### <span id="page-0-0"></span>Isotonic subgroup selection

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Henry Reeve Timothy Cannings Richard Samworth

▶ M., M. M., Reeve, H. W. J., Cannings, T. I. and Samworth, R. J. (2023). Isotonic subgroup selection. arXiv:2305.04852.

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#### Setting:

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(i) the regression function  $\eta(x):=\mathbb{E}(Y|X=x)$  is increasing\* on  $\mathbb{R}^d$ .

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(ii)  $\left\vert Y-\eta(X)\mid X\right\vert$  is sub-Gaussian with variance parameter  $\sigma^{2}.$ 

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### Notation:

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**►** Type I error control: Fix  $\alpha \in (0,1)$ . Require

$$
\inf_{P \in \mathcal{P}_{\text{Mon},d}(\sigma)} \mathbb{P}_P\{\hat{A}(\mathcal{D}) \subseteq \mathcal{X}_{\tau}(\eta)\} \ge 1 - \alpha.
$$

▶ Power: Want small expected regret

$$
\mathbb{E}\big\{\mu\big(\mathcal{X}_\tau(\eta)\setminus\hat{A}(\mathcal{D})\big)\big\}.
$$

For  $x_0 \in \mathbb{R}^d$ , define null hypothesis  $H_0(x_0) := \{P \in \mathcal{P}_{\mathrm{Mon},d}(\sigma) : \eta(x_0) < \tau\}.$ 



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- 3. Apply a multiple testing procedure to reject  $\mathcal{R}_{\alpha} \subseteq \{1, \dots, m\}$  with  $\mathbb{P}_P\big(\mathcal{R}_\alpha\cap\{\ell\in\{1,\ldots,m\}:P\in H_0(X_\ell)\}\neq\emptyset\mid (X_i)_{i=1}^m\big)\leq\alpha;$

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- 4. Output  $\hat A:=\big\{x\in\mathbb{R}^d: X_\ell\preccurlyeq x\text{ for some }\ell\in\mathcal{R}_\alpha\}.$

### p-value construction

Given  $x_0 \in \mathbb{R}^d,$  we seek a  $p$ -value for  $H_0(x_0) := \{ P \in \mathcal{P}_{\text{Mon},d}(\sigma) : \eta(x_0) < \tau \}.$ 

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Write  $\mathcal{I}(x_0) := \{i \in [n] : X_i \preccurlyeq x_0\}$ . Let  $X_{(i)}$  be the jth nearest neighbor in sup-norm of  $x_0$  among  $X_i,$   $i \in {\cal I } (x_0),$  and let  $Y_{(i)}$  be the corresponding response.



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Then,  $S_k := \sum_{j=1}^{|{\cal I}(x_0)|}(Y_{(j)}-\tau)/\sigma$  is a supermartingale under  $P \in H_0(x_0)$  . Combination with time-uniform bounds by [Howard et al. \(2021\)](#page-32-0) gives p-values.



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Combining the presented  $p$ -value construction with the just illustrated multiple testing procedure defines the proposed procedure  $\hat A^{\mathrm{ISS}}\equiv\hat A^{\mathrm{ISS}}_{\sigma,\tau,\alpha,m}.$ 

Theorem. For any  $n \in \mathbb{N}$ ,  $m \in [n]$ ,  $\alpha \in (0,1)$ ,  $\sigma > 0$ , and  $P \in \mathcal{P}_{\text{Mon }d}(\sigma)$ , along with  $\mathcal{D} \sim P^n,$  we have

$$
\mathbb{P}_P\left(\hat{A}_{\sigma,\tau,\alpha,m}^{\text{ISS}}(\mathcal{D})\subseteq\mathcal{X}_\tau(\eta)\mid\mathcal{D}_X\right)\geq 1-\alpha.
$$

Ideas: martingale test procedures [\(Duan et al., 2020\)](#page-32-1), time-uniform boundaries on martingales with sub-Gaussian increments [\(Howard et al., 2021\)](#page-32-0) and the sequential rejection principle [\(Goeman and Solari, 2010\)](#page-32-2).

Theorem. Let  $\sigma, \gamma > 0, \theta > 1$  and  $\lambda \in (0, 1)$ . There exists  $C \geq 1$ , depending only on  $(d, \theta)$ , such that for any  $P \in \mathcal{P}_{\text{Mon.}d}(\sigma) \cap \mathcal{P}_{\text{Reg.}d}(\tau, \theta, \gamma, \lambda), n \in \mathbb{N}$ ,  $m \in [n],$   $\alpha \in (0,1)$  and  $\mathcal{D} \sim P^n$  that<sup>a</sup>

$$
\mathbb{E}_{P}\{\mu(\mathcal{X}_{\tau}(\eta) \setminus \hat{A}^{\text{ISS}}(\mathcal{D}))\}
$$
  
\n
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\leq 1 \wedge C\left\{ \left(\frac{\sigma^2}{n\lambda^2} \log_+\left(\frac{m \log_+ n}{\alpha}\right)\right)^{1/(2\gamma+d)} + \left(\frac{\log_+ m}{m}\right)^{1/d} \right\}.
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\int_{a}^{a} \log_{+} x := \log(x \vee e).
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Theorem. Our procedure is minimax-optimal up to poly-logarithmic factors among procedures with Type I error control over  $\mathcal{P}_{\text{Mon.}d}(\sigma) \cap \mathcal{P}_{\text{Reg.}d}(\tau,\theta,\gamma,\lambda)$ .

### AIDS Clinical Trials Group Study 175 [\(Hammer et al., 1996\)](#page-32-3)



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Extensions and further results (see full paper for details):

▶ Variation tailored to bounded responses and classification.

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▶ ...

- <span id="page-32-1"></span>Duan, B., Ramdas, A., Balakrishnan, S., and Wasserman, L. (2020). Interactive martingale tests for the global null. Electronic Journal of Statistics, 14(2):4489–4551.
- <span id="page-32-2"></span>Goeman, J. J. and Solari, A. (2010). The sequential rejection principle of familywise error control. The Annals of Statistics, 38(6):3782–3810.
- <span id="page-32-3"></span>Hammer, S. M., Katzenstein, D. A., Hughes, M. D., Gundacker, H., Schooley, R. T., Haubrich, R. H., Henry, W. K., Lederman, M. M., Phair, J. P., Niu, M., et al. (1996). A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. New England Journal of Medicine, 335(15):1081–1090.
- <span id="page-32-0"></span>Howard, S. R., Ramdas, A., McAuliffe, J., and Sekhon, J. (2021). Time-uniform, nonparametric, nonasymptotic confidence sequences. The Annals of Statistics, 49:1055–1080.
- <span id="page-32-4"></span>Meijer, R. J. and Goeman, J. J. (2015). A multiple testing method for hypotheses structured in a directed acyclic graph. Biometrical Journal, 57(1):123–143.

Key idea: logical relationships of hypotheses  $H_0(x_i)$ ,  $i \in [m]$ , induce DAG with vertex set [m]. Careful  $\alpha$ -budget allocation and sequential rejections are then performed.

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Example: In the first iteration, no hypothesis has been rejected yet and only root nodes are assigned positive  $\alpha$ -budget.



Here, nodes 1, 6 and 7 are current rejection candidates, and 1 will be rejected, as  $p_1 = 0.01 \leq 0.0125$ .

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Example: After rejection of node 1 in the first step, we reallocate the  $\alpha$ -budget.



#### Here, node 7 will be rejected.

Key idea: logical relationships of hypotheses  $H_0(x_i)$ ,  $i \in [m]$ , induce DAG with vertex set [m]. Careful  $\alpha$ -budget allocation and sequential rejections are then performed.

Example: Now that node 7 has been rejected, its child 5 receives  $\alpha$ -budget sufficiently large for it to be rejected.



Although  $p_6$  is quite large, 6 is an ancestor of 5 in the induced DAG and will hence also be rejected.

Key idea: logical relationships of hypotheses  $H_0(x_i)$ ,  $i \in [m]$ , induce DAG with vertex set [m]. Careful  $\alpha$ -budget allocation and sequential rejections are then performed.

Example: None of the remaining three nodes (coincidentally, the leaf nodes), have a *p*-value smaller than their respective  $\alpha$ -budgets.



Nodes 1, 5, 6 and 7 have been rejected.

Given  $d \in \mathbb{N}, \tau \in \mathbb{R}, \theta > 1, \gamma > 0$  and  $\lambda \in (0, 1)$ , we let  $\mathcal{P}_{\text{Reg}, d}(\tau, \theta, \gamma, \lambda)$  denote the class of all distributions  $P$  on  $\mathbb{R}^d \times \mathbb{R}$  with marginal  $\mu$  on  $\mathbb{R}^d$  and associated regression function  $\eta$  such that

$$
\text{(i)}~~\theta^{-1}\cdot r^d\leq \mu\big(B_\infty(x,r)\big)\leq \theta\cdot (2r)^d\text{ for }x\in \mathcal{X}_\tau(\eta)\cap \text{supp}(\mu)~\text{and }r\in (0,1];
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(ii)  $B_{\infty}(x,r) \cap \mathcal{X}_{\tau+\lambda\cdot r^{\gamma}}(\eta) \neq \emptyset$  for  $x \in \mathcal{X}_{\tau}(\eta) \cap \text{supp}(\mu)$  and  $r \in (0,1],$ 

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The first condition ensures that  $\mu$  is genuinely d-dimensional.

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The second controls the way in which  $\eta$  grows around the  $\tau$ -boundary.

We conduct a simulation study to compare with other choices of multiple testing procedure.



Our regression functions  $\eta$  are obtained by rescaling f.

## Simulations: multiple testing procedure

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## Simulations: multiple testing procedure



Presented is the MC-based estimate of  $\mathbb{E}_P\{\mu(\mathcal{X}_\tau(\eta)\setminus\hat{A})\}$  for  $\hat{A} \in \{\hat{A}^{\text{ISS}}, \hat{A}^{\text{ISS},\text{H}}, \hat{A}^{\text{ISS},\text{Any}}\}.$  The last two use methods due to [Meijer](#page-32-4) [and Goeman \(2015\)](#page-32-4).