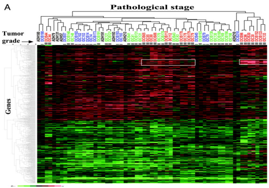
Controlling false discovery proportion in structured data sets

PhD defense, November 30 2023

Iqraa Meah

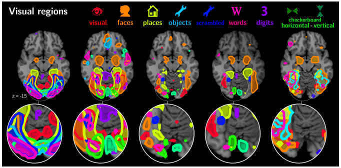
Multiplicity in scientific research

Molecular biology



Understand associations between genome and biological traits

Neuroscience



Identify brain regions associated with cognitive function/disorder

Also in medicine for clinical trials, astrophysics...

Multiplicity : statistical formalism

- Observe $X \sim P$ (unknown)
  X matrix of gene expression

- For $i \in \{1, \dots, m\}$ test simultaneously null hypotheses
  $H_{0,i}$: "gene i is not related to cancer" vs
  $H_{1,i}$: "gene i is related to cancer"

- P-value based testing:
  each $H_{0,i}$ is represented by $\boxed{\text{valid}}$ p-value $p_i(X) = p_i \in (0, 1)$

A valid p-value verifies

$$\mathbb{P}_{X \sim P}(p \leq u) \leq u, \text{ for all } u \in [0, 1], \text{ when } P \text{ satisfies } H_0$$

Multiple Testing (MT)

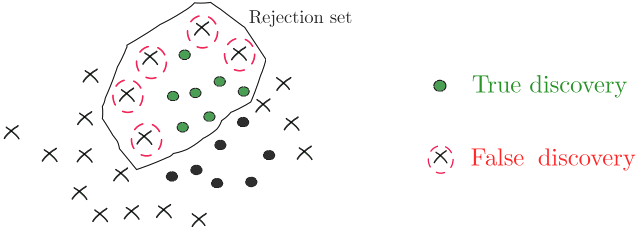
$\longrightarrow$ Goal: make interesting discoveries while limiting # errors

$\mathcal{H}_0$ (unknown)

contains true nulls ×

$\mathcal{H}_1$ (unknown)

contains true alternatives •



Uncorrected MT

$\longrightarrow$ Testing all $H_{0,i}$ at same level $\alpha \in (0,1)$

Individual Type I error controlled

$$\mathbb{P}(p_i(X) \leq \alpha) \leq \alpha \text{ for all } \alpha \in (0,1), \text{ and } i \in \mathcal{H}_0$$

Because p-values are valid

Overall nb errors in expectation explodes

Under global null, with $m \geq 1$ uniform p-values,

$$\mathbb{E}\left[\sum_{j=1}^{m} 1_{p_j \leq \alpha}\right] = m\alpha$$

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MT error metric

MT $\approx$ $\boxed{\text{assessing overall quality}}$ of decisions taken
$\longrightarrow$ Notion of Type I error accounting for multiplicity

False Discovery Proportion (FDP) [Benjamini and Hochberg, 1995]

$$\text{FDP} = \frac{\#\text{false discoveries}}{\#\text{discoveries}}$$

- Random quantity, thus either
  $\longrightarrow$ control expectation : False Discovery Rate (FDR)
  $\longrightarrow$ control tail distribution : provide confidence bounds

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FDP related risks

FDR control : prescribe rejection set

Design procedure $R : [0,1]^m \to \mathcal{P}(\{1,\dots,m\})$ s.t. for any $\alpha \in (0,1)$

$$\mathrm{FDR} := \mathbb{E}[\mathrm{FDP}(R)] \leq \alpha$$

FDP confidence bounds : evaluate selection sets

For $R \in \mathcal{P}(\{1,\dots,m\})$, provide upper bound $\overline{\mathrm{FDP}}(R)$ s.t

$$\mathrm{P}(\mathrm{FDP}(R) \leq \overline{\mathrm{FDP}}(R)) \geq 1-\delta,$$

for some $\delta \in (0,1)$

Goal: control + power

$\hookrightarrow$ few Type II error for FDR

$\hookrightarrow$ sharpness for confidence bounds

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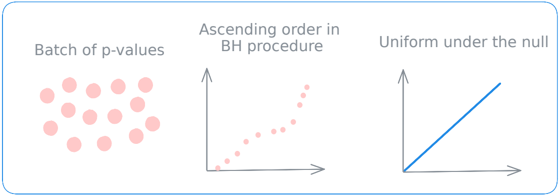
P-value structures

$\longrightarrow$ Classical methods derived for "canonical setting"



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  $\hookrightarrow$ rethink/adapt the methods

- Structure defined upon
  availability, ordering, and marginal distribution

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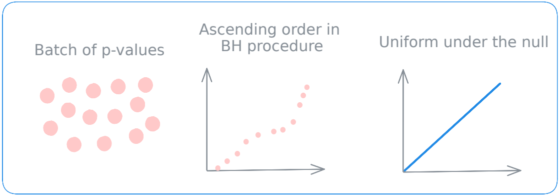

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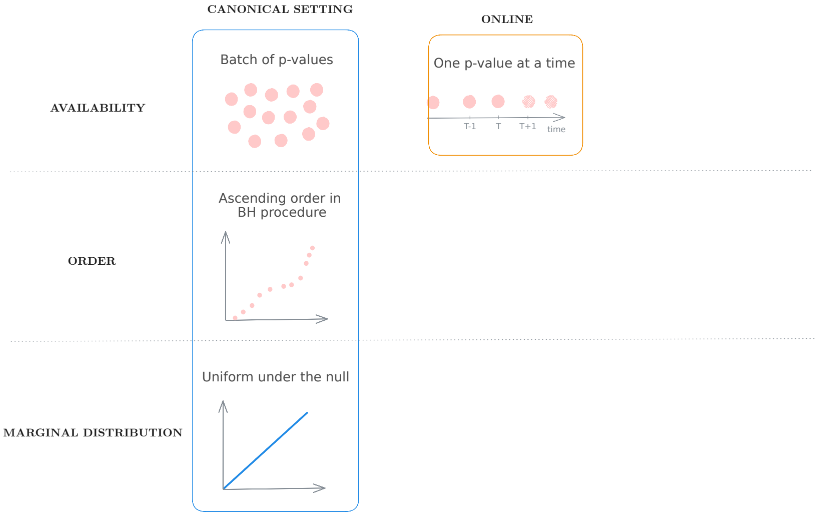
P-value structures

Informal presentation



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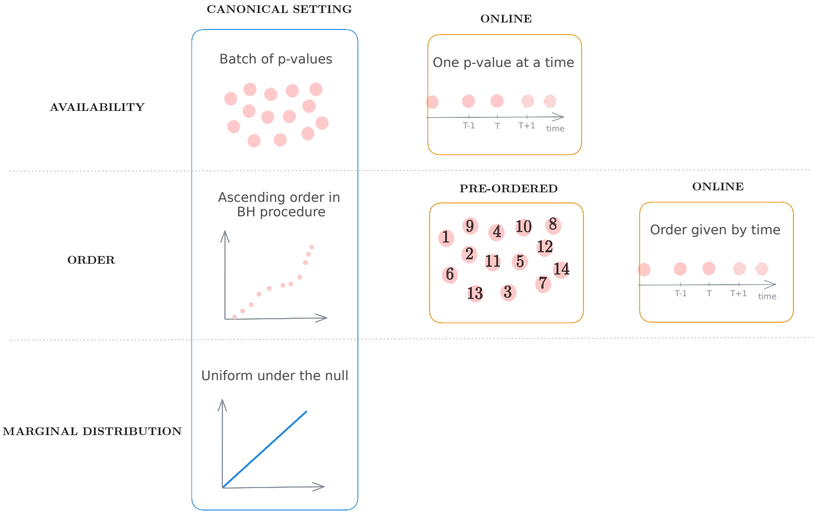

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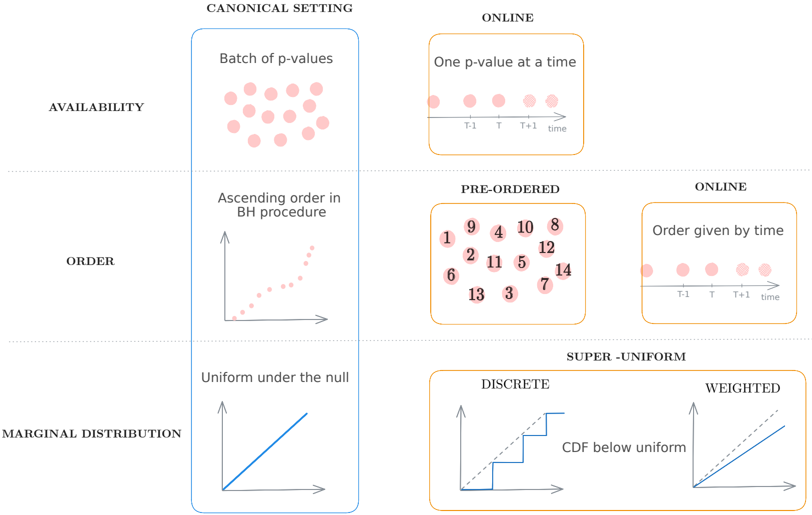

Presentation outline

Focus : combination of p-value structures + one MT goal

Chapter 2: Online multiple testing with super-uniformity reward
$\longrightarrow$ Online, discrete
$\longrightarrow$ Online mFDR control

Chapter 3: Consistent FDP bounds
$\longrightarrow$ Preordered (knockoff) p-values
$\longrightarrow$ Uniform FDP confidence bounds

Chapter 4: Unified class of π_0 estimators with plug-in FDR control
$\longrightarrow$ Discrete p-values
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Online multiple testing with super-uniformity reward
Sebastian Döhler, Iqraa Meah, Etienne Roquain

[] arXiv:2110.01255, in revision for EJS

Online multiple testing setting

Time

Null Hypothesis	Decision
$H_{0,1}$	$p_1 \leq \alpha_1$?
$H_{0,2}$	$p_2 \leq \alpha_2$?
$\vdots$	$\vdots$
$H_{0,t}$	$p_t \leq \alpha_t$?
$\vdots$	$\vdots$

$\mathcal{F}_{t-1} = \sigma\left(1_{p_1 \leq \alpha_1}, \ldots, 1_{p_{t-1} \leq \alpha_{t-1}}\right)$ represents past

Assumption

$$\mathbb{P}\left(p_t \leq u \mid \mathcal{F}_{t-1}\right) \leq u \text{ a.s. for all } u \in [0,1], \text{ with } t \in \mathcal{H}_0$$

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Online multiple testing setting

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$\rightarrow$ Goal: procedure with online mFDR $\leq \alpha$

Online error metric

For a procedure $\mathcal{A} = \{\alpha_t, t \geq 1\}$

$$\mathrm{mFDR}(\mathcal{A}) := \sup_{t \geq 1} \frac{\mathbb{E}[|\mathcal{H}_0 \cap R(t)|]}{\mathbb{E}[1 \vee |R(t)|]}$$

$\mathcal{H}_0$ set of true nulls

$R(t) = \{1 \leq i \leq t : p_i \leq \alpha_i\}$ rejection set up to time $t \geq 1$

- Tool : FDP estimation

$$\mathrm{FDP}(t) = \frac{\sum_{j \leq t, j \in \mathcal{H}_0} 1_{p_j \leq \alpha_j}}{1 \vee |R(t)|} \approx \frac{\sum_{j \leq t, j \in \mathcal{H}_0} \alpha_j}{1 \vee |R(t)|} \leq \frac{\sum_{j \leq t} \alpha_j}{1 \vee |R(t)|} := \widehat{\mathrm{FDP}}(t)$$

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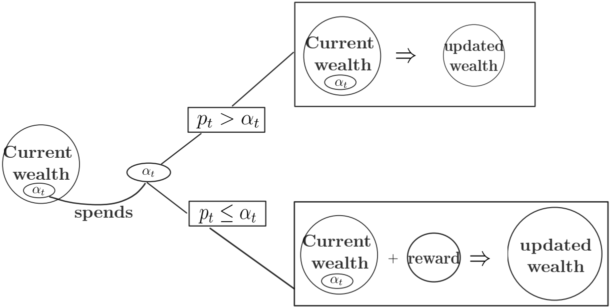
OMT procedure

Lemma [Ramdas et al., 2017]

For $\mathcal{A} = \{\alpha_t, t \geq 1\}$ s.t. $\forall t \geq 1$, $\sum_{j \leq t} \alpha_j \leq \alpha(1 \vee |R(t)|)$, $\mathrm{mFDR}(\mathcal{A}) \leq \alpha$

- Standard procedure : Level based On Recent Discoveries (LORD) [Javanmard and Montanari, 2018, Ramdas et al., 2017]
- Baseline strategy: Generalized α-investing (GAI) [Foster and Stine, 2008]
  $\hookrightarrow$ α wealth to pay errors



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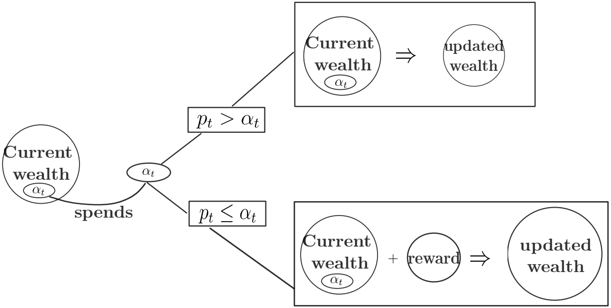
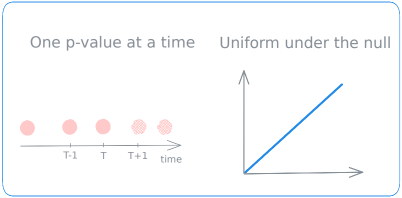
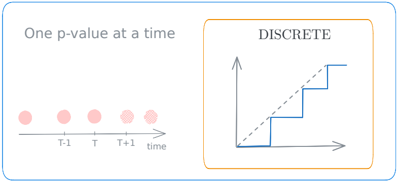


Super-uniformity

Classical setting
Adaptivity [Ramdas et al., 2018]
Asynchronous setting
[Zrnic et al., 2021]
Power study
[Chen and Arias-Castro, 2021]
⋮



Our focus



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a.s. for all $u \in [0,1]$, with $t \in \mathcal{H}_0$

Equality $\to$ Uniform
Strict inequality $\to$ over-conservativeness

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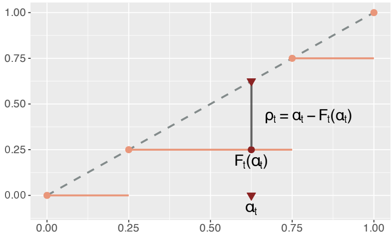
Discrete p-values



- Fisher Exact Tests (FETs) for association studies
  ↪ X: gene knocked out or not
  Y: change phenotype or not

	$Y = 1$	$Y = 0$	Total
$X = 0$	n_{11}	n_{12}	$n_{1\cdot}$
$X = 1$	n_{21}	n_{22}	$n_{2\cdot}$
Total	$n_{\cdot 1}$	$n_{\cdot 2}$	n

- Also Poisson, Binomial tests...

Contribution

Super-uniformity reward

$\longrightarrow$ Re-incorporate $\rho_t = \alpha_t - F_t(\alpha_t)$ as reward

Theorem [Döhler, M. and Roquain (2021)]

For any procedure $\mathcal{A}^0 = (\alpha_t^0, t \geq 1)$ satisfying almost surely, for all $t \geq 1$,

$$\sum_{1 \leq j \leq t} \alpha_j^0 \leq \alpha \, (1 \vee R(t)),$$

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$$\alpha_t = \alpha_t^0 + \sum_{1 \leq j \leq t-1} \gamma'_{t-j}(\alpha_j - F_j(\alpha_j))$$

with $\gamma' = (\gamma'_t)_{t \geq 1}$ sequence of non-negative values summing to one

- controls online mFDR at level α under conditional validity
- uniformly dominates the base procedure $\mathcal{A}^0$

Proof intuition : $\widehat{\mathrm{FDP}}(t) = \frac{\sum_{j \leq t} F_j(\alpha_j)}{1 \vee |R(t)|} \leq \frac{\sum_{j \leq t} \alpha_j}{1 \vee |R(t)|}$ tighter estimate

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- International Mice Phenotyping Consortium (IMPC) dataset
  $\hookrightarrow$ Study genotype effect on phenotype
  Is gene X related to eye color ?
  $\hookrightarrow$ In vivo study with gene knockout
- Benchmark dataset analyzed in online literature
- Analyzed using FETs

mFDR procedures	LORD	ρLORD	ALORD	ρALORD
# discoveries (male)	882	**972**	972	**1041**
# discoveries (female)	839	**946**	966	**1046**

Perspectives

Extensions

- Online p-value weighting using rewarding method
- Control online mFDR at stopping times
- FDR control by enforcing monotonous reward across time

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- Power study
  $\rightarrow$ Optimal smoothing sequence $(\gamma'_t)_{t\geq 1}$
  $\rightarrow$ Super-uniformity reward optimal for $\sum_{j\leq t} F_j(\alpha_j) \leq \alpha(1 \vee |R(t)|)$?

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Consistent false discovery proportion bounds

Gilles Blanchard, Iqraa Meah, Etienne Roquain

[🗎] arXiv:2306.07819, submitted

Aim recall

For $R \in \mathcal{P}(\{1, \ldots, m\})$, provide upper bound $\overline{\mathrm{FDP}}(R)$ s.t

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for some $\delta \in (0, 1)$

More informative = stronger statement than expectation

Posthoc confidence bounds

Design bounding function $\overline{\mathrm{FDP}}$ valued in $(0, 1)$ s.t

$$\mathrm{P}(\forall R \in \mathcal{P}(\{1, \ldots, m\}), \mathrm{FDP}(R) \leq \overline{\mathrm{FDP}}(R)) \geq 1 - \delta,$$

for some $\delta \in (0, 1)$

+ More analysis freedom [Genovese and Wasserman, 2006] [Goeman and Solari, 2011]

FDP confidence bounds

Quick background

Aim recall

For $R \in \mathcal{P}(\{1,\dots,m\})$, provide upper bound $\overline{\mathrm{FDP}}(R)$ s.t

$$\mathrm{P}(\mathrm{FDP}(R) \leq \overline{\mathrm{FDP}}(R)) \geq 1-\delta,$$

for some $\delta \in (0,1)$

More informative = stronger statement than expectation

Posthoc confidence bounds

Design bounding function $\overline{\mathrm{FDP}}$ valued in $(0,1)$ s.t

$$\mathrm{P}(\forall R \in \mathcal{P}(\{1,\dots,m\}), \mathrm{FDP}(R) \leq \overline{\mathrm{FDP}}(R)) \geq 1-\delta,$$

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Confidence bounds on a path

Focus on couple (FDR procedure, FDP bound)

Gain accuracy for set outputted by FDR procedure ?

Confidence bounds on a path **[Katsevich and Ramdas, 2020]**

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For $R_{\hat{k}_\alpha}$ output of FDR procedure at level α, $\boxed{\overline{\mathrm{FDP}}(R_{\hat{k}_\alpha}) \approx \alpha \text{ ?}}$

Consistency for couple (FDR procedure, FDP bound)

Formalism

Consistency [Blanchard, M. and Roquain (2023)]

$\forall \epsilon > 0$, $\forall \alpha_0 \in (0, 1)$,

$$\lim_{m \to \infty} \mathbb{P}^{(m)} \left(\sup_{\alpha \in [\alpha_0, 1)} \left\{ \overline{\mathrm{FDP}}_\alpha - \alpha \right\} \geq \epsilon \right) = 0.$$

with $\overline{\mathrm{FDP}}_\alpha = \overline{\mathrm{FDP}}(R_{\hat{k}_\alpha})$
where $R_{\hat{k}_\alpha}$ output of FDR procedure at level α,
and $\mathbb{P}^{(m)}$ sequence of standard models

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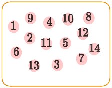
Pre-ordered path

Pre-ordered path : $R_k = \{\pi(i) : 1 \leq i \leq k,\ p_{\pi(i)} \leq s\}$
$\hookrightarrow s \in (0,1]$ signal zone threshold



$\widehat{\mathrm{FDP}}(R_k) = \widehat{\mathrm{FDP}}_k = \frac{s}{1-\lambda} \frac{1+\sum_{i=1}^{k} 1\{p_{\pi(i)} > \lambda\}}{1 \vee \sum_{i=1}^{k} 1\{p_{\pi(i)} \leq s\}}$ [Lei and Fithian, 2016]
$\hookrightarrow \lambda \in (0,1]$ error zone threshold

FDR procedure look for largest $\hat{k}_\alpha$ such that $\widehat{\mathrm{FDP}}_{\hat{k}_\alpha} \leq \alpha$

Encompasses [Barber and Candès, 2015] Knockoff procedure
binary p-values and $\lambda = s = 1/2$

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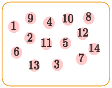

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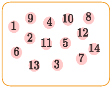

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Proposed bounds

KR bound [Katsevich and Ramdas, 2020]

$$\overline{\mathrm{FDP}}_k^{\mathrm{KR}} = 1 \wedge \left(\frac{\log(1/\delta)}{a\log(1+\frac{1-\delta^{B/a}}{B})} \frac{a + \frac{s}{1-\lambda}\sum_{i=1}^k 1\{p_{\pi(i)} > \lambda\}}{1 \vee \sum_{i=1}^k 1\{p_{\pi(i)} \leq s\}} \right)$$

with $a \geq 1$ free parameter, $B = s/(1-\lambda)$, and $\lambda \geq s$.

Default choice $a = 1$ suggested by KR.

KR-U bound (new) [Blanchard, M. and Roquain (2023)]

$$\overline{\mathrm{FDP}}_k^{\mathrm{KR\text{-}U}} = 1 \wedge \min_{a\in\mathbb{N}\setminus\{0\}} \left\{ \frac{\log(1/\delta_a)}{a\log(1+\frac{1-\delta_a^{B/a}}{B})} \frac{a + \frac{s}{1-\lambda}\sum_{i=1}^k 1\{p_{\pi(i)} > \lambda\}}{1 \vee \sum_{i=1}^k 1\{p_{\pi(i)} \leq s\}} \right\},$$

with $\delta_a = \delta/(\kappa a^2)$, $a \geq 1$, for $B = s/(1-\lambda)$, $\kappa = \pi^2/6$.

$\rightarrow$ Our proposal : KR + union bound over $a \in \mathbb{N}\setminus\{0\}$

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Proof intuition : Union bound allows a to be large slowly enough w.r.t $\hat{r}_\alpha$

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Illustration

[Lei and Fithian, 2016] VCT model

- Local alternative $\pi(i) = 1/2 + (0 \vee 1/2(\frac{z-i}{z-1}))$,
  $\hookrightarrow z > 1$ tells how slowly probability of observing signal deteriorates
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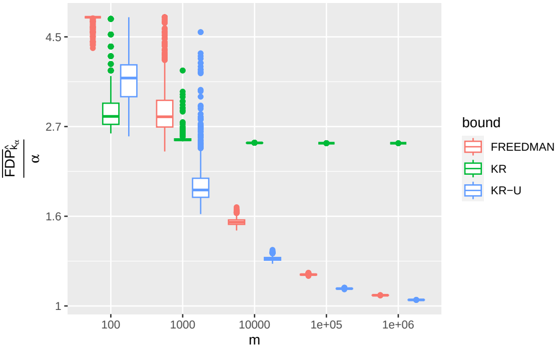

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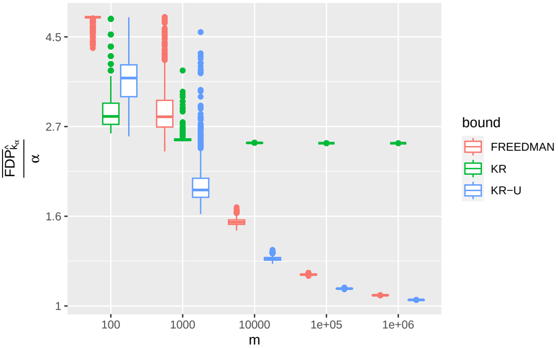

Outlook

Other covered settings:

- top-k: consistency for (BH, FDP bounds)
  Uniform improvement by π_0-estimation
- online : consistency for (LORD, FDP bounds)

A unifying class of π_0 estimators with plug-in FDR control
Sebastian Döhler, Iqraa Meah

[🗎] arXiv:2307.13557, In revision for Biometrical Journal

Unifying class of π_0 estimators with plug-in FDR control

$m_0 = |\mathcal{H}_0|$ #true nulls $\quad \pi_0 = \frac{m_0}{m}$ proportion of true nulls

$\mathrm{FDR}(\mathrm{BH}_\alpha) = \pi_0 \alpha \ll \alpha$ if dense signal
$\mathrm{FDR}(\mathrm{BH}_{\alpha/\pi_0}) = \alpha$ nice but π_0 unknown
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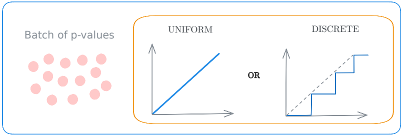
$\hookrightarrow$ sufficient condition for plug-in FDR control : [Benjamini et al., 2006] [Blanchard and Roquain, 2009] (BR)

Settings of interest



Aim : address

1 (Uniform) Anti-conservativeness
2 (Discrete) Bias inflation

Contribution: general class of estimators verifying (BR) condition
$\hookrightarrow$ encompasses existing + new estimators
$\hookrightarrow$ allows adaptation to discreteness

Perspective : discrete BH with discrete (BR) condition

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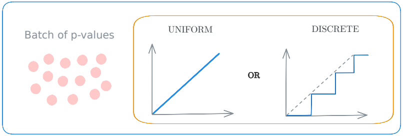

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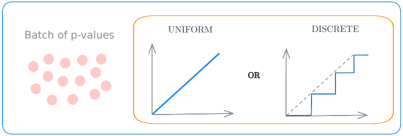

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Conclusion

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General perspectives :

- Power studies
  For optimal parameters
  $\hookrightarrow$ challenging in online and discrete setting
- Relax independence
  E-value based testing $\rightarrow$ discrete E-values ?

Conclusion

Thank you for your attention !

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Zrnic, T., Ramdas, A., and Jordan, M. I. (2021).

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Online p-value weighting

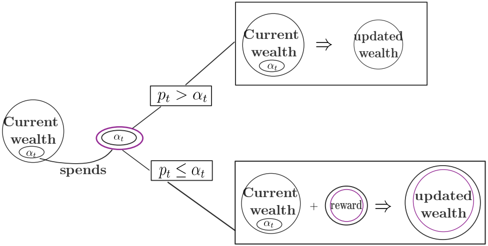
P-value weighting : ease rejection when confident

Test on $\tilde{p}_t = p_t / w_t \rightarrow$ prior knowledge

$\Leftrightarrow$ Test p_t with $\alpha_t w_t$

Well studied offline $\rightarrow$ $(w_t)_{1 \leq t \leq m}$ unit mean, not obvious online

Only solution [Ramdas et al., 2017] $\rightarrow$ no rescaling (called wGAI)

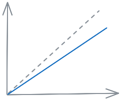


w_t inflates current investment if confident in rejection

$\rightarrow$ preserve wealth but less rejection reward to keep mFDR control

Online p-value weighting using super-uniformity

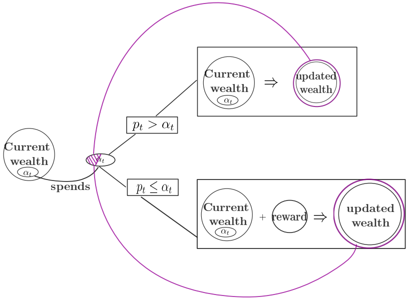
[Döhler, M. and Roquain (2021)]



$\boxed{\text{Idea: enforce super-uniformity with } w_t \in (0,1)}$

$\hookrightarrow$ Use only part of α_t if no confidence in rejection

$\rightarrow$ re-incorporate what was not used



mFDR procedures	LORD	wGAI	wLORD (new)
# discoveries	3550	1308	**3875**

Proof of concept on "airway" data set, with weights taken from [Ignatiadis et al., 2016]

Monotonicity of online procedure

α_t is a coordinate-wise nondecreasing function of past decisions:

Monotonicity

if $\tilde{R}_i \geq R_i$ for all $i \leq t-1$, then we have
$\alpha_t(\tilde{R}_1, \ldots, \tilde{R}_{t-1}) \geq \alpha_t(R_1, \ldots, R_{t-1})$

Rewarded procedures non monotone

Enforce monotonicity : look for "least favorable" super-uniformity reward over all possible past rejection sequences $\rightarrow$ intractable

Estimator $\widehat{\mathrm{FDP}}$ with adaptivity

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$$\widehat{\mathrm{FDP}}_\lambda(T, \mathcal{A}) = \frac{\alpha_T + \sum_{\substack{1 \le t \le T-1, \\ p_t \ge \lambda}} F_t(\alpha_t)}{(1-\lambda)(1 \vee R(T))},$$

with $\lambda \in [0, 1)$

$\rightarrow$ Intuition: count only for p-values above λ because these are potentially true nulls

Stopping time control for rewarded procedures

Define the stopping time τ as any r.v taking values in $\{1, 2, \ldots\}$ with

- $\tau < +\infty$ almost surely;
- $\{\tau = t\} \in \mathcal{F}_t$ for all $t \geq 1$.

Stopping time control

Consider a stopping time τ as above. For any procedure $\mathcal{A} = (\alpha_t, t \geq 1)$, if for some $\lambda \in [0, 1)$ we have $\sup_{T \geq 1} \widehat{\mathrm{FDP}}_\lambda(\mathcal{A}) \leq \alpha$ then $\mathrm{mFDR}_\tau(\mathcal{A}) \leq \alpha$.

→ Proof:

$$M_t = \sum_{i \leq t, i \in \mathcal{H}_0} \left(1\{p_i \leq \alpha_i\} - \frac{1\{p_i > \lambda\}}{1 - \lambda} F_i(\alpha_i) \right), \quad t \geq 1$$

is a super-martingale.

Online Bonferroni

$$\alpha_t = \alpha\gamma_t \quad \forall t \geq 1$$

with $\{\gamma_t\}_{t\geq 1}$ a nonnegative sequence summing to one

- Controls online FWER $\Rightarrow$ controls online mFDR
- α_t decrease quickly $\rightarrow$ low power, no discoveries in long run
- Idea : scale budget by $\#$ rejections

Level based On Recent Discoveries (LORD)

[Javanmard and Montanari, 2018, Ramdas et al., 2017]

$$\alpha_t = W_0\gamma_t + (\alpha - W_0)\gamma_{t-\tau_1} + \alpha \sum_{j\geq 2} \gamma_{t-\tau_j} \quad \forall t \geq 1$$

with $W_0 \in [0, \alpha]$ an initial wealth, and τ_j time of the j^{th} discovery

Spending procedure for FWER control

$$\alpha_1 = \alpha\gamma_1$$
$$\alpha_2 = \alpha\gamma_2$$
$$\alpha_3 = \alpha\gamma_3$$
$$\vdots$$

Investing procedures for mFDR control

$$\alpha_1 = W_0\gamma_1$$
$$\alpha_2 = W_0\gamma_2 \quad \text{rejection}$$
$$\alpha_3 = W_0\gamma_3 + (\alpha - W_0)\gamma_1$$
$$\alpha_4 = W_0\gamma_4 + (\alpha - W_0)\gamma_2 \quad \text{rejection}$$
$$\alpha_5 = W_0\gamma_5 + (\alpha - W_0)\gamma_3 + \alpha\gamma_1$$
$$\vdots$$

- Fisher Exact Tests (FETs) for association studies

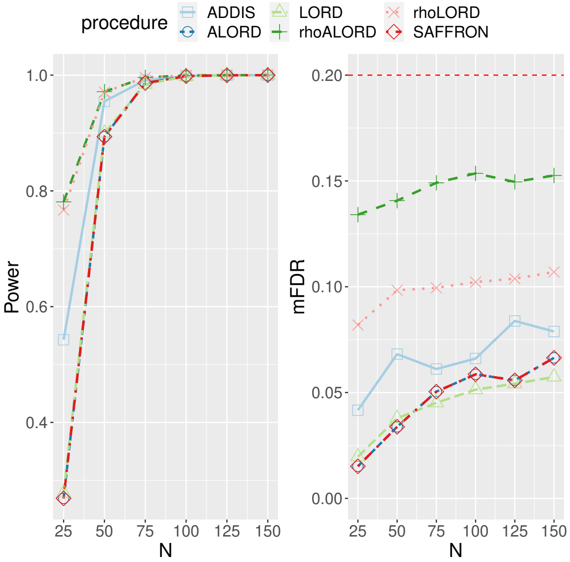
  $\hookrightarrow$ X: gene knocked out or not

  Y: change phenotype or not

	$Y=1$	$Y=0$	Total
$X=0$	n_{11}	n_{12}	$n_{1.}$
$X=1$	n_{21}	n_{22}	$n_{2.}$
Total	$n_{.1}$	$n_{.2}$	n

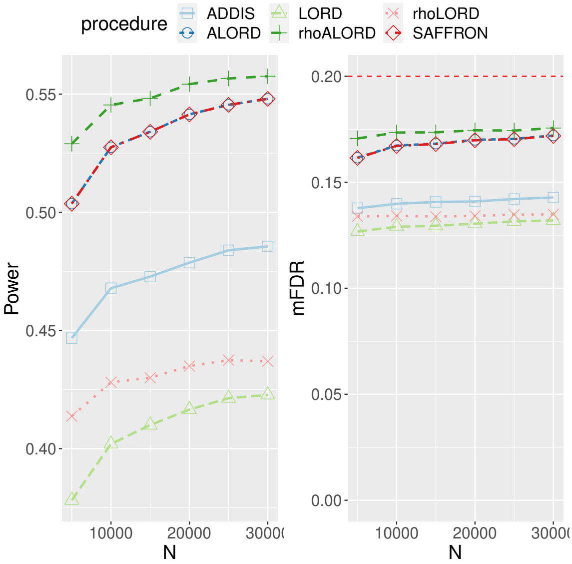
Numerical results on simulated data

Discreteness level



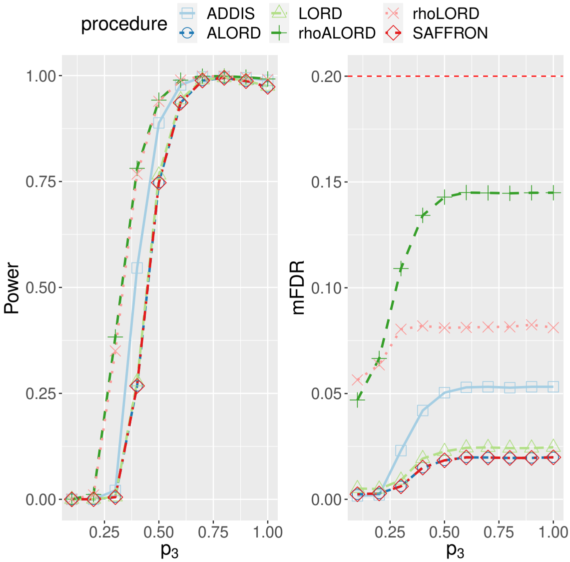
Numerical results on simulated data

Discreteness level



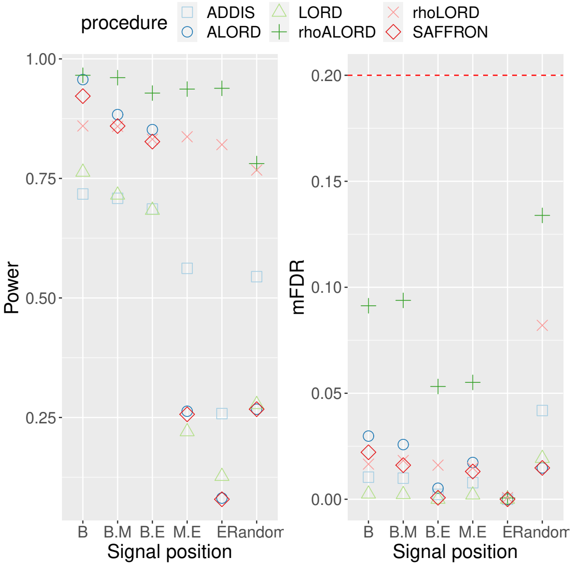
Numerical results on simulated data

Signal strength



Numerical results on simulated data

Signal position

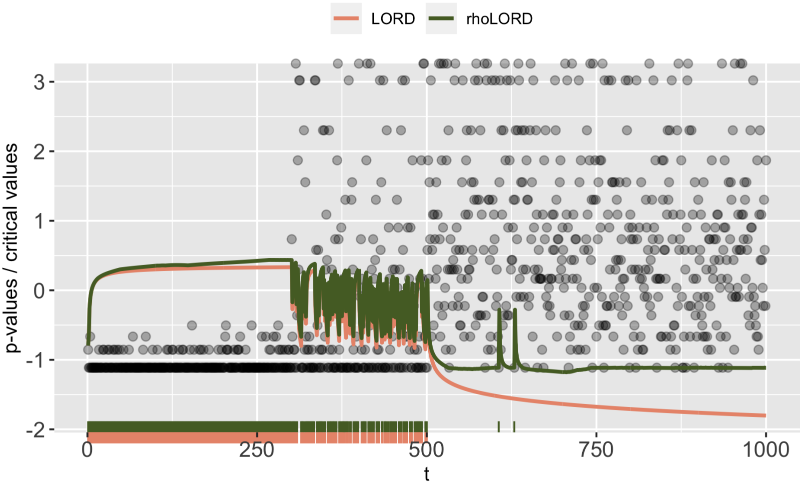


- Permutation tests

$$p(X) = (B+1)^{-1}\left(1 + \sum_{b=1}^{B} 1\left\{S\left(X^{\sigma_b}\right) \geq S(X)\right\}\right)$$

$$\mathbb{P}(p(X) \leq s) \leq F(s) = \frac{\lfloor (B+1)s \rfloor}{B+1}$$

Numerical results on simulated data



Unifying class of π_0 estimators with plug-in FDR control

Bias inflation

$$\text{Bias}(\hat{m}_0^{\text{Storey}}) = \frac{1}{1-\lambda} + \frac{1}{1-\lambda}\left(\sum_{i\in\mathcal{H}_0}\mathbb{E}[1_{p_i>\lambda}] + \sum_{i\in\mathcal{H}_1}\mathbb{E}[1_{p_i>\lambda}]\right) - m_0$$

- Under Uniform setting

$$\frac{1}{1-\lambda} + \frac{1}{1-\lambda}\left(\sum_{i\in\mathcal{H}_1}\mathbb{E}[1_{p_i>\lambda}]\right)$$

- Under Discrete setting

$$\frac{1}{1-\lambda} + \frac{1}{1-\lambda}\left(\sum_{i\in\mathcal{H}_0} 1 - F_i(\lambda) + \sum_{i\in\mathcal{H}_1}\mathbb{E}[1_{p_i>\lambda}]\right) - m_0$$