta,m}$ the $(1-\beta)$ quantile of Z_{0m} (independent copy of Z_m under full null, and independence).

sADDOW$_\beta$

Stabilization for weak signal

Main idea (under independence)

Weak signal $\Longrightarrow$ Z_m close to Z_{0m} in distribution, and

$$\begin{aligned}
\mathrm{FDR}\left(\mathrm{sADDOW}_\beta\right) &= \mathbb{E}\left[\phi_\beta \,\mathrm{FDP}\left(\mathrm{ADDOW}\right) + (1-\phi_\beta)\,\mathrm{FDP}\left(\mathrm{BH}\right)\right] \\
&\leq \mathbb{E}\left[\phi_\beta + \mathrm{FDP}\left(\mathrm{BH}\right)\right] \\
&\leq \mathbb{P}\left(Z_m > q_{\beta,m}\right) + \frac{m_0}{m}\alpha \\
&\lesssim \mathbb{P}\left(Z_{0m} > q_{\beta,m}\right) + \frac{m_0}{m}\alpha \\
&\leq \beta + \frac{m_0}{m}\alpha
\end{aligned}$$

- $\beta \to 0$?

sADDOW$_\beta$ equivalent to ADDOW

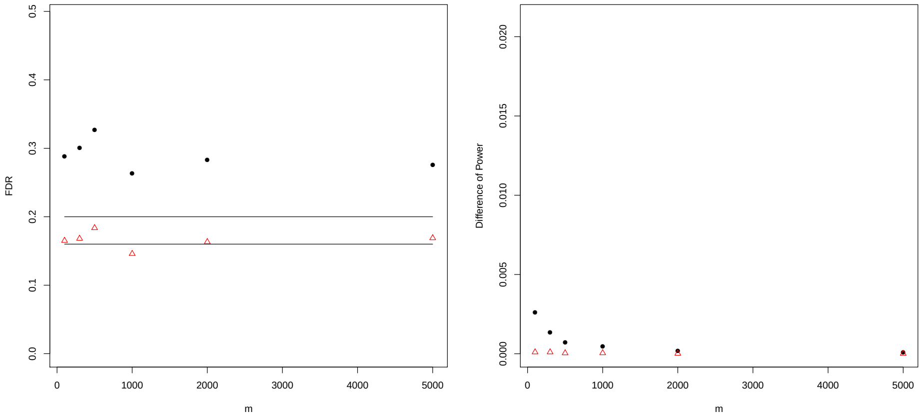
Theorem

sADDOW$_\beta$ is asymptotically equivalent to ADDOW because $\phi_\beta \xrightarrow{a.s.} 1$ when $m \to \infty$, even if $\beta = \beta_m \to 0$ not too slowly ($\beta_m \geq \exp\left(-m^{1-\nu}\right), \nu > 0$).

Proof relies on the DKWM inequality [Massart (1990)]

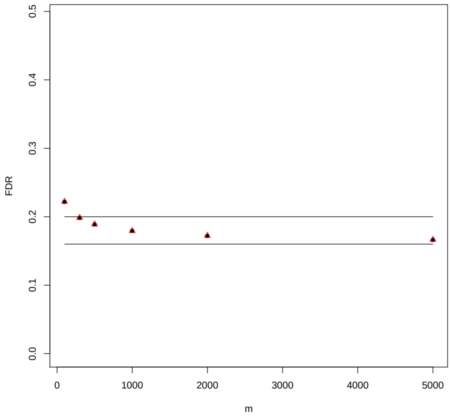
Stabilization for weak signal : $\bar{\mu} = 0.01$

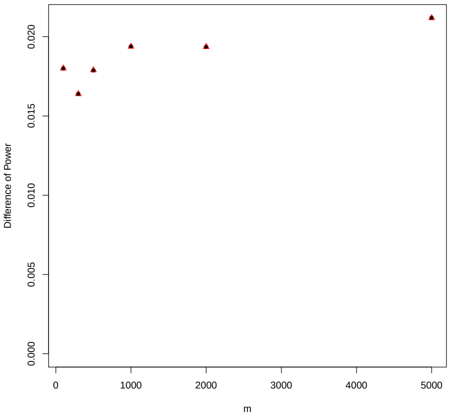
$\pi_1 = \pi_2 = 0.5$, $\pi_0 = 0.8$, $\mu_1 = \bar{\mu}$, $\mu_2 = 2\bar{\mu}$, 1000 replications



Stabilization for strong signal : $\bar{\mu} = 3$

$\pi_1 = \pi_2 = 0.5$, $\mu_1 = \bar{\mu}$, $\mu_2 = 2\bar{\mu}$, 1000 replications





Closed testing for post hoc inference

Designed for FWER control [Marcus, Eric, and Gabriel (1976)]

- Form $H_{0,I} = \bigcap_{i \in I} H_{0,i}$ all intersection hypotheses
- Have a collection of α level local test ϕ_I
- Examples:
  - Bonferroni test $\phi_I = 1$ if $\exists i \in I : p_i \leq \alpha/|I|$
  - Simes test $\phi_I = 1$ if $\exists i \in I : p_{(i:I)} \leq \alpha i/|I|$ (under PRDS)
- Test $H_{0,I}$ only if all $H_{0,J}$, $J \supseteq I$, are rejected
- Reject the individual hypotheses $H_{0,i}$ such that $H_{0,\{i\}}$ has been rejected that way
- Then FWER(Closed testing) $\leq \alpha$

Closed testing for post hoc inference

[Goeman and Solari (2011)]

Main idea

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

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

$$\mathbb{P}\left(\forall I \in \mathcal{X}, H_{0,I} \text{ is false}\right) \geq 1 - \alpha$$

Confidence bound derivation:

- $V_{\text{GS}}(S) = \max_{\substack{I \subseteq S \\ I \notin \mathcal{X}}} |I|$ is a confidence bound because

$$\begin{aligned} \exists S, |S \cap \mathcal{H}_0| > V_{\text{GS}}(S) &\Longrightarrow \exists S, S \cap \mathcal{H}_0 \in \mathcal{X} \\ &\Longrightarrow \exists I \in \mathcal{X}, H_{0,I} \text{ is true} \end{aligned}$$

- $V_{\text{GS}}(S) = V^*_{\mathfrak{R}}(S)$ with $\mathfrak{R} = (I, |I| - 1)_{I \in \mathcal{X}}$

DKWM use

- Let $S \subset \mathbb{N}_m$
- $N_t(S) = \sum_{i \in S} \mathbf{1}\{p_i(X) > t\}$
- $v = |S \cap \mathcal{H}_0|$

$$v \leq \min_{t \in [0,1)} \left(\frac{\sqrt{\log(1/\lambda)/2}}{2(1-t)} + \left\{ \frac{\log(1/\lambda)/2}{4(1-t)^2} + \frac{N_t(S)}{1-t} \right\}^{1/2} \right)^2$$

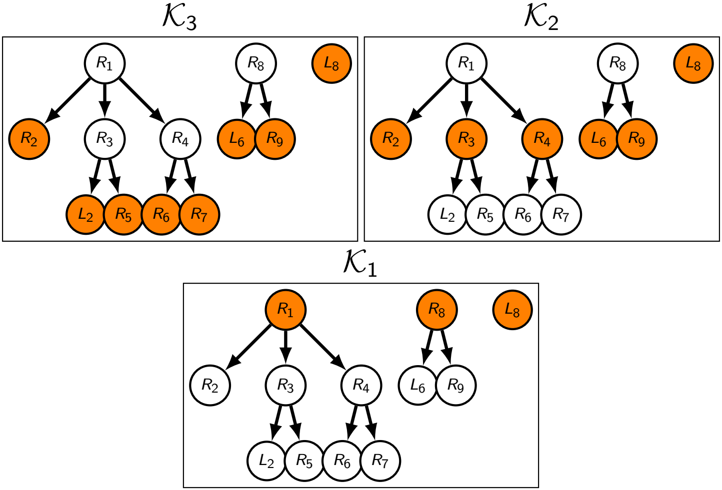
comes from

$$v^{-1} \sum_{i=1}^{v} \mathbf{1}\{U_i > t\} - (1-t) \geq -\sqrt{\log(1/\lambda)/(2v)}, \ \forall t \in [0,1],$$

with probability at least $1-\lambda$ ($U_1, \dots, U_v$ i.i.d. uniform, $N_t(S)$ dominates $\sum_{i=1}^{v} \mathbf{1}\{U_i > t\}$ by independence)

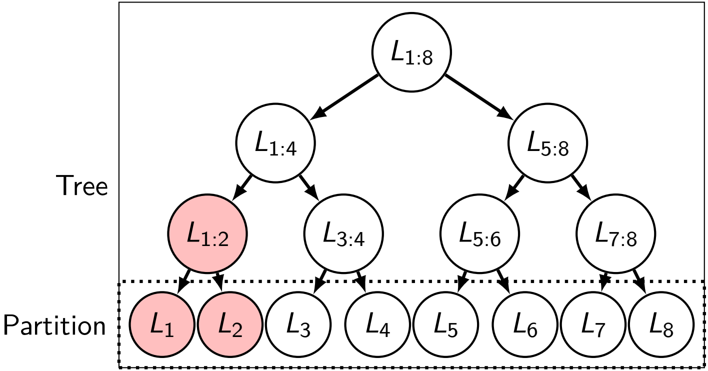
- $S = R_k$ and $\lambda = \alpha/K$ (union bound)

Forest algorithm



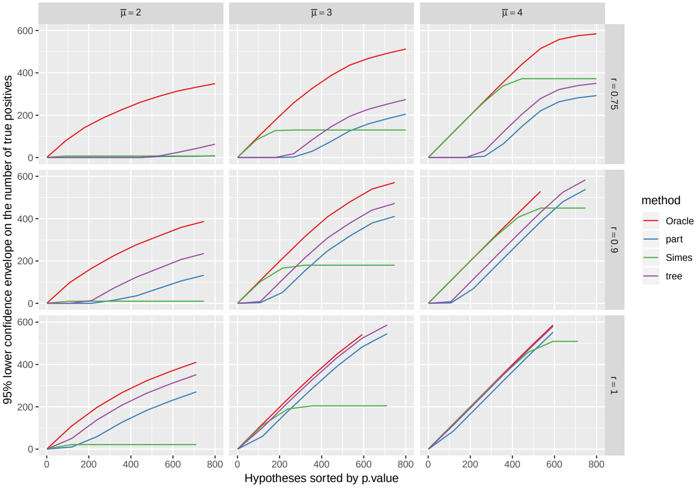
Comparison of Simes vs 2 new bounds

- V_{tree} and V_{part}: complete binary tree or only the leaves partition
- Signal in adjacent leaves, to test V_{tree} w.r.t V_{part}
- Parameters: signal $\bar{\mu}$ and signal proportion in active leaves r



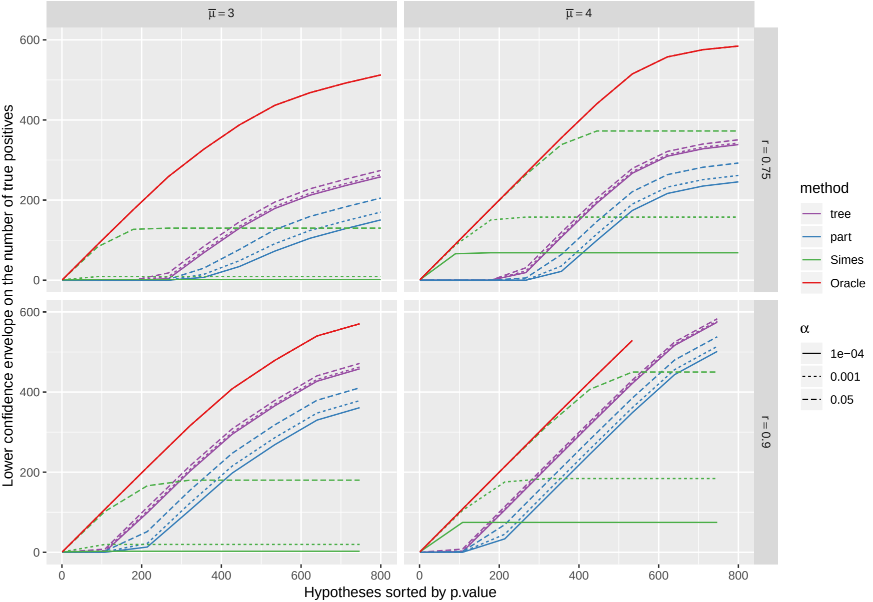
Comparison of Simes vs 2 new bounds

- The choice of S favors the Simes bound of BNR
- Simes better with $\bar{\mu}$, new bounds better with r
- V_{tree} better than V_{part}, despite union bound penalty



Comparison of 3 bounds

Influence of α



An example of discrete test

Fisher's exact test

- GWAS study
- Testing association between allele A and a phenotype (1) of interest

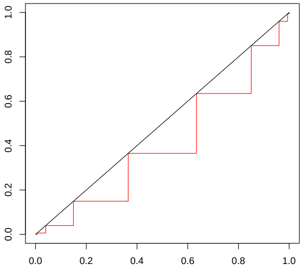
	Phenotype 1	Phenotype 2	Total
Allele A	$n_{1,\mathrm{A}}$	$n_{2,\mathrm{A}}$	n_A
Allele a	$n_{1,\mathrm{a}}$	$n_{2,\mathrm{a}}$	n_a
Total	n_1	n_2	N

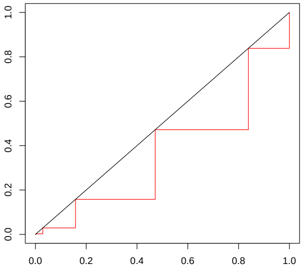
- For large samples, χ^2 approximation: $E_{1,\mathrm{A}} = \frac{n_1 n_\mathrm{A}}{N}$, $\frac{(n_{1,\mathrm{A}} - E_{1,\mathrm{A}})^2}{E_{1,\mathrm{A}}} + \dots$ follows χ^2 distribution under H_0
- What if we want an exact test ?
- Under H_0, conditionally to n_1 and n_A, $n_{1,\mathrm{A}} \sim \mathcal{H}(n_1, n_2, n_\mathrm{A})$, hypergeometric hence discrete

Issue of discrete p-values

Super-uniformity rather than uniformity under H_0

Let's see the c.d.f. of $\mathcal{H}(30, 30, 10)$ and $\mathcal{H}(14, 42, 6)$.





Super-uniformity under H_0

$$\mathbb{P}\left(p \leq u\right) \leq \mathbb{P}\left(U \leq u\right) = u$$

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

Issue of discrete p-values

Super-uniformity rather than uniformity under H_0

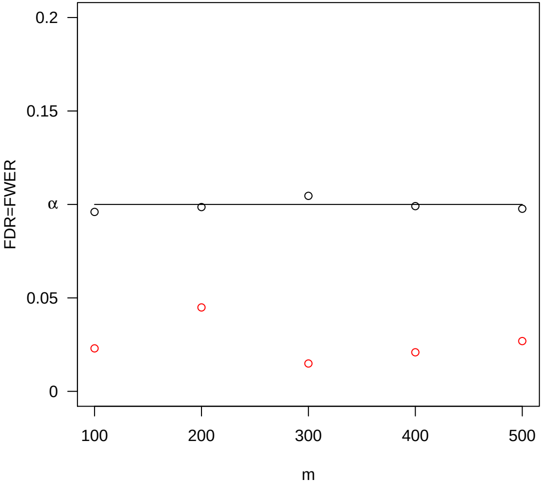
Problem

Usual MT procedures designed for uniformity

- As discrete p-values are larger than uniforms, classic thresholds are too conservative $\Longrightarrow$ loss of power

Issue of discrete p-values

Toy example: BH under full null, $m/2$ p-values $\sim \mathcal{H}(30, 30, 10)$, and $m/2$ p-values $\sim \mathcal{H}(14, 42, 6)$



In this section

- New procedures that use heterogeneous discrete distributions
- New FDR bounds and FDR control of our procedures
- Numerical illustrations

Back to BH (again)

- Reject all $p_i \leq \alpha \frac{\hat{k}}{m}$ where $\hat{k} = \max\{k : p_{(k)} \leq \alpha k/m\}$

Step-up procedure, critical constants

- Take a nondecreasing sequence (τ_k), the critical constants
- Reject all $p_i \leq \tau_{\hat{k}}$ where $\hat{k} = \max\{k : p_{(k)} \leq \tau_k\}$

Examples:

- BH: $\tau_k = \alpha k/m$
- BY [Benjamini and Yekutieli (2001)]: $\tau_k = \alpha k/(m \times \sum_{i=1}^{m} i^{-1})$

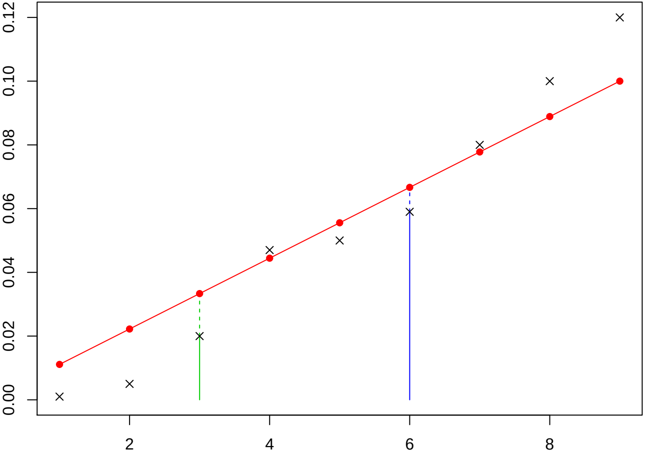
Step-down procedure

- Reject all $p_i \leq \tau_{\hat{k}}$ where $\hat{k} = \max\{k : \forall k' \leq k, p_{(k')} \leq \tau_{k'}\}$

Example:

- HB [Holm (1979)]: $\tau_k = \alpha/(m + k - 1)$

Step-up, step-down



Heyse procedure

[Heyse (2011)]

A step-up procedure

With $\tau_k = \max\{t \in \mathcal{A} \,:\, \overline{F}(t) \leq \alpha k/m\}$, where $\overline{F}(t) = \frac{1}{m}\sum_{i=1}^{m} F_i(t)$, F_i (known) c.d.f. under the null, $\mathcal{A}$ discrete support of p-values

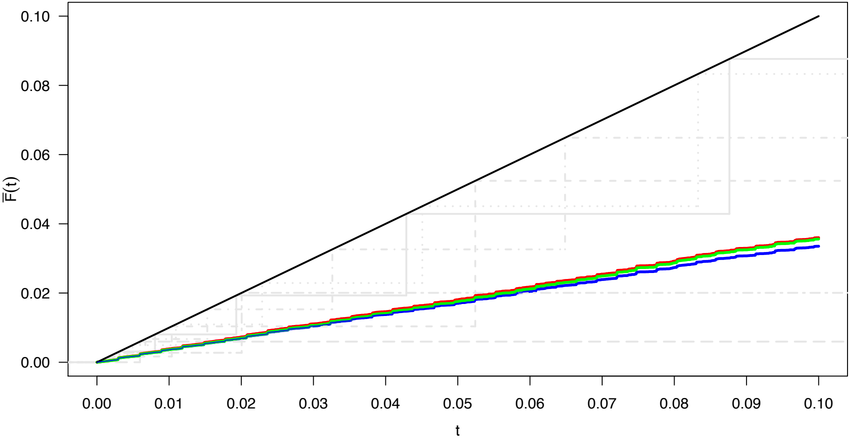
Main ideas:

- "Invert" $\overline{F}$ at $\alpha k/m$
- As $\overline{F}(t) \leq t$, this yields larger critical values than BH
- The more $\overline{F}(t)$ is small compared to t, the larger are the τ_k
- But heterogeneity also needed, otherwise Heyse $=$ BH (because $F_i(t) = t$ when $t \in \mathcal{A}_i$)

Heyse procedure

An illustration

- Compensation effect from heterogeneity



Heyse procedure

Problem

Heyse procedure does not control the FDR

Counter-examples exist

In the following

Build upon Heyse ideas but with FDR control

HSU and HSD

Slight modifications of $\overline{F}$

$$\overline{F}_{\mathrm{SU}}(t) = \frac{1}{m}\sum_{i=1}^{m}\frac{F_i(t)}{1 - F_i(\tau_m)}; \quad \overline{F}_{\mathrm{SD}}(t) = \frac{1}{m}\sum_{i=1}^{m}\frac{F_i(t)}{1 - F_i(t)}$$

where

$$\tau_m = \max\{t \in \mathcal{A} \, : \, \overline{F}_{\mathrm{SD}}(t) \leq \alpha\}$$

HSU

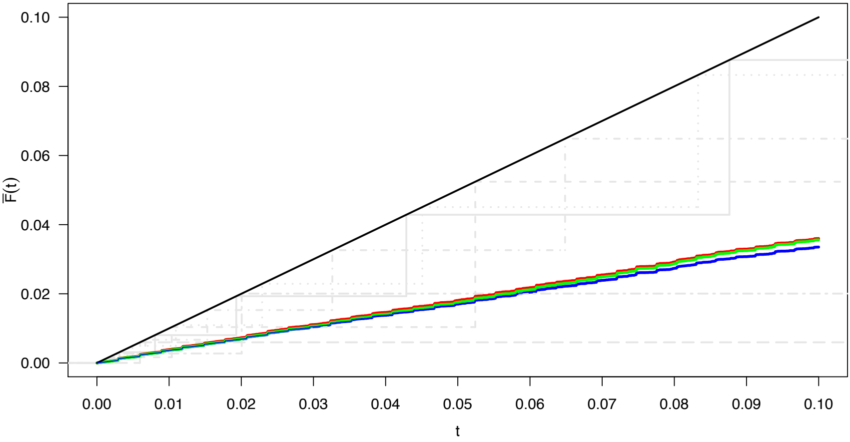
SU with $\tau_k = \max\{t \in \mathcal{A} \, : \, t \leq \tau_m, \, \overline{F}_{\mathrm{SU}}(t) \leq \alpha k/m\}$, $k \leq m - 1$

HSD

SD with $\tau_k = \max\{t \in \mathcal{A} \, : \, \overline{F}_{\mathrm{SD}}(t) \leq \alpha k/m\}$, $k \leq m$

HSU and HSD

- $\overline{F}_{\mathrm{SU}}, \overline{F}_{\mathrm{SD}} \geq \overline{F}$
- But not that much!



AHSU ans AHSD

Adaptive procedures

AHSU

SU with $\tau_k =$
$\max\left\{t \in \mathcal{A} : t \leq \tau_m, \left(\frac{F(t)}{1-F(\tau_m)}\right)_{(1)} + \cdots + \left(\frac{F(t)}{1-F(\tau_m)}\right)_{(m-k+1)} \leq \alpha k\right\}$,
$k \leq m-1$

AHSD

SD with
$\tau_k = \max\left\{t \in \mathcal{A} \,:\, \left(\frac{F(t)}{1-F(t)}\right)_{(1)} + \cdots + \left(\frac{F(t)}{1-F(t)}\right)_{(m-k+1)} \leq \alpha k\right\}$, $k \leq m$

AHSU ans AHSD

Why "adaptive" ?

Back to HB

- SD with $\tau_k = \alpha/(m+k-1)$
- Sequential point of view: if $p_{(1)} \leq \alpha/m$, then at most $m-1$ true nulls, let's see if $p_{(2)} \leq \alpha/(m-1)$...
- Adapts to the quantity of signal
- Controls the FWER

- HSD is the discrete version of GBS [Gavrilov, Benjamini, and Sarkar (2009)]: $\tau_k = \frac{\alpha k}{m-(1-\alpha)k+1}$
- GBS itself is the FDR version of HB

New FDR bounds

Under independence

Theorem

$$\mathrm{FDR}(\mathbf{SU}(\tau)) \leq \min\left(\sum_{i=1}^{m} \max_{k} \frac{F_i(\tau_k)}{k},\right.$$
$$\left.\max_{k} \frac{1}{k}\left(\left(\frac{F(\tau_k)}{1-F(\tau_m)}\right)_{(1)} + \cdots + \left(\frac{F(\tau_k)}{1-F(\tau_m)}\right)_{(m-k+1)}\right)\right)$$

New FDR bounds

Under independence

Theorem

$$\mathrm{FDR}(\mathbf{SD}(\tau)) \leq \min\left(\sum_{i=1}^{m} \max_k \frac{F_i(\tau_k)}{k},\right.$$
$$\left.\max_k \frac{1}{k}\left(\left(\frac{F(\tau_k)}{1-F(\tau_k)}\right)_{(1)} + \cdots + \left(\frac{F(\tau_k)}{1-F(\tau_k)}\right)_{(m-k+1)}\right)\right)$$

Direct corollaries

Corollary

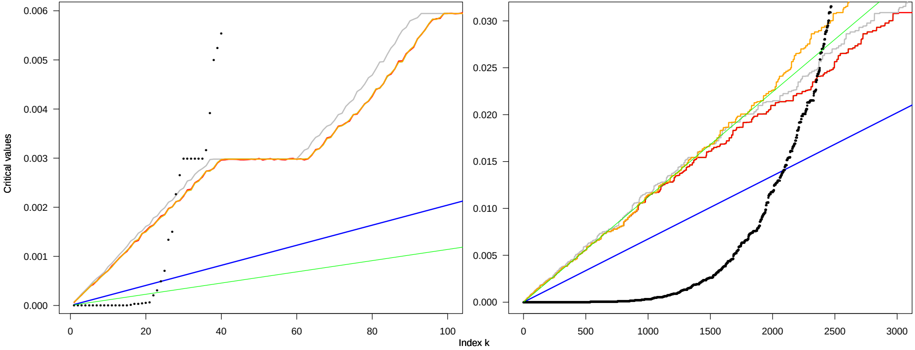
HSU, HSD, AHSU, AHSD all control the FDR under indepence

Also recovery of other results

- FDR control under independence of BH and GBS
- [Blanchard and Roquain (2009)] recovered in a special case
- [Roquain and van de Wiel (2009)] recovered in finite sample $\Longrightarrow$ connection with weighting

Real data analysis

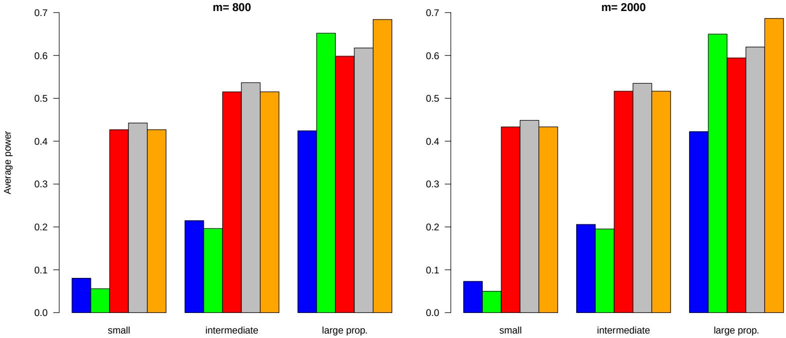
Pharmacovigilance data [Heller and Gur (2011)] and methylation data [Chen and Doerge (2015)]



- Blue: BH
- Green: Storey with $\lambda = 1/2$ but without censoring [Storey, Taylor, and Siegmund (2004)]
- Grey: Heyse
- Red: HSU
- Orange: AHSU

Simulations

Fisher's exact test on m contingency tables



$$\pi_0 = 0.9, 0.7, 0.2$$

Conclusion

- New powerful procedures well-suited for discrete tests under independence
- New bounds also relevant in other contexts (i.e. weighting)
- Positive dependence ? Any dependence ? [Döhler (2016)]
- π_0 estimation ?

A discrete procedure always better than BH: RBH

SU procedure

With $\tau_k = \lambda_\alpha k/m$, $\lambda_\alpha = \max\{\lambda \in [0,1] : \Psi(\lambda_\alpha) \leq \alpha\}$, and

$$\Psi(\lambda) = \min\left(\lambda, \max_{1\leq k\leq m}\left(\frac{1}{k}\sum_{i=1}^{m}\frac{F_i(\lambda k/m)}{1-F_i(\lambda)}\right)\right)$$

- FDR control by the new FDR bounds
- If $\Psi(\lambda_\alpha) = \alpha$ then RBH always better than BH because $\alpha \leq \lambda_\alpha$