BH procedure using data-driven optimal weights for grouped hypotheses

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Motivation
Grouped hypotheses

Context

The hypotheses we want to test are grouped :
Same distribution under $\mathscr{H}_1$ in each group

Examples :

- The Adequate Yearly Progress data set where grouping schools by size avoids a preference for large schools.
- Search for differently expressed genes between individuals with normal copy number or amplified one. Tests are more efficient when the ratio "normal vs amplified copy numbers" is near 1.
- Grouping genes by pathway is also possible.

The well-known BH procedure

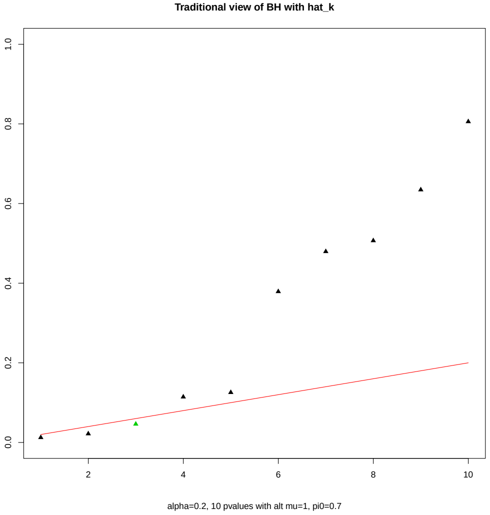
- Order p-values : $p_{(1)} \leq \cdots \leq p_{(m)}$
- Compute $\hat{k} = \max\{k : p_{(k)} \leq \alpha k/m\}$
- Reject all $p_i \leq \alpha \frac{\hat{k}}{m}$
- FDR control at level $\pi_0 \alpha$ when wPRDS

Another formulation

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

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

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



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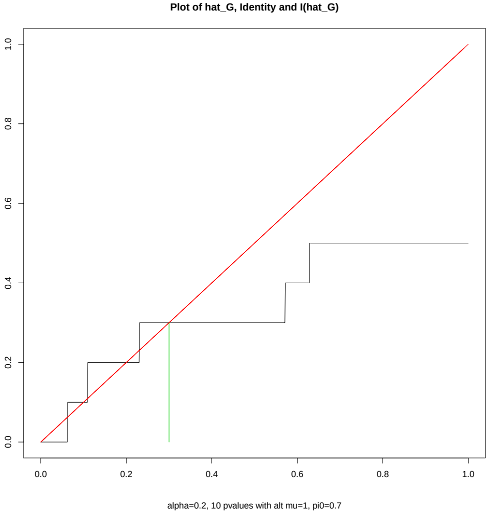


Weighted-BH

With given weights $(w_i)_{1\leq i\leq m}$ such that $\sum_i w_i = m$ (called a weight vector), form

$$\widehat{G}_w : u \mapsto m^{-1} \sum_{i=1}^{m} \mathbb{1}_{\{p_i \leq \alpha u w_i\}}$$

and reject all $p_i \leq \alpha \hat{u} w_i$ with $\hat{u} = \mathcal{I}\left(\widehat{G}_w\right)$.

BH is a weighted-BH procedure with $\forall i, w_i = 1$.

Weighted-BH
A generalization : weight functions

From Roquain and Van De Wiel 2009 :

Take a function W such that $(W_i(u))_i$ is a weight vector for all u and

$$\widehat{G}_W : u \mapsto m^{-1} \sum_{i=1}^{m} \mathbb{1}_{\{p_i \leq \alpha u W_i(u)\}}$$

is non-decreasing, then reject all $p_i \leq \alpha \hat{u} W_i(\hat{u})$ with $\hat{u} = \mathcal{I}\left(\widehat{G}_W\right)$.

Weighted-BH

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

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

For each $k \in [\![1, m]\!]$, compute the $\frac{p_i}{W_i(\frac{k}{m})}$ and take q_k the k-th smallest. Let $q_0 = 0$.
Then $\mathcal{I}\left(\widehat{G}_W\right) = m^{-1} \max\{k \in [\![0, m]\!] : q_k \leq \alpha \frac{k}{m}\}$.

Optimal weighting

- Unconditional model : $\forall i, \mathbb{P}(i \in \mathscr{H}_0) = \pi_0$.
- Consider the procedure R_m^u rejecting p_i if $p_i \leq \alpha u w_i$ for all u.
- Its power is $\mathrm{Pow}_w(u) := (1-\pi_0)m^{-1}\sum_{i=1}^m F_i(\alpha u w_i)$ (F_i the c.d.f. under the alternative).
- Maximize it for all u :

Definition of optimal weights :

$$W^*(u) = \underset{(w_i) s.t. \sum_i^m w_i = m}{\mathrm{argmax}} \mathrm{Pow}_w(u)$$

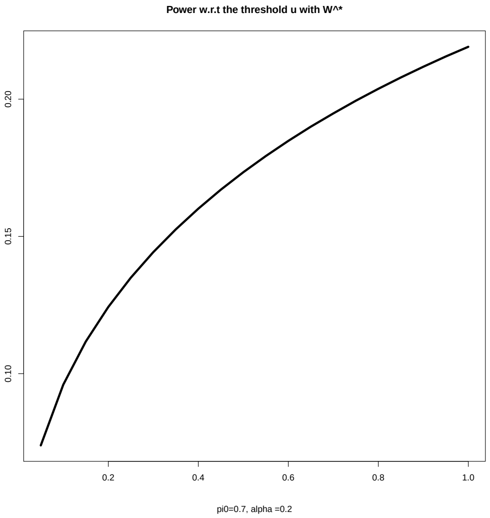
Optimal weighting
Existence and uniqueness

Assume some regularity properties of the F_i, fulfilled in the gaussian 1-sided framework.

Theorem (Roquain and Van De Wiel 2009)

Then we have existence, uniqueness and continuity of W^*, and $u \mapsto uW_i^*(u)$ is non-decreasing.

Illustration of $W^*(u)$ as an argmax



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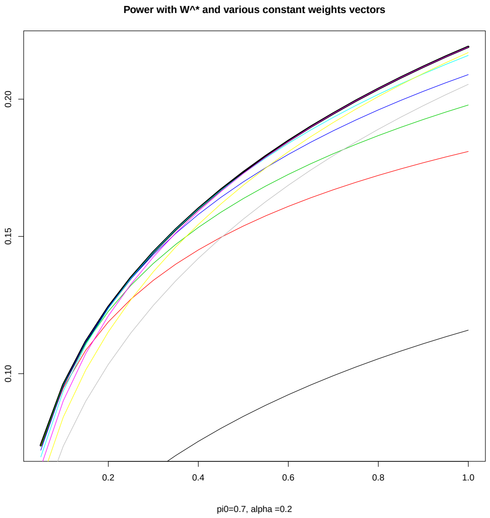

Optimal weighting
Main problem and resulting motivation

- F_i unknown under the alternative ! So is W^*.
- Goal : estimate W^*, obtain asymptotical results on FDR control and power optimality.
- Leads to data-driven optimal weighting.

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Data-driven optimal weighting

- Assume that the p-values have uniform distribution under the null.

Main idea :

$W^*(u)$ is also the unique maximizer of

$$G_w(u) = \mathbb{E}\left[\widehat{G}_w(u)\right] = \pi_0 m^{-1} \sum_{i}^{m} \max(\alpha u w_i, 1) + \mathrm{Pow}_w(u)$$

the mean proportion of rejections done by the procedure R_m^u.

Data-driven optimal weighting

So we can estimate W^* by maximizing G_w's empiric counterpart $\widehat{G}_w$.

Define $\widehat{W^*}(u)$ as :

$$\widehat{W^*}(u) \in \underset{w \geq 0 : \sum_i w_i = m}{\operatorname{argmax}} \widehat{G}_w(u) = \operatorname{argmax} \frac{1}{m} \sum_{i=1}^{m} \mathbb{1}_{p_i \leq \alpha u w_i}$$

Data-driven optimal weighting

Assumptions

- All previous assumptions.
- G groups of sizes $(m_g)_{1\leq g\leq G}$, where p-values have the same distribution.
- p-values are independent.
- $f_g(0^+) = \infty \ \forall g$.
- $\frac{m_g}{m} \underset{m\to\infty}{\longrightarrow} \pi_g > 0$.

Proofs of the following results inspired by Roquain and Van De Wiel 2009, Zhao and Zhang 2014 and Hu, Zhao, and Zhou 2010.

The two main results

Theorem (FDR control)

$$\mathrm{FDP}\left(BH\left(\widehat{W}^*\right)\right) \xrightarrow{a.s.} \pi_0\alpha$$

$$\mathrm{FDR}\left(BH\left(\widehat{W}^*\right)\right) \longrightarrow \pi_0\alpha$$

Theorem (power optimality)

Note by $\mathscr{W}$ the set of all sequences $\left(w^{(m)}\right)$ such that $w_g \geq 0$ and $\sum m_g w_g^{(m)} = m$. Then :

$$\lim_{m\to\infty} \mathrm{Pow}\left(BH\left(\widehat{W}^*\right)\right) \geq \sup_{\left(w^{(m)}\right)\in\mathscr{W}} \limsup_{m\to\infty} \mathrm{Pow}\left(BH\left(w^{(m)}\right)\right).$$

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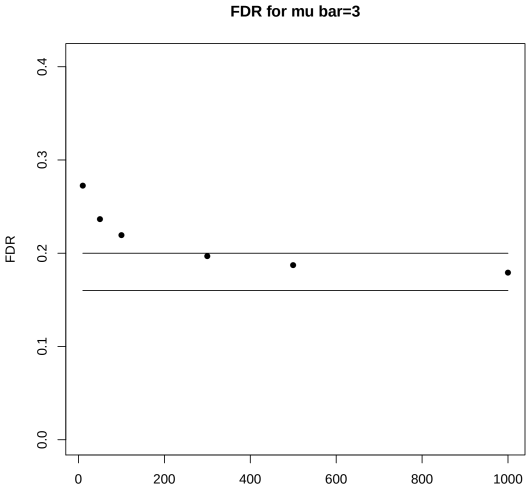
About the computation of $\widehat{W}^*$

Key ideas

- We use only $\widehat{W}^*(u)$ for $u = \frac{1}{m}, \frac{2}{m}, \dots, \frac{m-1}{m}, 1$.
- Max over $w : \sum m_g w_g = m$ = max over $w : \sum m_g w_g \leq m$.
- Given a u, $w \mapsto \widehat{G}_w(u)$ discrete, only jumps at the $\frac{p_{g,i}}{\alpha u} \Longrightarrow$ search $\widehat{W}^*_g(u)$ as a $\frac{p_{g,i_g}}{\alpha u}$ such that $\sum m_g \frac{p_{g,i_g}}{\alpha u} \leq m$.
- $\widehat{G}_w(u)$ nondecreasing in u AND w : attempt to reject 1 hyp, then 2, then 3... for $\frac{1}{m}$, when fail at k hyp, try to reject k hyp for $\frac{2}{m}$, and so on.

FDR plot

$\alpha = 0.2$, 80% true null, $\pi_1 = \pi_2 = 0.5$



- $\mu_1 = \bar{\mu}$ and $\mu_2 = 2\bar{\mu}$.
- x axis : m.
- y axis : the FDR of our procedure over 1000 replications.

Difference of power with BH

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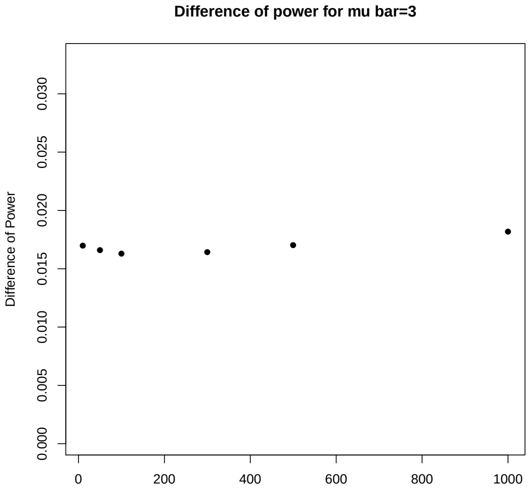

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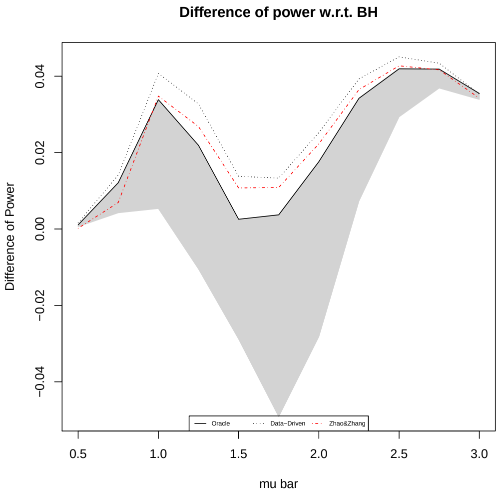
Comparison with other methods

$\alpha = 0.05$, 70% true null, $m_1 = m_2 = 500$



- $\mu_1 = \bar{\mu}$ and $\mu_2 = 2\bar{\mu}$.
- 1000 replications.
- Zhao&Zhang is a an adapation of Zhao and Zhang 2014 without $\hat{\pi}_0$.
- Grey area delimited by min and max for many weighted-BH procedures.
- Overfitting in our method.

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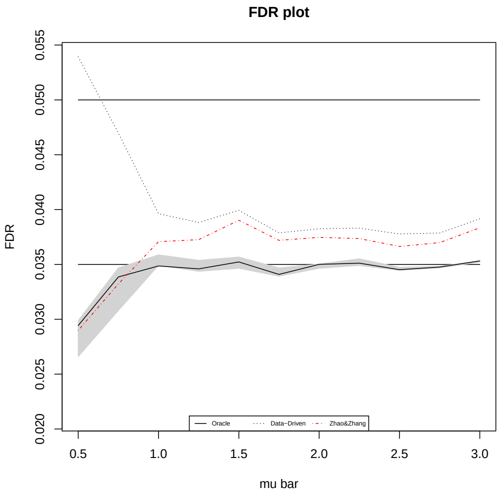

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Some perspectives

- Estimate π_0 to control the FDR at level α instead of $\alpha\pi_0$.
- A different π_0 in each group ?
- Use wPRDS instead of independence ?
- Optimize the computation ?
- Estimate G_w with a better function than $\widehat{G}_w$?
- Bad method when small signal :

FDR plot

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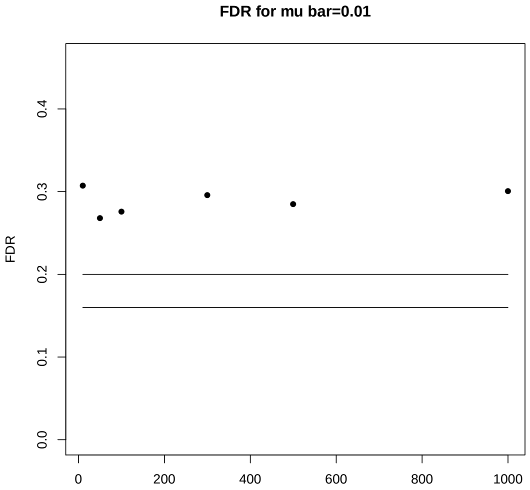

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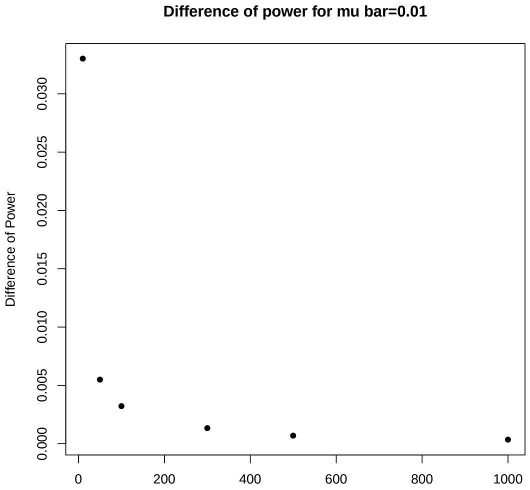

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- Hu, James X., Hongyu Zhao, and Harrison H. Zhou (2010). "False discovery rate control with groups". In: *Journal of the American Statistical Association* 105.491.
- Roquain, Etienne and Mark A. Van De Wiel (2009). "Optimal weighting for false discovery rate control". In: *Electronic Journal of Statistics* 3, pp. 678–711.
- Zhao, Haibing and Jiajia Zhang (2014). "Weighted p-value procedures for controlling FDR of grouped hypotheses". In: *Journal of Statistical Planning and Inference* 151, pp. 90–106.

The end

Thank you for your attention !

Existence and uniqueness of oracle optimal weights

Assumptions

From Roquain and Van De Wiel 2009 :

- F_i is strictly concave and continuous on $[0,1]$
- F_i has a derivative f_i on $(0,1)$
- $f_i(0^+)$ is constant for all i, same for $f_i(1^-)$
- $\lim_{y \to f_i(0^+)} \frac{f_j^{-1}(y)}{f_i^{-1}(y)}$ exists in $[0,\infty]$ for all i,j

These hypotheses are fulfilled in the gaussian 1-sided framework.

Optimal weighting
Existence and uniqueness

Proof ideas

Compute an explicit formula using the Lagrange multiplier method :

$$L(\lambda, w) = m^{-1} \sum_{i=1}^{m} F_i(\alpha u w_i) - \lambda \left(\sum_{i=1}^{m} w_g - m \right)$$

gives us

$$W_i^*(u) = \frac{1}{\alpha u} f_i^{-1} \left(\Psi^{-1}(\alpha u) \right)$$

where $\Psi(x) = m^{-1} \sum_{i=1}^{m} f_i^{-1}(x)$.

Some notations

- From now W^* is the asymptotic optimal weight when the F_g are known :

$$W^*(u) = \underset{w:\sum \pi_g w_g = 1}{\operatorname{argmax}} \; G_w^\infty(u)$$
$$= \underset{w:\sum \pi_g w_g = 1}{\operatorname{argmax}} \sum_g \pi_g D_g(\alpha u w_g)$$

with $D_g(\cdot) = \pi_0 \max(\cdot, 1) + (1 - \pi_0) F_g(\cdot)$.

- $P_W^\infty(u) = (1 - \pi_0) \sum_g \pi_g F_g(\alpha u W_g(u))$.
- $\hat{u} = \mathcal{I}\left(\widehat{G}_{\widehat{W}^*}\right)$ and $u^* = \mathcal{I}(G_{W^*}^\infty)$.

A chain of technical results

A first lemma

$$\sup_{u\in[0,1]} \sup_{w\in(\mathbb{R}^+)^G} \left| \widehat{G}_w(u) - G_w^\infty(u) \right| \xrightarrow{a.s.} 0$$

by Glivenko-Cantelli theorem and $\frac{m_g}{m} \to \pi_g$.

The main technical proposition

Proposition

$$\sup_{u\in[0,1]} \left| \widehat{G}_{\widehat{W}^*}(u) - G^{\infty}_{W^*}(u) \right| \xrightarrow{a.s.} 0$$

or, equivalently,

$$\sup_{u\in[0,1]} \left| G^{\infty}_{\widehat{W}^*}(u) - G^{\infty}_{W^*}(u) \right| \xrightarrow{a.s.} 0.$$

The main technical proposition

Proof ideas

- Play with the triangular inequality and remove the absolute values when able by using the maximality of $\widehat{G}_{\widehat{W}^*}(u)$ and $G^{\infty}_{W^*}(u)$

Problem

They are not maxima on the same sets :
$K^m = \{w : m^{-1} \sum m_g w_g = 1\}$ versus $K^{\infty} = \{w : \sum \pi_g w_g = 1\}$

The main technical proposition
Proof ideas

- We introduce two shifts $\delta(u) = \sum \pi_g \widehat{W}_g^*(u) - 1$ and $\delta'(u) = \sum \frac{m_g}{m} W_g^*(u) - 1$.
- Then we form shifted weights $\widehat{W}^{\sim}(u) = \widehat{W}^*(u) - \boldsymbol{\delta}(u) \in K^{\infty}$ and $W^{\sim}(u) = W^*(u) - \boldsymbol{\delta}'(u) \in K^m$.

The main technical proposition

Final ideas

- Make appear $\left|G^{\infty}_{\widehat{W}^{\sim}}(u) - G^{\infty}_{W^*}(u)\right| = G^{\infty}_{W^*}(u) - G^{\infty}_{\widehat{W}^{\sim}}(u)$.
- End up with $\sup_u \left|G^{\infty}_{\widehat{W}^*}(u) - G^{\infty}_{W^*}(u)\right| \leq \sup_u \left(\widehat{G}_{W^{\sim}}(u) - \widehat{G}_{\widehat{W}^*}(u)\right) + o_{a.s.}(1)$.
- Use that $\widehat{G}_{W^{\sim}}(u) - \widehat{G}_{\widehat{W}^*}(u) \leq 0$. $\square$

The second important proposition

Proposition

$$\hat{u} \xrightarrow[m\to\infty]{a.s.} u^*$$

from which we deduce $\widehat{G}_{\widehat{W}^*}(\hat{u}) \xrightarrow{a.s.} G^{\infty}_{W^*}(u^*)$ by continuity.

Note $X_m = \sup_{u\in[0,1]} \left| \widehat{G}_{\widehat{W}^*}(u) - G^{\infty}_{W^*}(u) \right| \xrightarrow{a.s.} 0$, take a δ in $(0, u^*)$, note $u^0 = u^* - \delta$ and for all $\delta' \geq \delta$, $u' = u^* + \delta'$.

The second important proposition
Proof

- $s_\delta = \max_{\delta' \geq \delta} \left(G^{\infty}_{W^*}(u') - u' \right) < 0$ because if $s_\delta = 0$ it would contradict u^* maximality.
- $sup_{\delta' \geq \delta} \left(\widehat{G}_{\widehat{W}^*}(u') - u' \right) \leq s_\delta + X_m \to s_\delta < 0$
- So when $m \to \infty$ we must have $\hat{u} < u^* + \delta$.

The second important proposition
Proof

- $G^{\infty}_{W^*}(u^0) \geq G^{\infty}_{w}(u^0)$ with $w = W^*(u^*)$ by maximality.
- $G^{\infty}_{w}(u^0) = \frac{G^{\infty}_{w}(u^0)}{u^0} u^0 > \frac{G^{\infty}_{w}(u^*)}{u^*} u^0 = u^0$ by strict concavity.
- $\widehat{G}_{\widehat{W}^*}(u^0) - u^0 \geq G^{\infty}_{W^*}(u^0) - u^0 - X_m \to G^{\infty}_{W^*}(u^0) - u^0 > 0.$
- So when $m \to \infty$ we must have $\hat{u} > u^* - \delta$. $\square$

Third and last proposition

We have shown that $\widehat{G}_{\widehat{W}^*}(\hat{u}) \xrightarrow{a.s.} u^*$, that is for the denominator of the FDP. Showing that the numerator converges to $\pi_0 \alpha u^*$ is straightforward after this :

Proposition

$$\widehat{W}^*(\hat{u}) \xrightarrow{a.s.} W^*(u^*),$$

or, equivalently,

$$\widehat{W}^{\sim}(\hat{u}) \xrightarrow{a.s.} W^*(u^*).$$

Third and last proposition
Proof ideas

- One can show with the previous results and the triagular inequality that $\left| G^{\infty}_{\widehat{W}^{\sim}(\hat{u})}(u^*) - G^{\infty}_{W^*}(u^*) \right| \xrightarrow{a.s.} 0$.
- By contradiction, if $\widehat{W}^{\sim}(\hat{u}) \overset{a.s.}{\nrightarrow} W^*(u^*)$ then we find a $w^l \neq W^*(u^*)$ maximizing $G^{\infty}_{w}(u^*)$ but $W^*(u^*)$ is unique. □

Optimality in power
Proof ideas

- First, $\mathrm{Pow}\left(\widehat{W}^*\right) = \mathbb{E}\left[\widehat{P}_{\widehat{W}^*}(\hat{u})\right]$ where $\widehat{P}_W(u)$ is m^{-1} times the number of true alternative rejected.
- $\widehat{P}_{\widehat{W}^*}(\hat{u}) \xrightarrow{a.s.} P^{\infty}_{W^*}(u^*)$.
- For each accumulation point for $\mathrm{Pow}(w^{(m)})$ there is an accumulation point w for $w^{(m)}$.
- $\hat{u}^{(m'')} \xrightarrow{a.s.} \mathcal{I}\left(G^{\infty}_w\right)$ and then
- $\widehat{P}_{w^{(m'')}}\left(\hat{u}^{(m'')}\right) \xrightarrow{a.s.} P^{\infty}_w\left(\mathcal{I}\left(G^{\infty}_w\right)\right) \leq P^{\infty}_{W^*}\left(\mathcal{I}\left(G^{\infty}_w\right)\right) \leq P^{\infty}_{W^*}(u^*)$. □

More about the computation of $\widehat{W}^*$

Start of the algorithm

- Fix $u = \frac{1}{m}$, form $\tilde{p}_{gi} = \frac{p_{gi}}{\alpha u}$ and order the $\tilde{p}_{gi}$ in each group :

  $$\tilde{p}_{g,1} \leq \cdots \leq \tilde{p}_{g,m_g}.$$

  Also note $\tilde{p}_{g,0} = 0$.
- If $\forall g, \tilde{p}_{g,1} > m$, no rejection and move to $u = \frac{2}{m}$. If $\exists g, \tilde{p}_{g,1} \leq m$, continue and at least 1 rejection.

More about the computation of $\widehat{W}^*$

Start of the algorithm

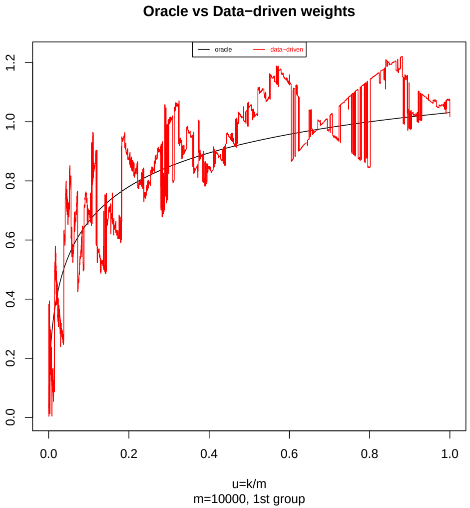
- Form all G-tuples $\boldsymbol{j} : \sum j_g = 2$ and check if there is one $\boldsymbol{j}$ such that $\sum m_g \tilde{p}_{g,j_g} \leq m$
  - If there is one, at least 2 rejections and continue with G-tuples of sum equal to 3.
  - If not, 1 rejection and use a $w_g = \tilde{p}_{g,j_g}$ with a $\boldsymbol{j} = (0, \dots, 0, \overbrace{1}^{h\text{-th position}}, 0, \dots, 0)$ such that $\tilde{p}_{h,1} \leq m$, then try to reject 2 hypotheses with $u = \frac{2}{m}$.

More about the computation of $\widehat{W}^*$

At rejection level k

- Form all G-tuples $\boldsymbol{j} : \sum j_g = k$ and check if there is one $\boldsymbol{j}$ such that $\sum m_g \tilde{p}_{g,j_g} \leq m$
  - If there is one, at least k rejections and continue with G-tuples of sum equal to $k+1$.
  - If not, $k-1$ rejections and use a $w_g = \tilde{p}_{g,j_g}$ with a $\boldsymbol{j}$ that was suitable for $k-1$, then try to reject k hypotheses with $u = \frac{2}{m}$.

Illustration of $\widehat{W}^*(u)$



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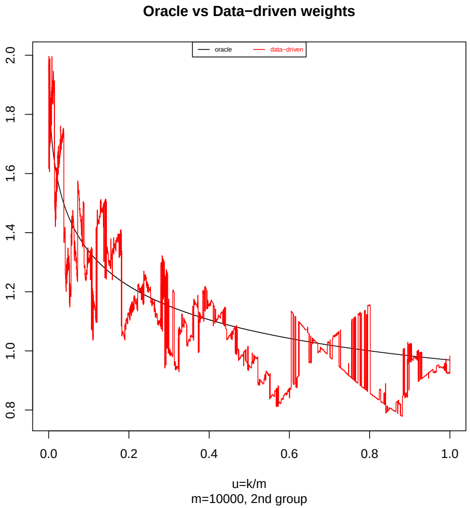
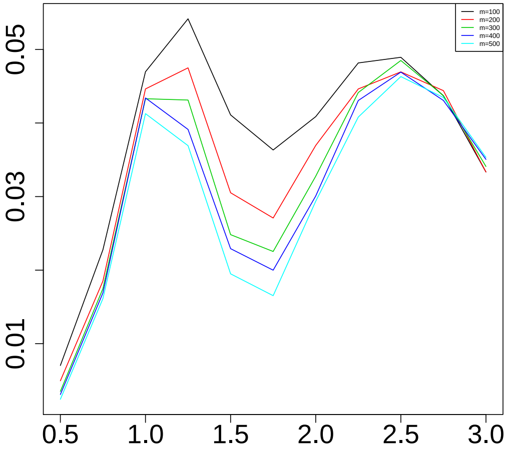


The overfitting decreases with m

$\alpha = 0.05$, 70% true null, $\pi_1 = \pi_2 = 0.5$



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