Improved post hoc bounds for localized signal

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Joint work with Gilles Blanchard, Pierre Neuvial and Etienne Roquain

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Replication crisis

Toy example

GWAS study with 10^6 genetic variants, apply a multiple testing procedure (MTP) over the 1000 smallest p-values

p-hacking

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

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Selective inference

Develop new methods that account for the selection step to provide statistical guarantees.

1. Conditionally to the selection event [Fithian, Sun, et al. (2017), Lee, Sun, et al. (2016), and Tibshirani, Taylor, et al. (2016)]
2. Simultaneously over all possible selection events [Goeman and Solari (2011), Berk, Brown, et al. (2013), and Blanchard, Neuvial, et al. (2018)]

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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 : $\mathbb{P}_{P \in H_{0,i}}(p_i \leq \alpha) \leq \alpha$
- Classic theory: form a rejection set R with a guarantee on $V(R) = |R \cap \mathcal{H}_0|$

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Our goal

A simultaneous inference problem

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)]
- Not a classic MTP: a guarantee over any selected set instead of a rejected set
- Also named "post hoc inference"

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BNR methodology

[Blanchard, Neuvial, et al. (2018)]

Key concept: reference family

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

$$\mathbb{P}\left(\forall k, |R_k \cap \mathcal{H}_0| \leq \zeta_k\right) \geq 1 - \alpha$$

- Confidence bound only on the members of $\mathfrak{R}$
- $\Longrightarrow$ Derivation of a global confidence bound

Two different bounds

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

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BNR methodology

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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In this talk

- Consider the realistic case where the signal is localized in some regions (e.g. active genes in same chromosomes)
- Accordingly, find adapted new structures where $V^*_{\mathfrak{R}}$ is also easy to compute
- Fix the regions (i.e. R_k non random) and estimate the true nulls inside them (i.e. ζ_k random): opposite of [Blanchard, Neuvial, et al. (2018)]

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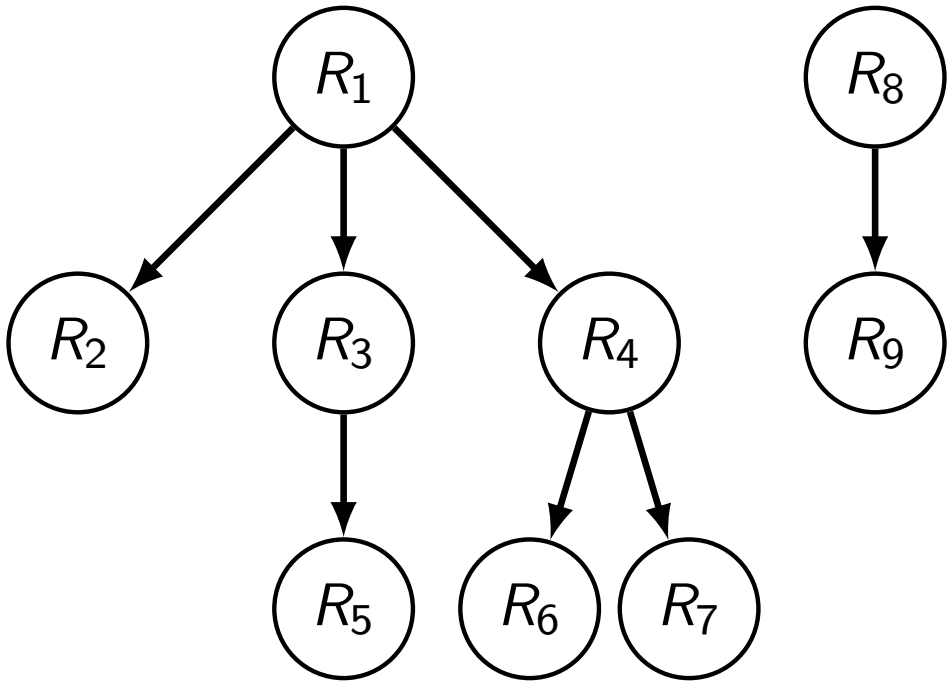
Forest structure

New 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 signal localization through the "leaves"



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

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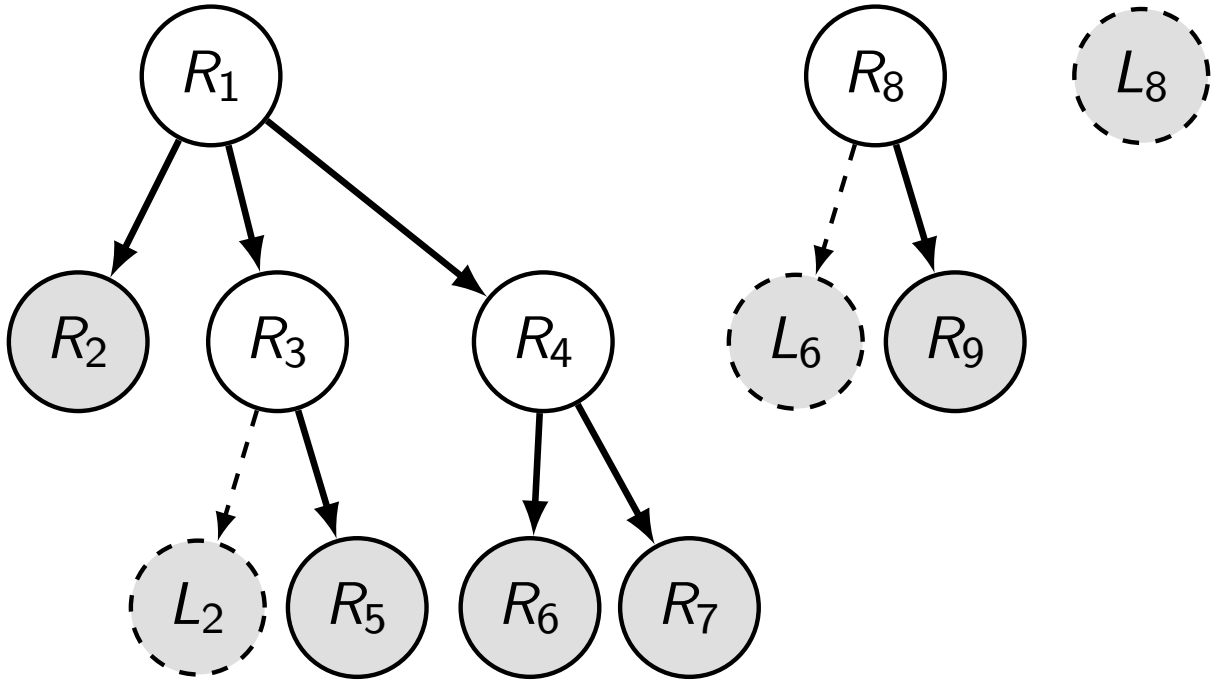
Forest structure

Other important property

Each forest structure can be completed to includes all leaves



New post hoc bounds

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

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

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).

Corollary

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

Main results

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

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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True nulls estimation

Under independence

- 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, Kiefer, et al. (1956) and Massart (1990)]
- Replace $\min_{t\in[0,1)}$ and t above by $\min_{0\leq\ell\leq s}$ and $p_{(\ell)}$ for practical computation
- α/K instead of α in C: union bound
- Dependence on α only through a log
- $\zeta_k > 0$ (entry cost)

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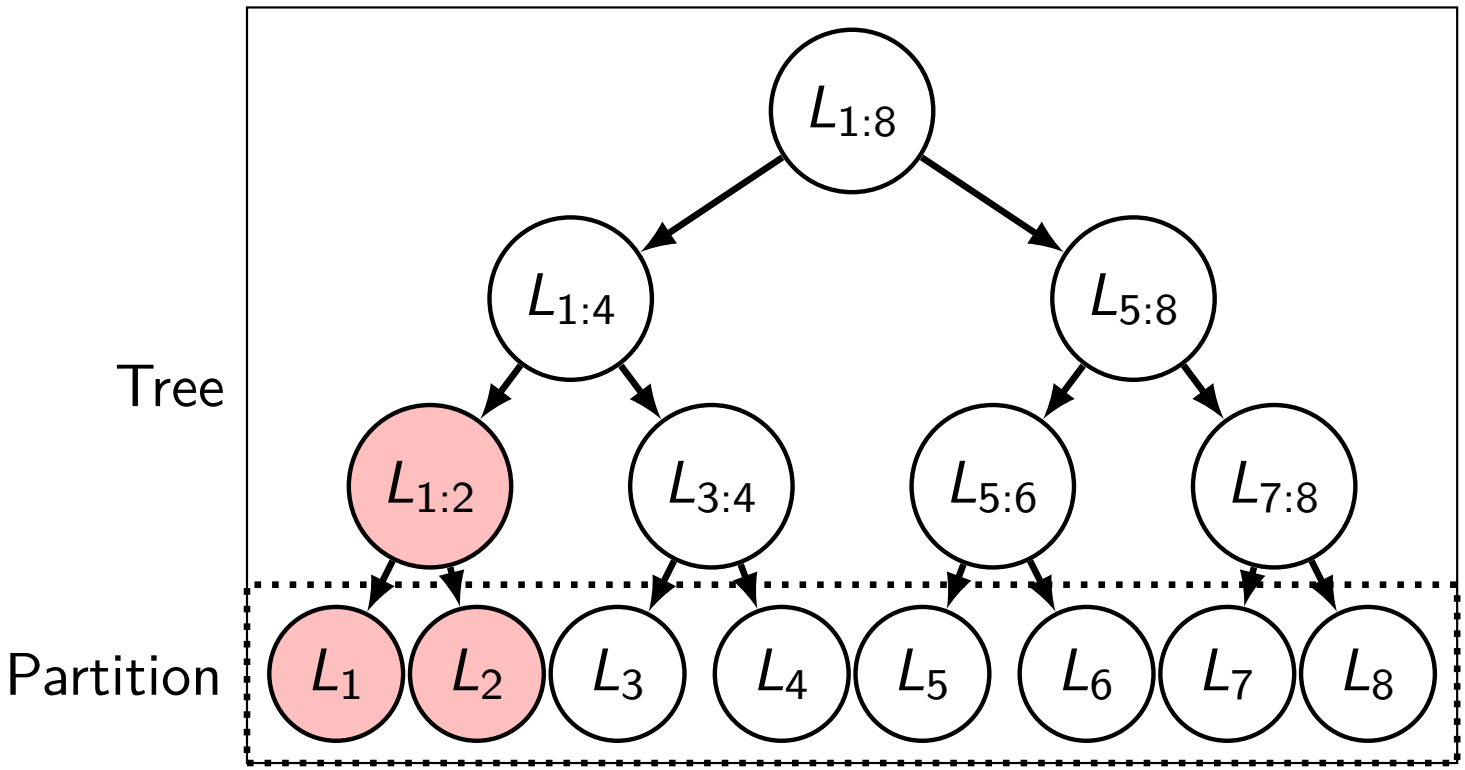
Comparison of 3 bounds

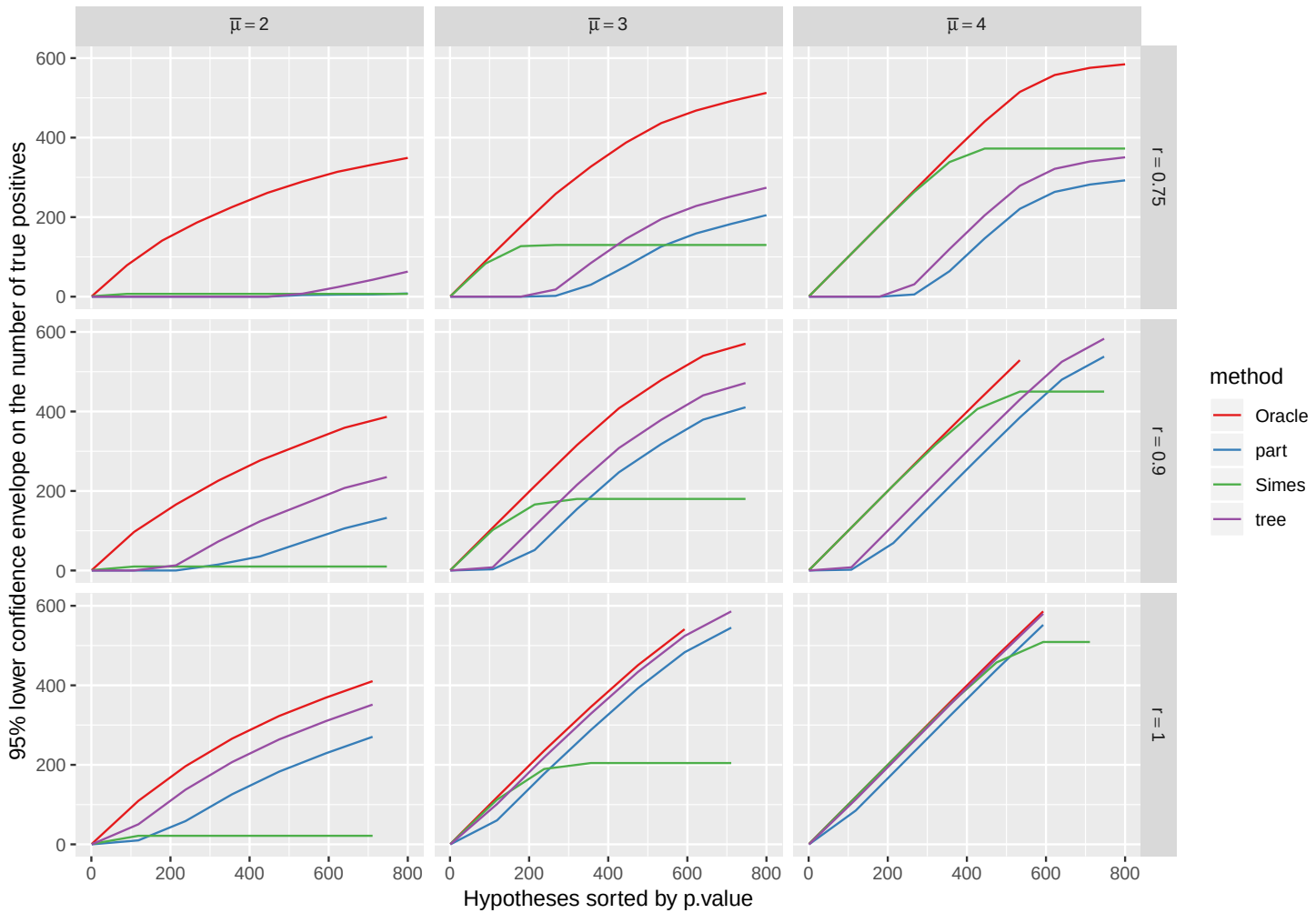
Simes bound of BNR, and 2 new

- 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
- Parameters: signal $\bar{\mu}$ and signal proportion in active leaves r



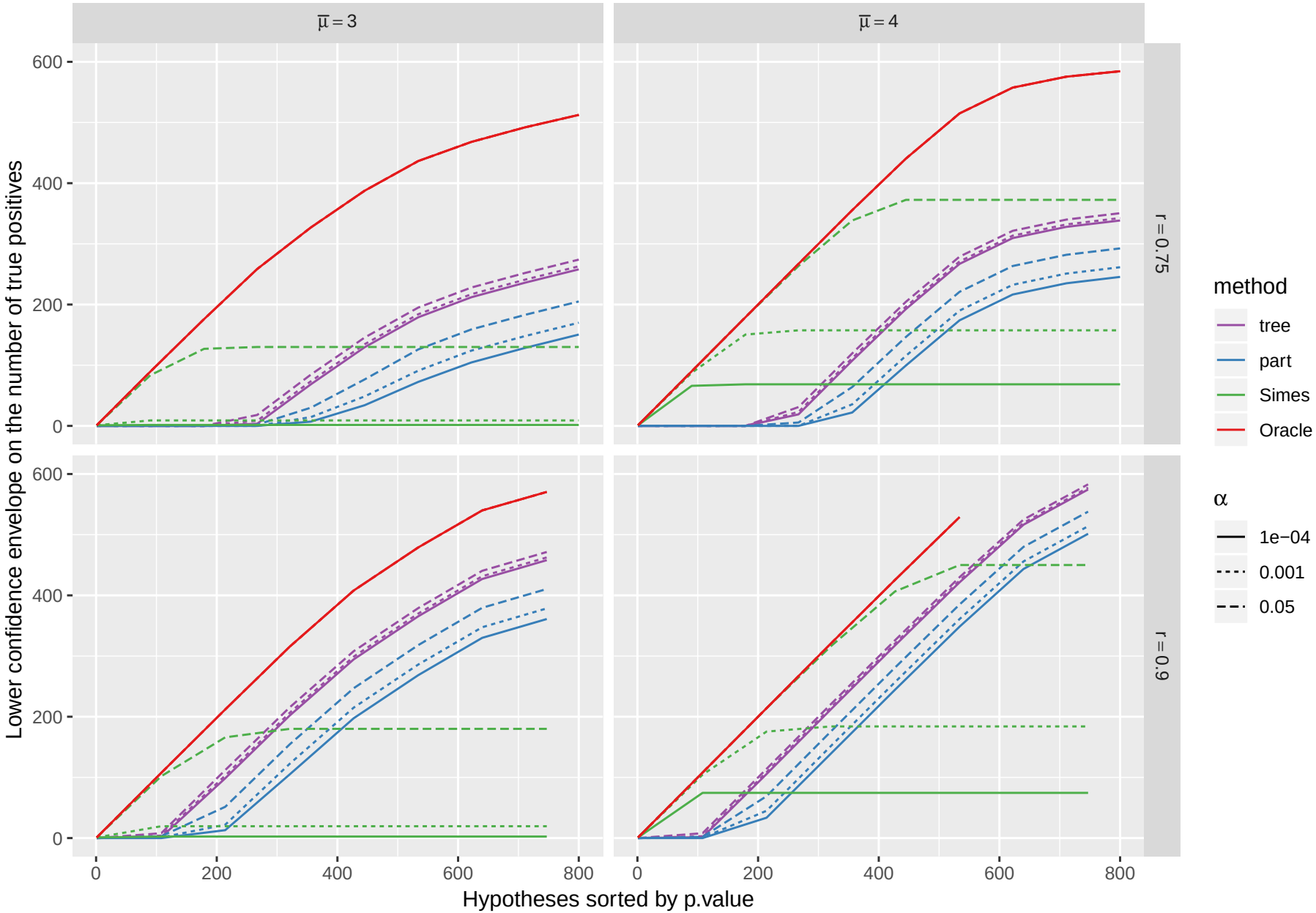
Comparison of 3 bounds

- 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



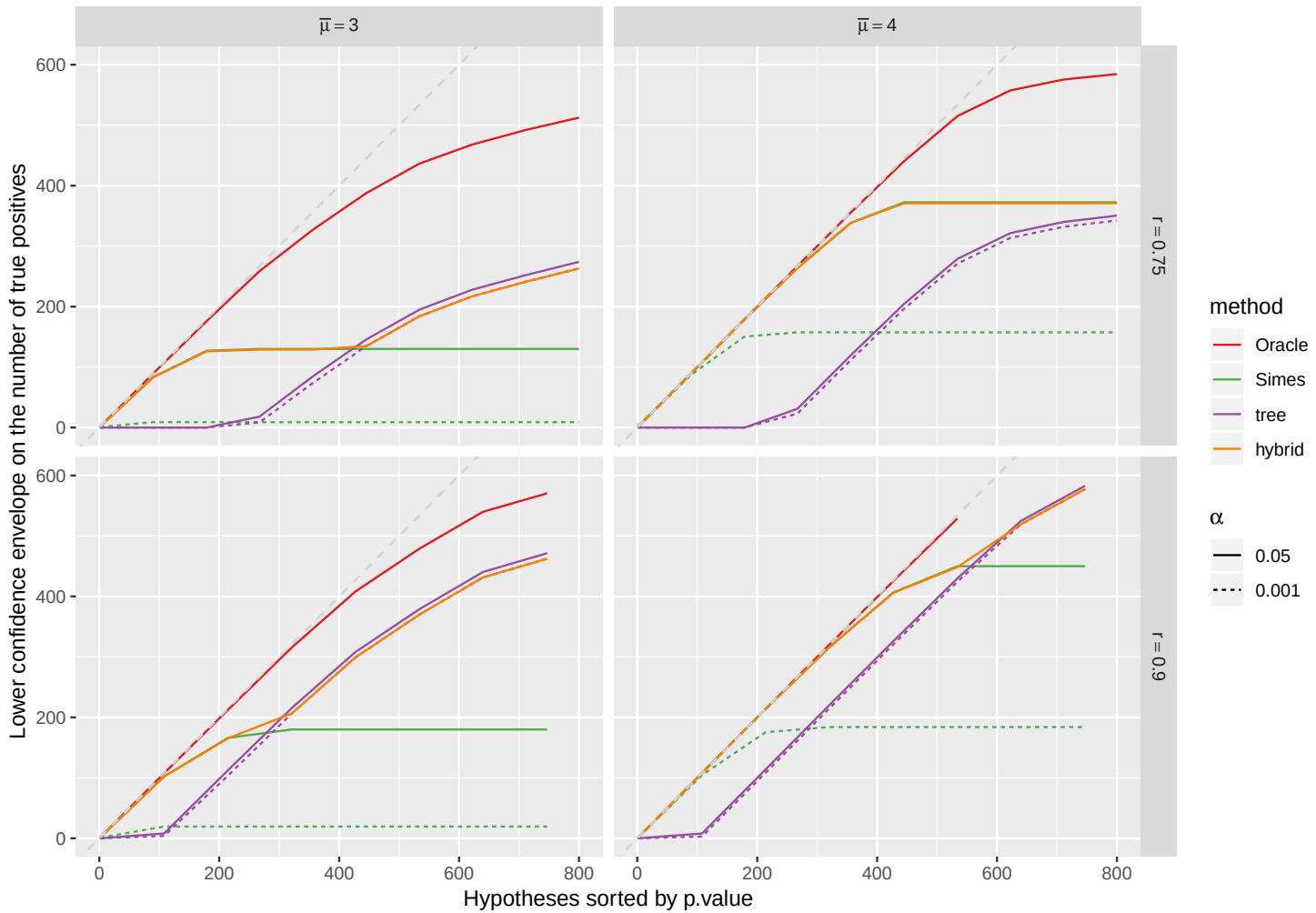
Comparison of 3 bounds

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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Conclusion

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

Preprint available: arXiv:1807.01470
R package available from github: sansSouci

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

False Discovery Rate (FDR)

- $\mathrm{FDR}(R) = \mathbb{E}\left[\frac{V(R)}{|R| \vee 1}\right]$
- Benjamini-Hochberg method for positive dependence

Closed testing for post hoc inference

Designed for FWER control [Marcus, Eric, 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

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

- $V_{\mathrm{GS}}(S) = V^*_{\mathfrak{R}}(S)$ 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