AdaPT: A New Class of Ordered Testing Procedures

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Multiple Testing Problem with FDR Control

- General setup: a sequence of hypotheses $H_1, H_2, \ldots, H_n$;
- $\mathcal{H}_0 = \{i : H_i \text{ is true}\}$ be the set of *null* hypotheses;
- $\mathcal{S} = \{i : H_i \text{ is rejected}\}$ be the set of *discoveries*;
- $\mathrm{FDP} = \frac{V}{R \vee 1}$ be the *False Discovery Proportion* with $V = |\mathcal{S}|$ and $R = |\mathcal{S} \cap \mathcal{H}_0|$;
- $\mathrm{FDR} = \mathbb{E}\mathrm{FDP}$ be the *False Discovery Rate*, the target that a procedure should control.
- A procedure that control FDR at level 0.1 produces a rejection set $\mathcal{S}$ with roughly 90% being the true discoveries.

Ordered Hypothesis Testing

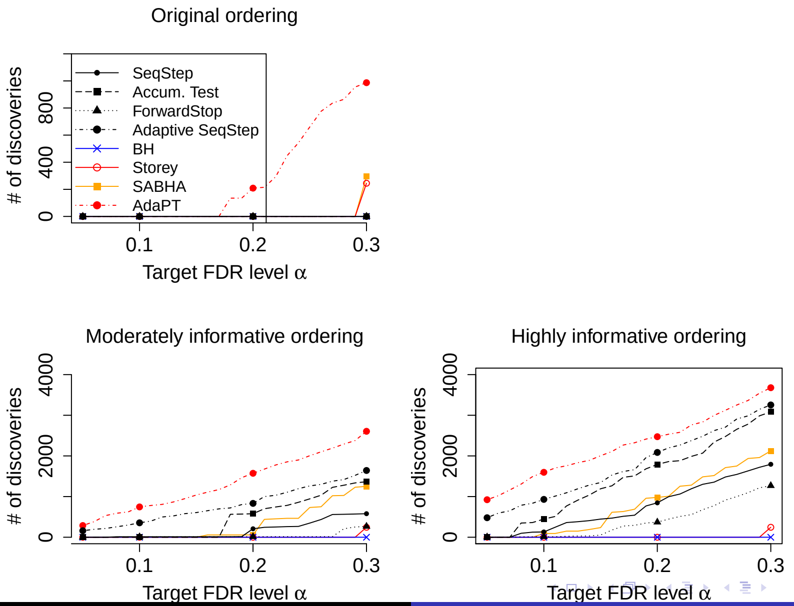
- Domain knowledge might be used to indicate which hypothesis is more "promising", i.e. likely to be rejected;
- Heuristically, more focus should be put on "promising" hypotheses;
- Sort $H_1, \ldots, H_n$ from most "promising" to least "promising" via the prior knowledge;
- A procedure that takes advantage of the ordering is called an *ordered hypothesis testing procedure*.

Example: GEOquery Data

- GEOquery data[1][LB15] consists of gene expression measurements in response to estrogen in breast cancer cells;
- Consists of $n = 22283$ genes and two groups (a treatment group and a control group) with 5 trials in each;
- Test $H_i : F_{0i} = F_{1i}$, where F_{0i} and F_{1i} are the distributions of gene expression of gene i in the control group and the treatment group, respectively;
- $H_1, \ldots, H_n$ are ordered by auxiliary data.

[1] http://www.ncbi.nlm.nih.gov/sites/GDSbrowser?acc=GDS2324

Example: GEOquery Data



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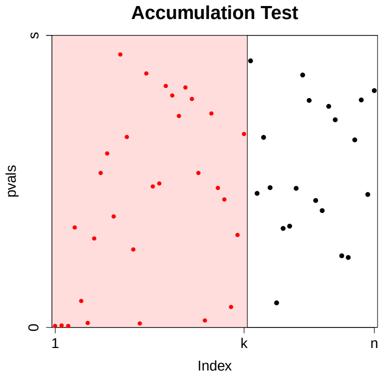
Existing Methods Revisited: Accumulation Test

$$\widehat{\mathrm{FDP}}_{AT} = \frac{C + \sum_{i=1}^{k} h(p_i)}{k+1}$$



- $h \in [0, C]$, $\int_0^1 h(x)dx = 1$;
- Find the maximum k such that $\widehat{\mathrm{FDP}}_{AT} \le q$;
- ForwardStop[GWCT15]:

$$h(x) = -\log(1-x);$$

- Seqstep[BC15]:

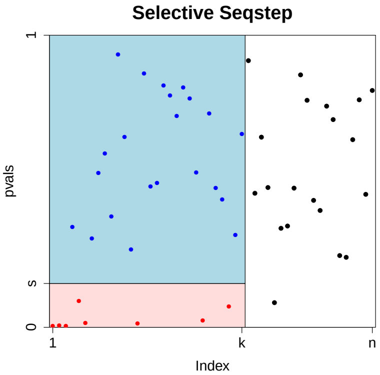
$$h(x) = \frac{I(x > \lambda)}{1-\lambda};$$

- HingeExp[LB15]:

$$h(x) = -\frac{I(x > \lambda)}{1-\lambda}\log\left(\frac{1-x}{1-\lambda}\right).$$

Existing Methods Revisited: Selective Seqstep

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



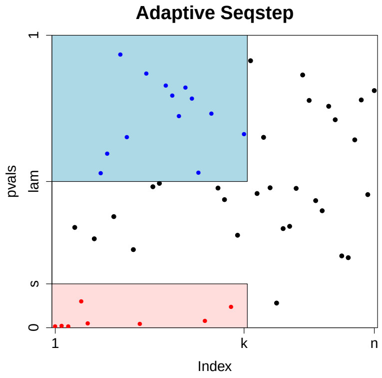
- $R(k;s) = |\{i \le k : p_i \le s\}|$;
- $A(k;s) = |\{i \le k : p_i > s\}|$;
- s is pre-fixed;
- Find the maximum k such that $\widehat{\mathrm{FDP}}_{SS} \le q$.
- Turns out that the blue term should be an approximation of $\pi_{0,k}$,

$$\pi_{0,k} = \frac{|\{1,\ldots,k\} \cap \mathcal{H}_0|}{k};$$

- Too conservative for small s.

Existing Methods Revisited: Adaptive Seqstep

$$\widehat{\mathrm{FDP}}_{AS} = \frac{ks}{R(k;s) \vee 1} \cdot \frac{A(k;\lambda) + 1}{k(1-\lambda)}$$



- $R(k;s) = |\{i \le k : p_i \le s\}|$;
- $A(k;\lambda) = |\{i \le k : p_i > \lambda\}|$;
- s and λ are is pre-fixed;
- Find the maximum k such that $\widehat{\mathrm{FDP}}_{AS} \le q$;
- Much less conservative if a large λ, say 0.5, is used.

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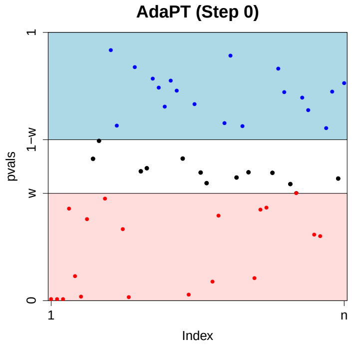
$$\widehat{\mathrm{FDP}}_{\mathrm{AdaPT}} = \frac{A(k;\lambda)+1}{R(k;s)\vee 1}$$



- $R(k;w) = |\{i : p_i \le w_i\}|$;
- $A(k;w) = |\{i : p_i > 1 - w_i\}|$;

AdaPT

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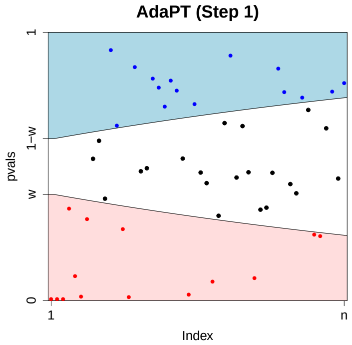

- $R(k;w) = |\{i : p_i \le w_i\}|$;
- $A(k;w) = |\{i : p_i > 1 - w_i\}|$;
- Estimate next w by $\tilde{p}_i$:

$$\tilde{p}_i = \begin{cases} p_i & (p_i \text{ is black}) \\ \mathrm{NA} & (p_i \text{ is red or blue}) \end{cases}$$

- Repeat until $\widehat{\mathrm{FDP}}_{\mathrm{AdaPT}} \le q$.

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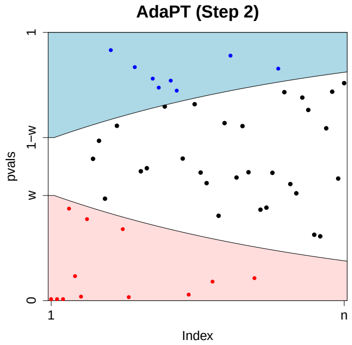

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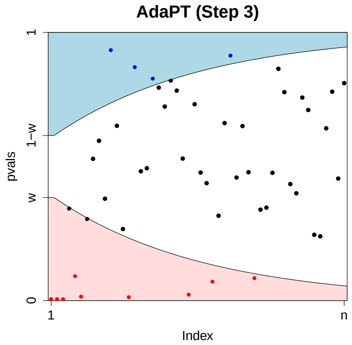

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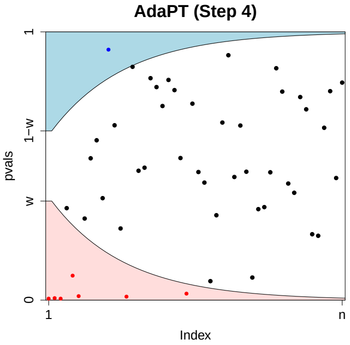

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- Repeat until $\widehat{\mathrm{FDP}}_{\mathrm{AdaPT}} \le q$.

Theorem 1.

Assume that

1. $\{p_i : i = 1, \ldots, n\}$ *are independent;*
2. $\{p_i : i \in \mathcal{H}_0\}$ *are i.i.d. uniformly distributed on* $U[0, 1]$.

Then AdaPT controls FDR at level q.

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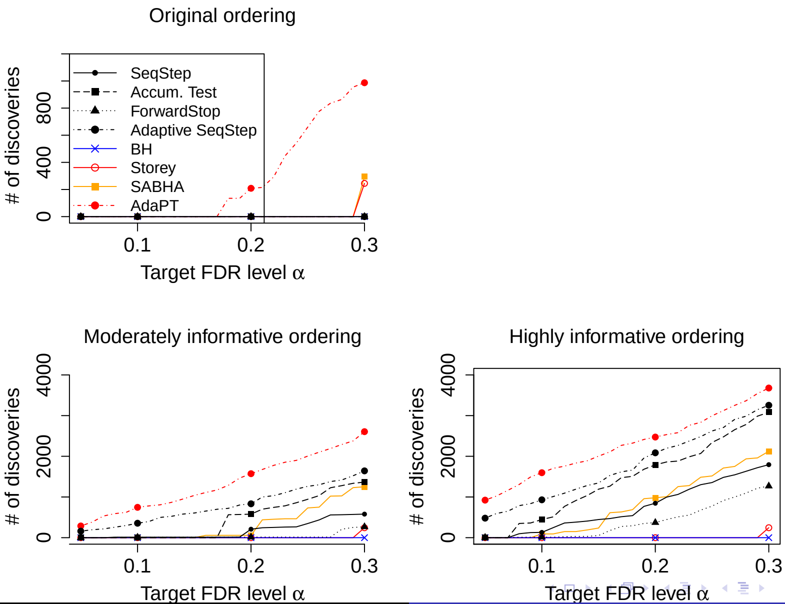
Then AdaPT controls FDR at level q.

Any method to update w guarantees the FDR control!

Real Example: GEOquery Data



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THANK YOU!