

AdaPT: Interactive Multiple Testing with Side Information

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Multiple Hypothesis Testing

Setting: hypotheses H_1, \dots, H_n with p -values p_1, \dots, p_n

Notation:

- $\mathcal{H}_0 = \{i : H_i \text{ is true}\}$: null hypotheses
- $\mathcal{S} = \{i : H_i \text{ is rejected}\}$: set of rejections (discoveries)
- $R = |\mathcal{S}|$ total rejections (discoveries)
- $V = |\mathcal{S} \cap \mathcal{H}_0|$ incorrect rejections (false discoveries)

False Discovery Proportion $\text{FDP} = \frac{V}{R \vee 1}$

Goal: control False Discovery Rate [Benjamini and Hochberg, 1995]

$$\text{FDR} = \mathbb{E}[\text{FDP}] \leq \alpha$$

Side Information

Observe **side information** $x_i \in \mathcal{X}$ for each H_i

[Ferkingstad et al., 2008, Ignatiadis et al., 2016, Li and Barber, 2016b]

x_1, \dots, x_n treated as fixed

Ordered multiple testing

[Foster and Stine, 2008, G'Sell et al., 2015, Li and Barber, 2016a]

- H_1 most “promising,” then H_2, \dots, H_n ($x_i = i$)
- Focus power on early hypotheses

Examples:

- Sample variance / total count
- Data for gene i from one or more similar experiments
- Spatiotemporal location / location on a graph
- “Collaborative filtering” e.g. H_{ij} : drug i kills cancer j

Idea: if we **learn** a region of \mathcal{X} has many non-nulls, can relax multiplicity correction in that region

Motivating Example: Gene/Drug Response Data

Li and Barber [2016a] proposed ingenious ordered analysis of gene expression data [Coser et al., 2003, Davis and Meltzer, 2007]

Expression in breast cancer cells in response to estrogen

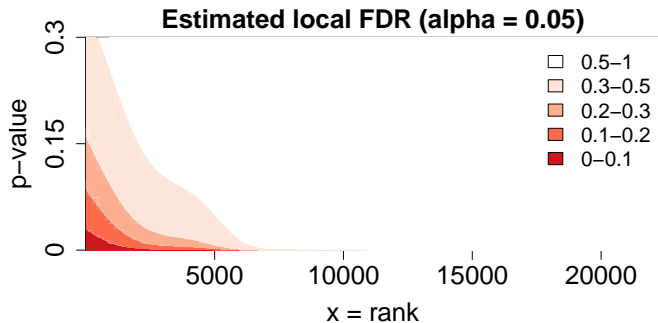
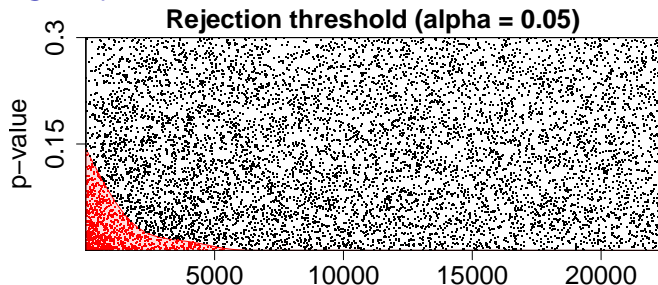
- $n = 22283$ genes, 25 trials at 5 doses incl. control
- H_i : no differential response in low-dose vs. control
- p_i computed via two-sample permutation t -test

Ordered by \tilde{p}_i , permutation p -value comparing high-dose vs. pooled sample of low-dose + control

Can show p_i independent of \tilde{p}_i if H_i true

$$x_i = \text{Rank}(\tilde{p}_i) \in \{1, \dots, n\}$$

Gene/Drug response Data



Gene/Drug Response Data

Empirical Bayes: estimate $\text{fdr}(p | x) = \mathbb{P}(H_i \text{ false} | x_i = x, p_i = p)$

Reject p -values with small $\widehat{\text{fdr}}(p_i | x_i)$

Key questions:

- Which level curve?
- Can we control FDR despite “double-dipping”?
- Is there a “price” for adaptivity?
- What if eBayes model is wrong?

Gene/Drug response Data

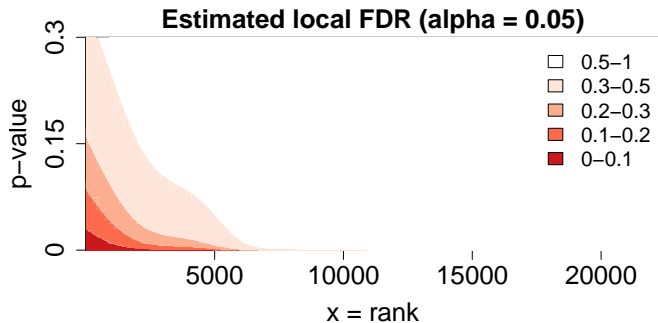
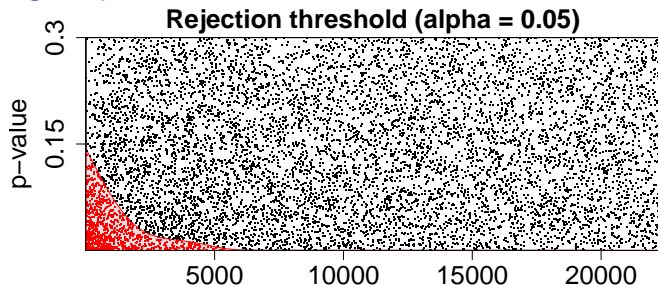


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Adaptive p -Value Thresholding (AdaPT)

Iterative method: steps $t = 0, 1, 2, \dots$

Step t : consider rejection threshold $s_t(x)$, compute:

$$R_t = |\{i : p_i \leq s_t(x_i)\}|$$

$$A_t = |\{i : p_i \geq 1 - s_t(x_i)\}|$$

$$\widehat{\text{FDP}}_t = \frac{1 + A_t}{R_t \vee 1}$$

If $\widehat{\text{FDP}}_t \leq \alpha$, stop and reject $\{H_i : p_i \leq s_t(x_i)\}$

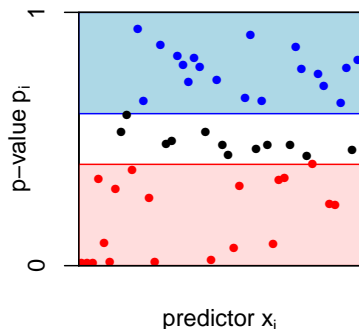
Else, choose stricter threshold $s_{t+1}(x) \leq s_t(x)$ and continue

Update rule must be chosen based on **partially masked data**
(Keeps us from cheating!)

AdaPT, Visualized

$$\widehat{\text{FDP}}_t = \frac{A_t + 1}{R_t \vee 1}$$

AdaPT



Covariate-dependent threshold $s_t(x)$

Mirror image $1 - s_t(x)$

$R_t = \#$ red points

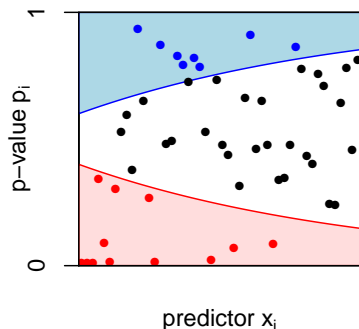
$A_t = \#$ blue points

$A_t \approx V_t = |\{i \in \mathcal{H}_0 : p_i \leq s_t(x_i)\}|$

AdaPT, Visualized

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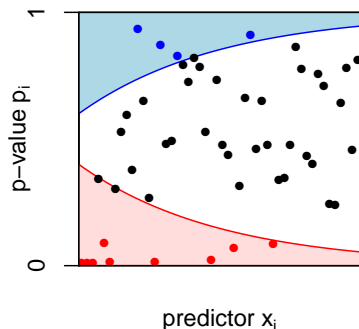
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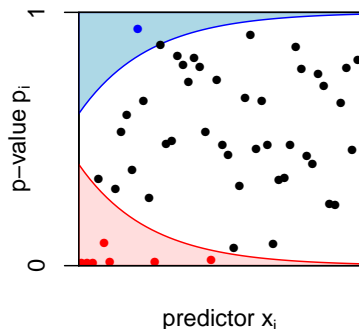
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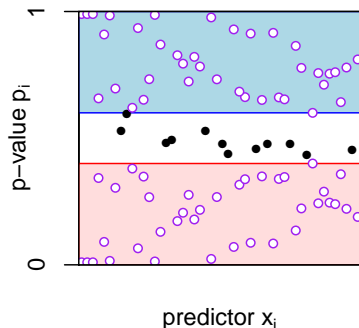
$A_t \approx V_t = |\{i \in \mathcal{H}_0 : p_i \leq s_t(x_i)\}|$

AdaPT, “Analyst View”

Define partially masked p -values:

$$\tilde{p}_{t,i} = \begin{cases} p_i & s_t(x_i) < p_i < 1 - s_t(x_i) \\ \{p_i, 1 - p_i\} & \text{otherwise.} \end{cases}$$

AdaPT (Analyst View)



To select $s_{t+1}(x)$, we can only use:

- x_1, \dots, x_n
- $\tilde{p}_{t,1}, \dots, \tilde{p}_{t,n}$
- A_t, R_t

(and same for $t' < t$)

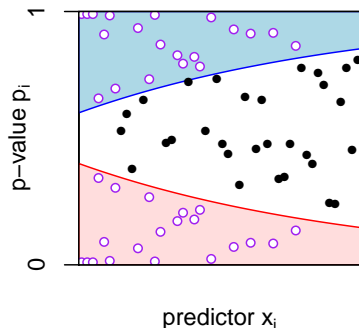
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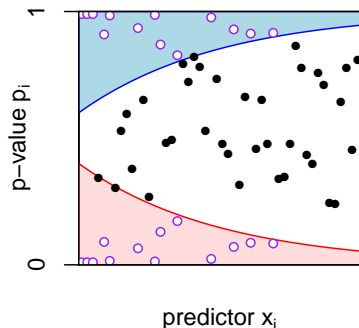
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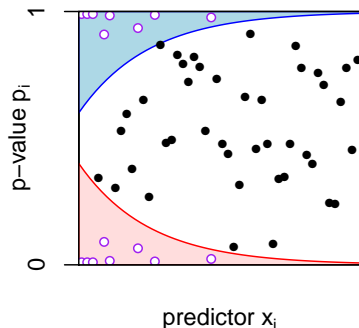
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(and same for $t' < t$)

Any such update rule is OK

Filtrations

Key questions of selective inference

What did the analyst know, and when did she know it?

σ -field formalizes “what we know” at time t :

$$\mathcal{F}_t = \sigma((x_i)_{i=1}^n, (\tilde{p}_{t,i})_{i=1}^n, A_t, R_t) \\ \triangleq \{S \subseteq (\mathcal{X} \times [0, 1])^n : \text{analyst knows if } (x_i, p_i) \in S \text{ at time } t\}$$

Filtration formalizes increasing knowledge over time

$$\mathcal{F}_0 \subseteq \mathcal{F}_1 \subseteq \dots$$

Stopping time: $\{\hat{t} \leq t\} \in \mathcal{F}_t$

Supermartingale: M_t known by \mathcal{F}_t , $\mathbb{E}[M_{t+1} \mid \mathcal{F}_t] \leq M_t$ a.s.

Optional stopping theorem: $\mathbb{E}[M_{\hat{t}}] \leq M_0$ a.s.

Animation: Gene/Drug Response Data

AdaPT: Finite-Sample FDR Control

Theorem 1 (Lei and F, 2016).

Assume that, conditional on $(x_i)_{i=1}^n$ and $(p_i)_{i \notin \mathcal{H}_0}$, the null p -values $(p_i)_{i \in \mathcal{H}_0}$ are independent and mirror-conservative. Then AdaPT controls FDR at level α .

Finite-sample, no assumptions on update rule

Mirror-conservative: $f(p) \leq f(1 - p)$, $\forall p \leq 0.5$. Includes:

- Uniform
- Discrete p -values after randomization
- Permutation test p -values
- One-sided tests for
 - MLR families (e.g. log-concave location, exponential family)
 - Symmetric unimodal location families

Proof Sketch (* uniform nulls case)

Define

$$V_t = |\{i \in \mathcal{H}_0 : p_i \leq s_t(x_i)\}|$$

$$U_t = |\{i \in \mathcal{H}_0 : p_i \geq 1 - s_t(x_i)\}| \leq A_t$$

$$\mathcal{F}_t^+ = \sigma((p_i)_{i \in \mathcal{H}_0^c}, \mathcal{F}_t)$$

Ingredients:

- 1 $M_t = V_t / (1 + U_t)$ is \mathcal{F}_t^+ -supermartingale (*)
- 2 \hat{t} is \mathcal{F}_t^+ -stopping time
- 3 $\mathbb{E}M_0 \leq 1$, $\widehat{\text{FDP}}_t \leq \alpha$
- 4 $M_t \cdot \widehat{\text{FDP}}_t = \frac{1+U_t}{1+U_t} \cdot \text{FDP}_t \geq \text{FDP}_t$

Then:

$$\text{FDR} \leq \mathbb{E} \left[M_{\hat{t}} \cdot \widehat{\text{FDP}}_{\hat{t}} \right] \leq \alpha \mathbb{E}M_{\hat{t}} \leq \alpha$$

Similar argument in Storey et al. [2004], Barber and Candès [2015b]

Prior Work on FDR Control with Side Information

Methods using generic x_i to learn data-adaptive weights for weighted BH:

Independent Hypothesis Weighting (IHW): [Ignatiadis et al., 2016]

- Bin x_i , estimate optimal stepwise rejection thresholds
- Asymptotic FDR control
- **Problem:** how to choose bin width?

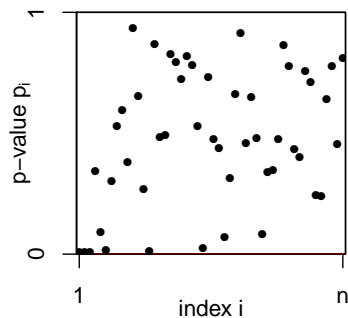
Structure-Adaptive BH Algorithm (SABHA): [Li and Barber, 2016b]

- Estimate $\pi_0(x)$ using truncated $p_i 1\{p_i > \tau\}$
- Can't reject $p_i > \tau$, can't learn from $p_i \leq \tau$
- Correct α for Rademacher complexity of $\hat{\pi}_0$
- Finite-sample control of FDR
- **Problem:** No way to estimate alternative distribution

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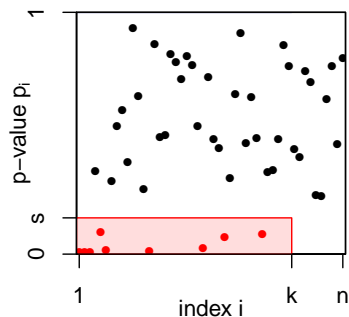
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Review of Existing Methods: General Recipe



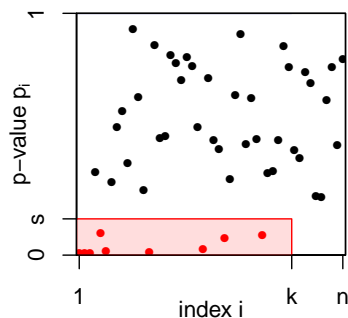
- p-values p_1, \dots, p_n

Review of Existing Methods: General Recipe



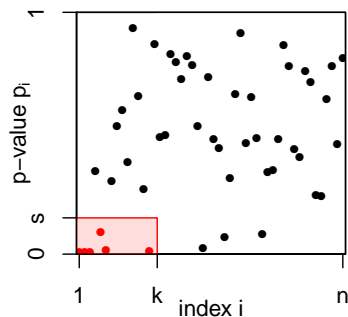
- p -values p_1, \dots, p_n
- **Rejection Set:** a rectangular region indexed by $s \in [0, 1]$ and $k \in \{1, \dots, n\}$

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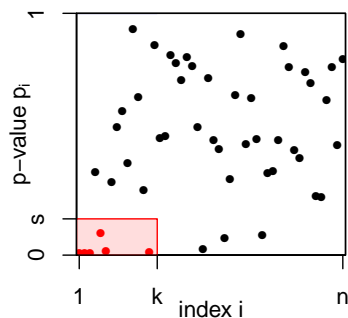
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Review of Existing Methods: General Recipe



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- Gradually reduce k or s until $\widehat{\text{FDP}} \leq \alpha$

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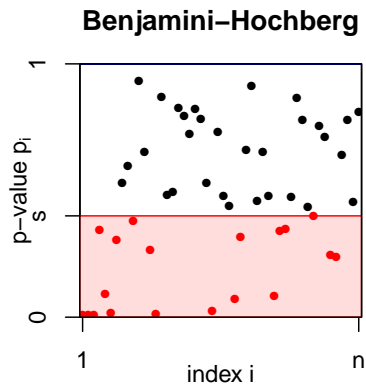


- p -values p_1, \dots, p_n
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- Estimator $\widehat{\text{FDP}}(k, s)$
- Gradually reduce k or s until $\widehat{\text{FDP}} \leq \alpha$
- Reject $\{H_i : i \leq \hat{k}, p_i < \hat{s}\}$ (red points)

Methods differ on sequence of rectangles, formula for $\widehat{\text{FDP}}$

Benjamini–Hochberg Procedure [Benjamini and Hochberg, 1995]

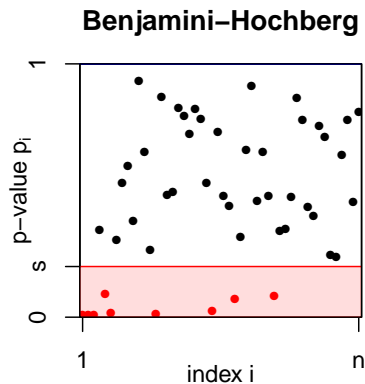
$$\widehat{\text{FDP}}_{\text{BH}} = \frac{ns}{R(s)}$$



- $R(s) = |\{i : p_i \leq s\}|$
- Optional stopping argument [Storey et al., 2004]
- Conservative: $\text{FDR} \leq \alpha\pi_0$ ($\pi_0 = |\mathcal{H}_0|/n$)

Benjamini–Hochberg Procedure [Benjamini and Hochberg, 1995]

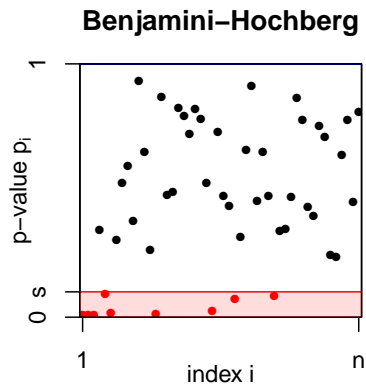
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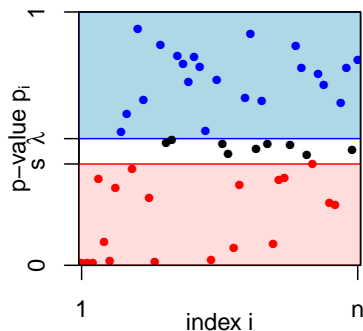


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Storey-BH Procedure [Storey et al., 2004]

$$\widehat{\text{FDP}}_{\text{SBH}} = \frac{ns}{R(s)} \cdot \frac{A(\lambda) + 1}{(1 - \lambda)n}$$

Storey-BH

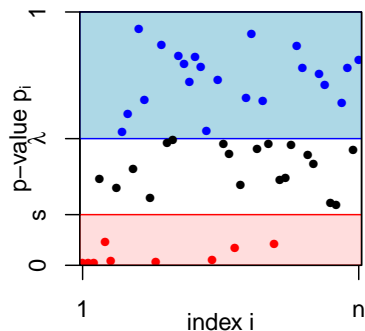


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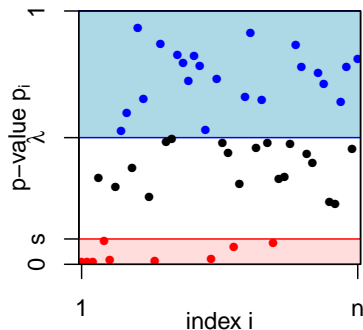


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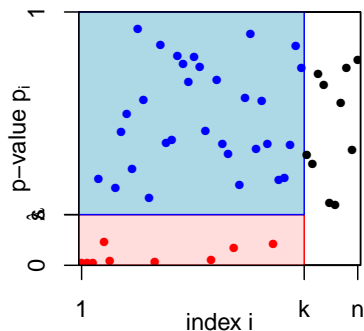


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Selective SeqStep [Barber and Candès, 2015a]

$$\widehat{\text{FDP}}_{\text{SS}} = \frac{ks}{R(k, s)} \cdot \frac{A(k, s) + 1}{k(1 - s)}$$

Selective SeqStep

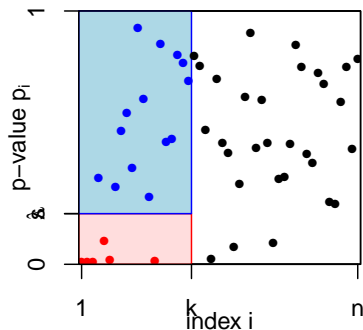


- $R(k, s) = |\{i \leq k : p_i \leq s\}|$
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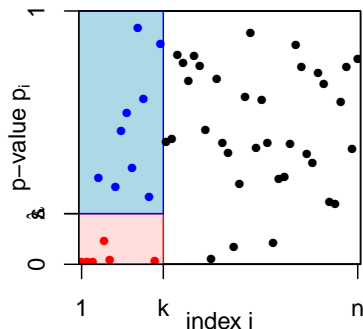


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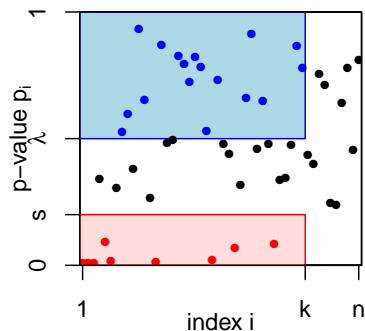


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Adaptive SeqStep

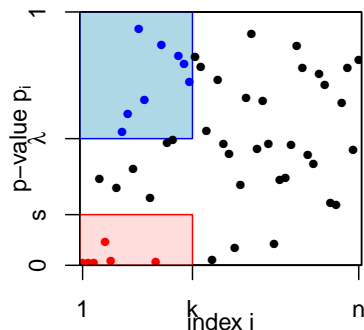


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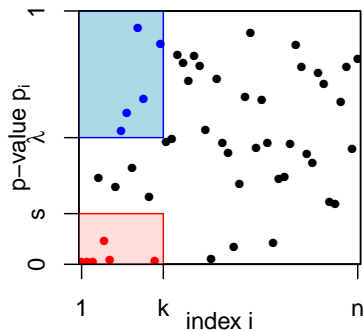


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Conditional Two-Groups Model

Frame threshold choice in terms of **conditional two-groups model**:

$$H_i \mid x_i \sim \text{Bernoulli}(\pi_1(x_i))$$
$$p_i \mid H_i, x_i \sim \begin{cases} \text{Unif} & \text{if } H_i = 0 \\ f_1(p \mid x_i) & \text{if } H_i = 1 \end{cases}.$$

Mixture density $f(p \mid x) \rightarrow$ conditional **local fdr** [Efron et al., 2001]

$$\text{fdr}(p \mid x) = \mathbb{P}(H_i \text{ is null} \mid x_i = x, p_i = p) = \frac{1 - \pi_1(x)}{f(p \mid x)}$$

Estimate $\widehat{\text{fdr}}(p \mid x)$ using models for $\pi_1(x), f_1(\cdot \mid x)$

Impute masked p_i using (e.g.) EM

AdaPT-GLM

Simple choice of model, given featurization $\phi : \mathcal{X} \rightarrow \mathbb{R}^d$

Logistic regression for π_1 , 1-parameter beta GLM for f_1

$$\log \frac{\mathbb{P}(H = 1 \mid x)}{\mathbb{P}(H = 0 \mid x)} = \beta' \phi(x)$$
$$f_1(p \mid x, H = 1) = \frac{1}{\gamma' \phi(x)} p^{\gamma' \phi(x) - 1} \quad (0 < p < 1)$$

For 1-dimensional examples, ϕ typically a natural cubic spline basis

Expectation-Maximization: alternate between

- Impute H_i and masked p_i (both binary, knowing \mathcal{F}_t)
- Estimate β, γ via `glm` or `glmnet` (regularized)

adaptMT R package: `adapt_glm`, `adapt_glmnet`

Updating the Threshold

Theorem 2 (Lei and F, 2016).

Under mild assumptions, the optimal threshold $s(x)$ is a level surface of local FDR.

- Step 1. Use **your favorite method** to fit **your favorite model**
- Step 2. Estimate level surfaces of local FDR
- Step 3. Move the threshold to a smaller level surface, re-fit

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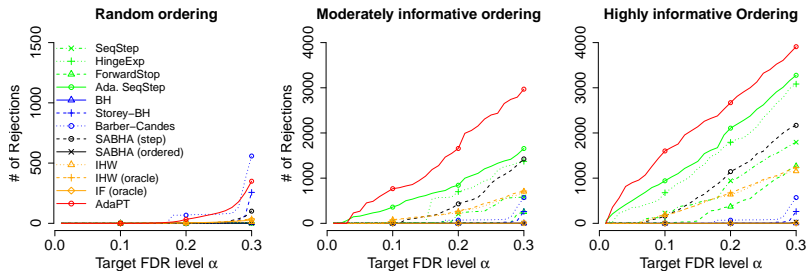
Gene/Drug response Data: Power Comparison

Compared AdaPT to competing methods using three orderings:

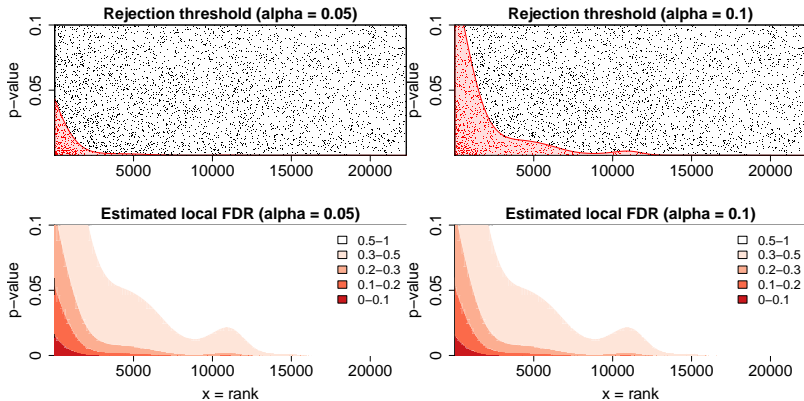
- Random ordering
- Moderate dose ordering (dose 2 vs. pooled doses 0 & 1)
- High dose ordering (dose 4 vs. pooled doses 0 & 1)

Natural-spline GLM for $\pi_1(x)$, $f_1(p | x)$ (fit by EM)

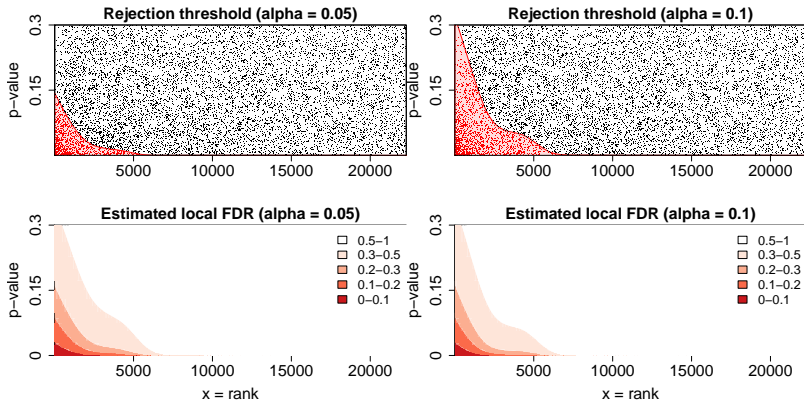
Number of Rejections (Gene/Drug Response)



Gene/Drug response Data: Moderate Dose Ordering



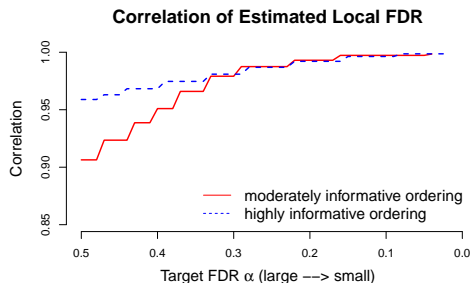
Gene/Drug response Data: High Dose Ordering



Convergence of fdr estimates

$\widehat{\text{fdr}}(p_i | x_i)$ at step $t \rightarrow \widehat{\text{fdr}}(p_i | x_i)$ estimated using all data

Corr $\geq 90\%$ once $\widehat{\text{FDP}} \leq 0.3$.



Dependent p -values

Can deal with some forms of dependence using ideas from knockoff filter [Barber and Candès, 2015a]

Assume we observe correlated z -values $Z \sim N_d(\mu, \Sigma)$

Find diagonal $D \succeq \Sigma$, generate noise $\epsilon \sim N_d(0, D - \Sigma)$:

$$\begin{pmatrix} Z + \epsilon \\ W \end{pmatrix} \sim N \left(\begin{pmatrix} \mu \\ (I - \Sigma D^{-1})\mu \end{pmatrix}, \begin{pmatrix} D & 0 \\ 0 & * \end{pmatrix} \right)$$

where $W = Z - \Sigma D^{-1}(Z + \epsilon)$

Compute $p_i = 2 - 2\Phi(|Z_i + \epsilon_i|)$, use filtration

$$\mathcal{F}_t = \sigma(W, (x_i)_{i=1}^n, (\tilde{p}_{t,i})_{i=1}^n, A_t, R_t)$$

STAR: Multiple Testing With Structural Constraint



Lihua Lei (Berkeley Statistics)



Aaditya Ramdas (CMU Statistics)

STAR: Multiple Testing With Structural Constraint

Extension with Lihua Lei and Aaditya Ramdas

Want to detect a subset of hypotheses subjected to certain structural constraint, i.e. $\{x_i : H_i \text{ rejected}\} \in \mathcal{K} \subseteq 2^{[n]}$:

- (spatial-temporal multiple testing)
 x_i : geographic location, \mathcal{K} : all convex sets;
- (hierarchical testing)
 x_i : node of a tree, \mathcal{K} : all subtrees;
- (Selection under strong/weak heredity principles)
 x_i : node of a DAG, \mathcal{K} : all subgraphs st. heredity principles

Animation: STAR in Convex Region Detection

Summary

AdaPT: Interactive multiple testing with side information

Estimate local fdr using **partially masked** data (impute p_i)

Unrestricted estimation of optimal threshold

Finite-sample FDR control

Thanks!

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