Contrôle post hoc des faux positifs pour des hypothèses structurées

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Exploratory analysis in multiple testing

Search interesting hypotheses that will be cautiously investigated after.
Desired properties, as stated by [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 seing the data

Example of post hoc decision

GWAS study with 10^6 genetic variants, select the 157 smallest p-values after seing a gap between the 157th and 158th smallest p-values.

Exploratory analysis in multiple testing

[Goeman and Solari (2011)]

This reverses the traditional roles of the user and procedure in multiple testing. Rather than, as in FWER-or FDR-based methods, 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.

$$\mathrm{FWER}(R) = \mathbb{P}(|R \cap \mathcal{H}_0| > 0), \quad \mathrm{FDR}(R) = \mathbb{E}\left[\frac{|R \cap \mathcal{H}_0|}{|R| \vee 1}\right]$$

Post hoc and replication crisis

Replication crisis: many results poorly interpretable and non reproductible

Post hoc done wrong: *p*-hacking

- Pre-selecting variables that seem significant, exclude others from experiment
- Theoretical results no longer hold

Example

- GWAS study with 10^6 genetic variants
- Apply the Bonferroni procedure (FWER control) over the 1000 smallest *p*-values and report the result
- Problem: Bonferroni correction: $\alpha/1000$ instead of $\alpha/10^6$!

Selective inference against replication crisis

Selective inference: methods that account for a post hoc selection step and still provide statistical guarantees.

1. Conditionally to the selection event (e.g. Lasso selected features) [Fithian et al. (2017), Lee et al. (2016), and Tibshirani et al. (2016)]
2. Simultaneously over all possible selection events [Goeman and Solari (2011), Berk et al. (2013), and Blanchard et al. (2020)]

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2. Simultaneously over all possible selection events [Goeman and Solari (2011), Berk et al. (2013), and Blanchard et al. (2020)] $\leftarrow$ The context of this work

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Multiple testing setting

- Data $X \in (\mathcal{X}, \mathfrak{X})$ with $X \sim P \in \mathcal{P}$ a collection of distributions, P unknown
- m null hypotheses $H_{0,i}$ on P which are subsets of $\mathcal{P}$
- m is large!
- $\mathcal{H}_0 = \{i : P \in H_{0,i}\}$: $i \in \mathcal{H}_0 \Leftrightarrow H_{0,i}$ is true
- m p-values $p_i = p_i(X)$ such that $p_i \succeq \mathcal{U}([0,1])$ if $i \in \mathcal{H}_0$
  - Each p_i provides an α level test : $\mathbb{P}_{P \in H_{0,i}}(p_i \leq \alpha) \leq \alpha$
- Definition: for every subset of hypothese S: $V(S) = |S \cap \mathcal{H}_0|$

Classic MT theory: form a rejection set R with a guarantee on $V(R)$

- $\mathrm{FWER}(R) = \mathbb{P}(V(R) > 0)$
- $\mathrm{FDR}(R) = \mathbb{E}\left[\frac{V(R)}{|R| \vee 1}\right]$

Our goal: post hoc inference

Or simultaneous inference

Confidence bounds on any set of selected variables

A confidence 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
- Originates from [Genovese and Wasserman (2006) and Meinshausen (2006)]
- A guarantee over any selected set instead of a rejected set: advise some $\widehat{S}$ instead of prescribe one R
- The MT paradigm is reversed

BNR formalism

[Blanchard et al. (2020)]

Key concept: reference family

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

$$\mathrm{JER}(\mathfrak{R}) = \mathbb{P}\left(\exists k, |R_k \cap \mathcal{H}_0| > \zeta_k\right) \leq \alpha$$

- Conversely, $\mathbb{P}\left(\forall k, |R_k \cap \mathcal{H}_0| \leq \zeta_k\right) \geq 1 - \alpha$
- Confidence bound only on the members of $\mathfrak{R}$
- $\Longrightarrow$ Derivation of a global confidence bound by interpolation

BNR formalism

[Blanchard et al. (2020)]

Two different bounds

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

Main idea: the only information on $\mathcal{H}_0$ is that $\mathcal{H}_0 \in \{A, \forall k, |R_k \cap A| \leq \zeta_k\}$

$$
\begin{aligned}
|S \cap A| &= |(S \cap R_k) \cap A| + |(S \setminus R_k) \cap A| \\
&\leq |R_k \cap A| + |S \setminus R_k| \\
&\Longrightarrow V^*_{\mathfrak{R}}(S) \leq \overline{V}_{\mathfrak{R}}(S)
\end{aligned}
$$

BNR formalism

A flexible and unified approach

- Compatible with previous works, like the closed testing approach of [Goeman and Solari (2011)]
- BNR approach: $\zeta_k = k - 1$ and find $R_k = \{i : p_i < t_k\}$ such that JER control. Example: $t_k = \alpha k/m$ (Simes inequality)
  - JER control becomes "simultaneous k-FWER control"
- Property: if R_k nested, then $\overline{V}_{\mathfrak{R}} = V^*_{\mathfrak{R}}$

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Spatial structure

Informal assumption

The signal is localized in some spatially structured regions, with, possibly, different levels (e.g. active SNPs into genes into chromosomes)

[Meijer et al. (2015)]

Considering the data at the region level is not only useful because these regions can be the fundamental units of interest, but also because these regions can have an increased signal-to-noise-ratio

- Accordingly, find adapted new reference families
- We want $V^*_{\mathfrak{R}}$ to be easy to compute
- Our approach: deterministic R_k's capturing spatial hierarchy, estimate the true nulls inside them (i.e. ζ_k random)
  - opposite of [Blanchard et al. (2020)]

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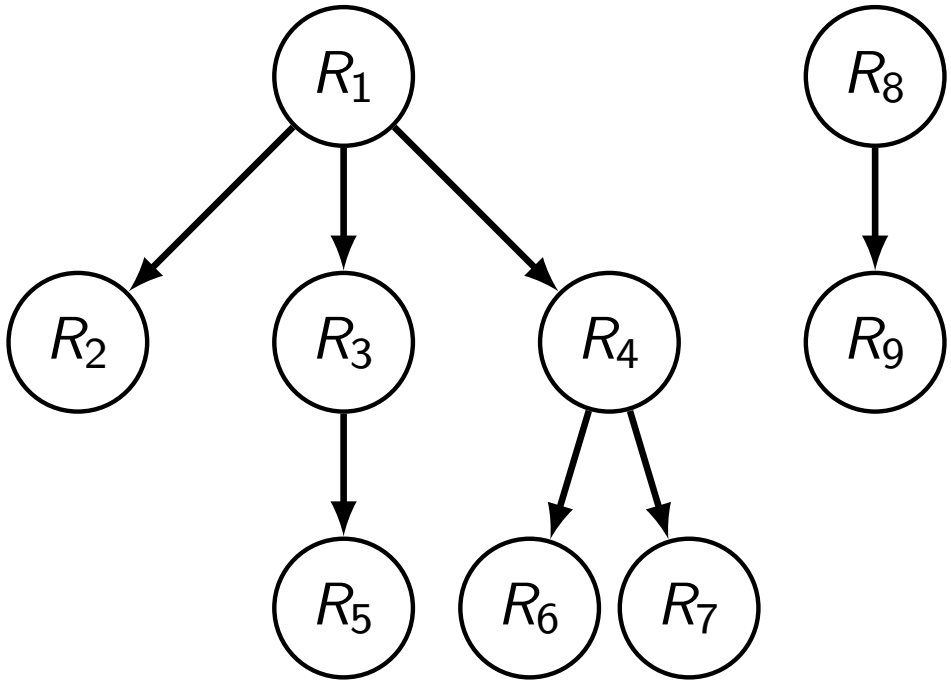
Forest structure

- $\forall k, k' \in \mathcal{K},\ \ R_k \cap R_{k'} \in \{R_k, R_{k'}, \varnothing\}$
- Includes nested families or totally disjoint families
- Accommodates to different levels of signal localization through the different depths of the nodes



Forest structure

Important property

Property

There is a partition $(L_n)_{1\leq n\leq N}$ of $\mathbb{N}_m$ (the leaves) such that for each $k \in \mathcal{K}$, there exists some (i,j) with $1 \leq i \leq j \leq N$ and $R_k = L_{i:j}$, where we denote

$$L_{i:j} = \bigcup_{i\leq n\leq j} L_n$$

Identification:

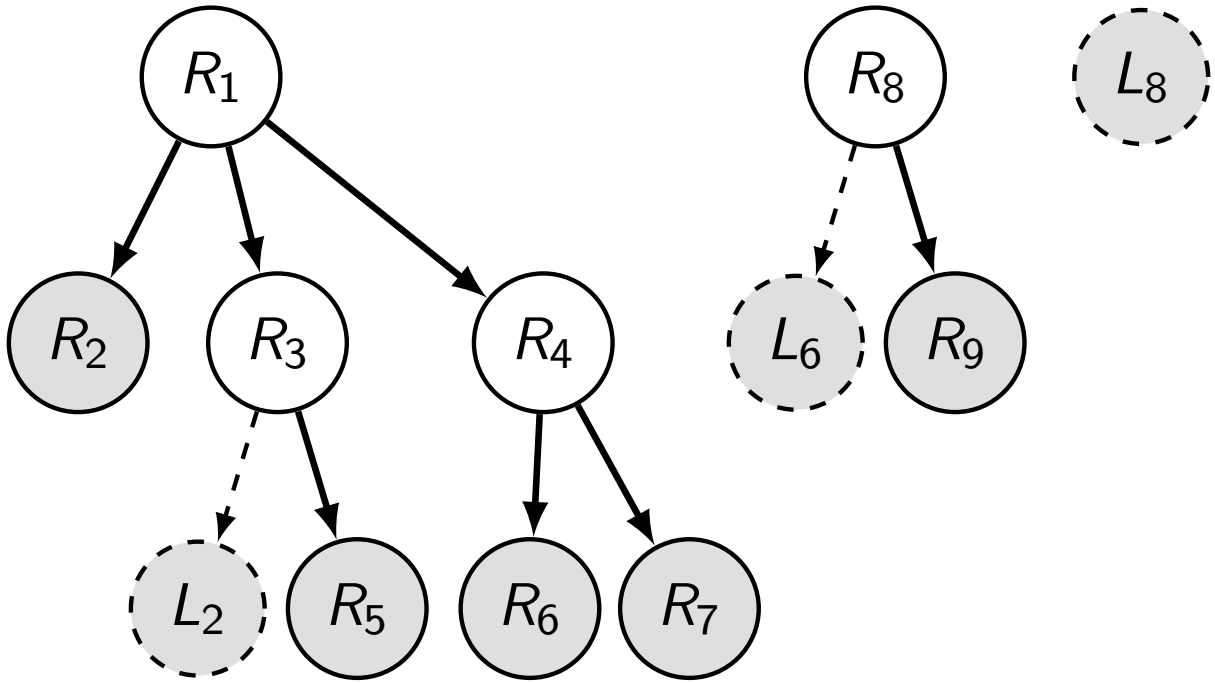
$$\mathfrak{R} = (R_k, \zeta_k)_{k\in\mathcal{K}} \quad \text{or} \quad \mathfrak{R} = (L_{i:j}, \zeta_{i,j})_{(i,j)\in\mathcal{K}}$$

$\Longrightarrow$ leaves represent the thinnest division possible of the structure

Forest structure

Other important property

- Each forest structure can be completed to includes all leaves
- For an added leaf $L_{i:i}$, just state $\zeta_{i,j} = |L_{i:i}|$



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New interpolation bounds

Goal: compute $V^*_{\mathfrak{R}}$ easily with forest structure

Definition

For any $q \leq K = |\mathcal{K}|$,

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

and

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

Property

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

Main results

Compute $V^*_{\mathfrak{R}}$ easily with forest structure

Theorem

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

More precisely,

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

with $\ell =$ number of leaves (without completion).

Proof by construction $\Longrightarrow$ computation algorithm

Corollary

$\ell = 1$ for nested families and BNR property is recovered

Main results

Compute $V^*_{\mathfrak{R}}$ easily with forest structure

Corollary

There is a simple and efficient algorithm to compute $\widetilde{V}_{\mathfrak{R}}$ if $\mathfrak{R}$ is complete ($O(Hm)$ complexity).

Lemma

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

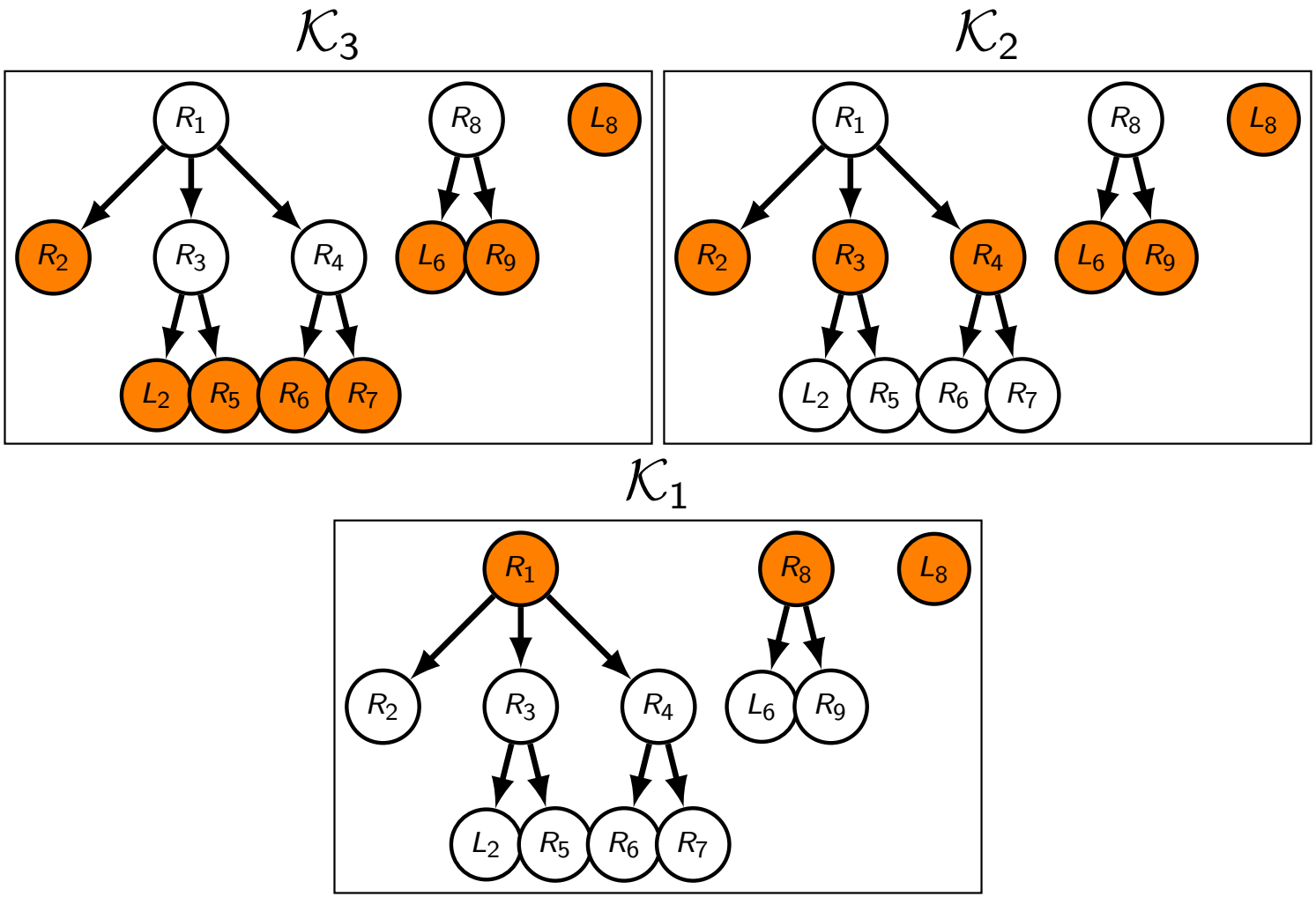
Corollary

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

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

Note: all of the above does not depend on the choice of the ζ_k and works for random R_k.

Forest algorithm



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True nulls estimation inside regions

That is, ζ_k computation

- K deterministic regions, let $C = \sqrt{\frac{1}{2}\log\left(\frac{K}{\alpha}\right)}$
- $\zeta_k = |R_k| \wedge \min_{t\in[0,1)} \left\lfloor \frac{C}{2(1-t)} + \left(\frac{C^2}{4(1-t)^2} + \frac{\sum_{i\in R_k} \mathbf{1}\{p_i > t\}}{1-t} \right)^{1/2} \right\rfloor^2$
- Comes from carefully handling the DKWM inequality [Dvoretzky et al. (1956) and Massart (1990)]
  - Requires independence!
- Replace $\min_{t\in[0,1)}$ and t above by $\min_{0\le\ell\le s}$ and $p_{(\ell)}$ for practical usage $\Longrightarrow$ computation of $(\zeta_k)_k$ is also $O(Hm)$ complex
- α/K instead of α in C: union bound
- Dependence on α (and to K!) only through a log
- $\zeta_k > 0$ (entry cost)

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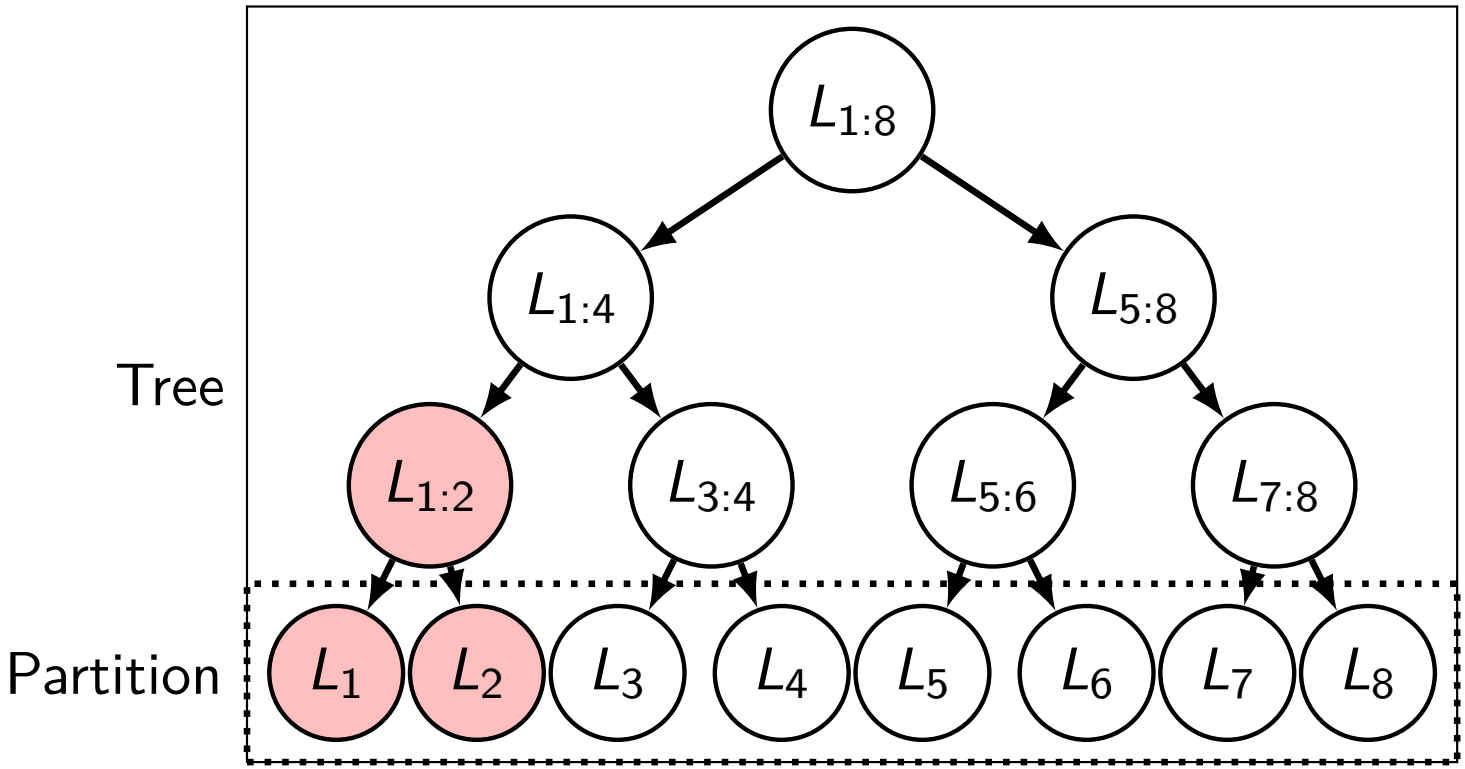
Comparison of 3 bounds

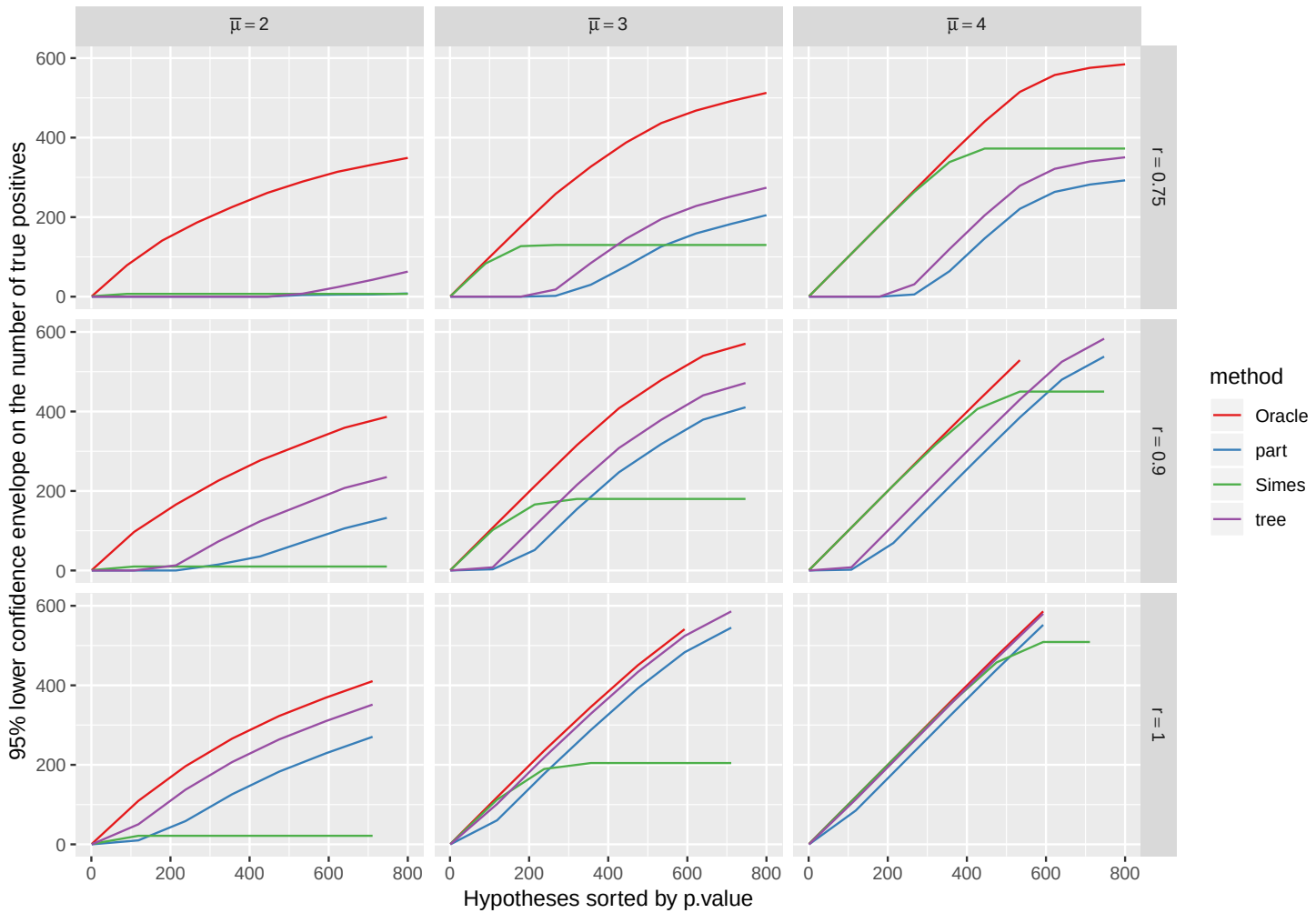
Simes bound of BNR, and 2 new

- V_{tree} and V_{part}, from a complete binary tree or only the partition of leaves
- Signal in adjacent leaves, good performance of V_{tree} expected despite worst K
- Parameters: signal $\bar{\mu}$ and signal proportion in active leaves r



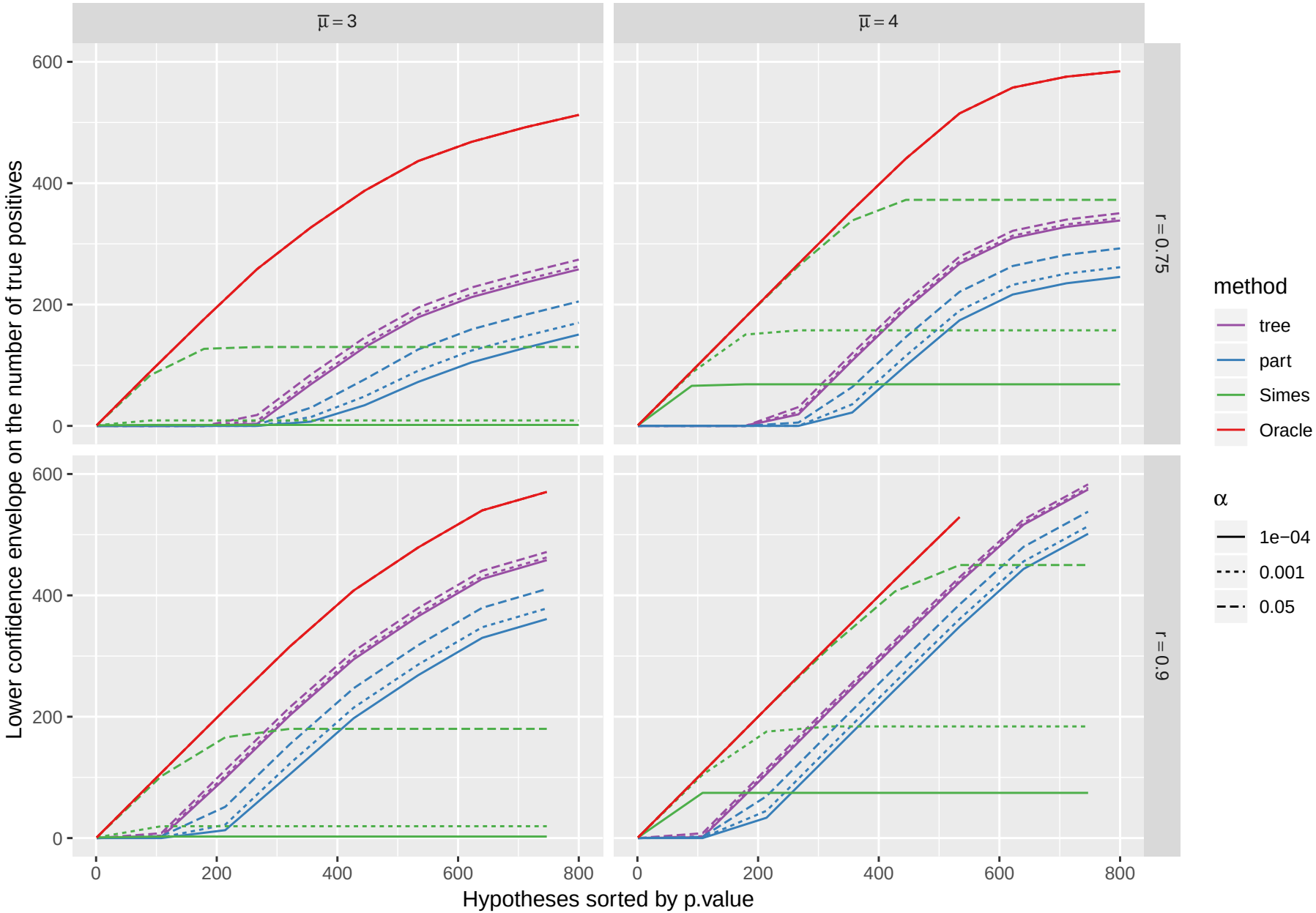
Comparison of 3 bounds

- The choice of S favors the Simes bound of BNR
- But for large r, new bounds better
- V_{tree} better than V_{part} as expected, despite a worst union bound correction



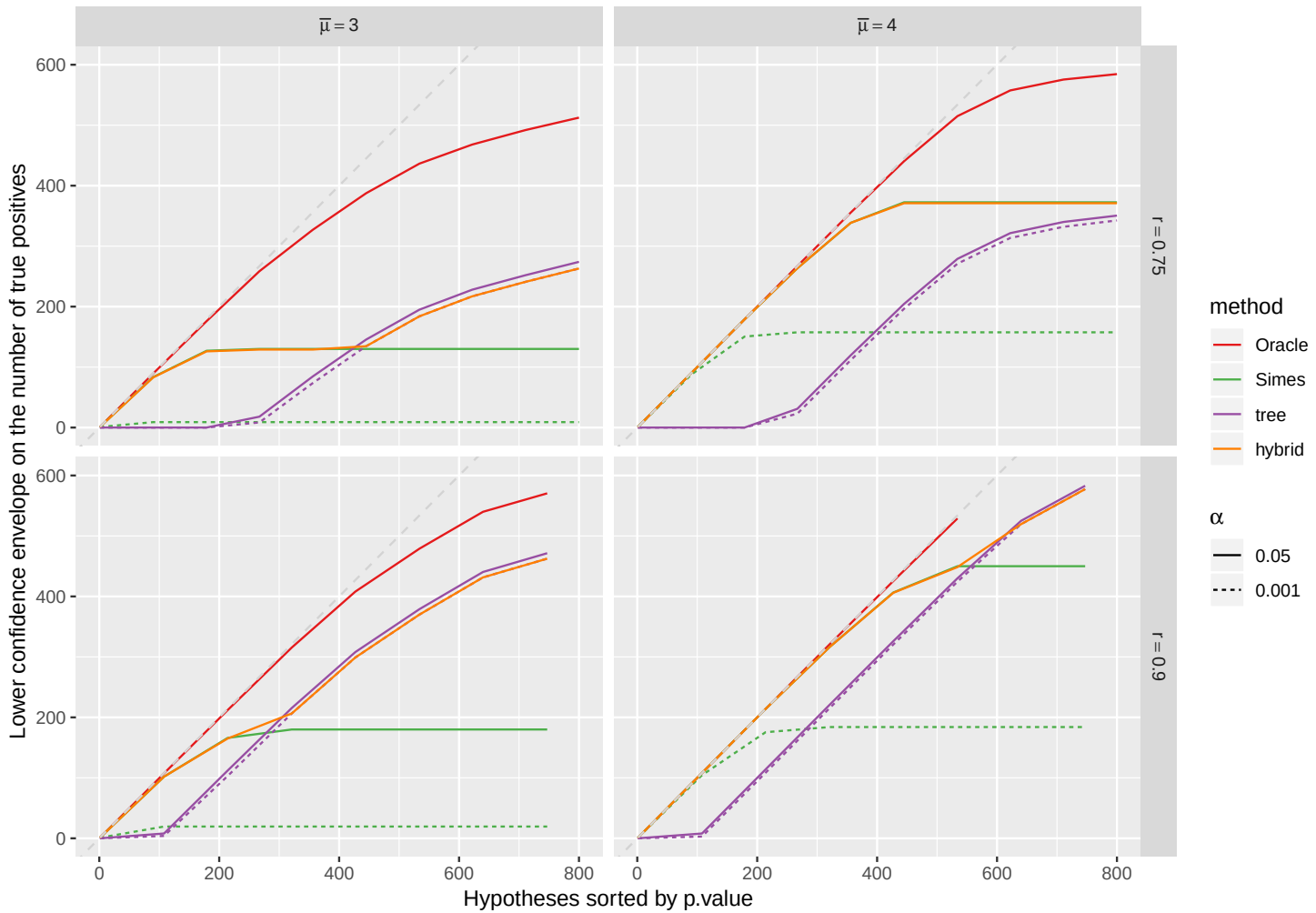
Comparison of 3 bounds

Influence of α



New hybrid bound suggested by the simulations

- $V^{\gamma}_{\text{hybrid}}(\alpha, S) = \min\left(V_{\text{Simes}}((1-\gamma)\alpha, S), V_{\text{tree}}(\gamma\alpha, S)\right)$
- $\gamma = 0.02$: favors Simes, not a problem because V_{tree} is little sensitive to small α



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Recap

New confidence bounds that exploit the signal localization to improve on existing bounds, with an acceptable computation time
Limitations:

- DKWM inequality involves independence
- The chosen ζ_k can't reject a whole subset (including individual hypotheses)
- The R_k have to be fixed before seeing the data (not post hoc!)
- The union bound correction chosen may induce conservativeness

Published paper in Scandinavian Journal of Statistics (2020) [Durand et al. (2020)]
Also on arXiv: 1807.01470
R package available on github: sansSouci

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Next steps I

- Depart from independence with $\zeta_k(X) = L_k(\alpha/K)$ such that $\mathbb{P}_{X\sim P}\Big(|R_k \cap \mathcal{H}_0(P)| \leq L_k(\lambda)\Big) \leq \lambda$
  - Concentration inequalities for dependent variables?
  - λ-calibration under known dependence or permutation invariance [Hemerik and Goeman (2018) and Blanchard et al. (2020)]
  - Use local tests [Goeman and Solari (2011) and Meijer et al. (2015)], App. B. of my thesis
  - Different L_k at different hierarchical levels [Dobriban et al. (2015)]
- Reduce union bound penalty with some α-recycling (App. B of my thesis)
- Other families combining BNR approach and a deterministic partition
  - $\mathfrak{R} = (R_{k,i_k}, \zeta_{k,i_k})_{\substack{k\in\mathcal{K} \\ 1\leq i_k\leq |R_k|}}, \zeta_{k,i_k} = i_k - 1$
  - The results on forest structures allows the regions to be random
  - A first step toward automatic selection of the forest structure

Next steps II

- Reuse some of those ideas to go back to FWER control (App. B of my thesis)
- Pursue work on closed testing shortcuts for post hoc bounds (App. A.1 of my thesis)
- Applications, real-life favorable cases like neuroimagery [Vesely et al. (2021)]

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Classical theory

Family-Wise Error Rate (FWER)

- $\mathrm{FWER}(R) = \mathbb{P}(V(R) > 0)$
- Bonferroni method: reject all $p_i \leq \frac{\alpha}{m}$ (union bound)
- Variant: k-$\mathrm{FWER}(R) = \mathbb{P}(V(R) \geq k)$
  - Choice of k? Often post hoc!

False Discovery Rate (FDR)

- $\mathrm{FDR}(R) = \mathbb{E}\left[\frac{V(R)}{|R| \vee 1}\right]$
- Benjamini-Hochberg method for positive dependence
  - Reject all $p_i \leq \frac{\alpha \hat{k}}{m}$
  - $\hat{k} = \max\{k : p_{(k)} \leq \frac{\alpha k}{m}\}$, $p_{(1)} \leq \cdots \leq p_{(m)}$

Closed testing for post hoc inference

Designed for FWER control [Marcus et al. (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:

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

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

- $V_{\mathrm{GS}}(S) = V^*_{\mathfrak{R}}(S)$ 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 $1-\lambda$ ($U_1, \ldots, U_v$ 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

Computation of $V^*_{\mathfrak{R}}(S)$

Data: $\mathfrak{R} = (L_{i:j}, \zeta_{i,j})_{(i,j)\in\mathcal{K}}$ and $S \subset \mathbb{N}_m$.
Result: $V^*_{\mathfrak{R}}(S)$.
$\mathfrak{R} \longleftarrow \mathfrak{R}^{\oplus}$; $\mathcal{K} \longleftarrow \mathcal{K}^{\oplus}$ (completion);
$H \longleftarrow \max_{k\in\mathcal{K}} \phi(k)$ (max depth);
$V \longleftarrow (\zeta_k \wedge |S \cap R_k|)_{k\in\mathcal{K}^H}$;
for $h \in \{H-1, \ldots, 1\}$ **do**
  $newV \longleftarrow (0)_{k\in\mathcal{K}^h}$;
  for $k \in \mathcal{K}^h$ **do**
    $Succ_k \longleftarrow \{k' \in \mathcal{K}^{h+1} : R_{k'} \subset R_k\}$;
    $newV_k \longleftarrow \min\left(\zeta_k \wedge |S \cap R_k|, \sum_{k'\in Succ_k} V_{k'}\right)$;
  end
  $V \longleftarrow newV$;
end
return $\sum_{k\in\mathcal{K}^1} V_k$.