Large-Scale Inference: Empirical Bayes Methods for Estimation, Testing and Prediction

Ch.3 Significance Testing Algorithms

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Outline

1. Stepwise Algorithms

2. Permutation Algorithms

3. Other Control Criteria

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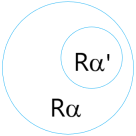
3. Other Control Criteria

P value and Rejection Region

We construct a rejection region class $\{R_\alpha\}_{\alpha \in I}$ for an index set I such that

1. $\mathrm{P}(X \in R_\alpha | H_0) = \alpha$
2. $R_\alpha \supseteq R_{\alpha'}$ if $\alpha \geq \alpha'$



Thus,

$$\mathrm{P}(\inf_u \{X \in R_u\} \leq \alpha | H_0) = \mathrm{P}(X \in R_\alpha | H_0) = \alpha.$$

p-value: $p(x) = \inf_u \{x \in R_u\}$.

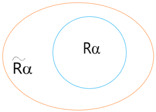
P value and Rejection Region

We construct two rejection region classes $\{R_\alpha\}_{\alpha \in I}$ and $\{\tilde{R}_\alpha\}_{\alpha \in I}$ for an index set I such that

1. $\mathrm{P}(X \in R_\alpha | H_0) = \alpha$ and

$\mathrm{P}(X \in \tilde{R}_\alpha | H_0) = \alpha$

2.$R_\alpha \subseteq \tilde{R}_\alpha$



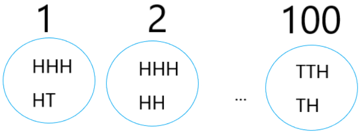
we have

$$\tilde{p}(x) = \inf_u \{x \in \tilde{R}_u\} \leq \inf_u \{x \in R_u\} = p(x).$$

P value and Adjusted p-value

A example: Toss five fair coins.

- $\mathrm{P}(HHHHH) = 1/32 \approx 0.031.$
- $\mathrm{P}($ at least one $HHHHH$ at 100 trials$) = 1 - (1 - 1/32)^{100} \approx 0.958.$



Adjusted p-Values and the FWER

- The family-wise error rate

$$\text{FWER} = \Pr\{\text{Reject } \mathit{any} \text{ true } H_{0i}\}$$

- $\text{FWER}_\alpha(x)$: FWER control procedure

  Input: $p_1(x), \ldots, p_N(x)$

  Output: the list of accepted and rejected H_{0i}s

subject to the constraint

$$\text{FWER} \leq \alpha$$

for any preselected value of α.

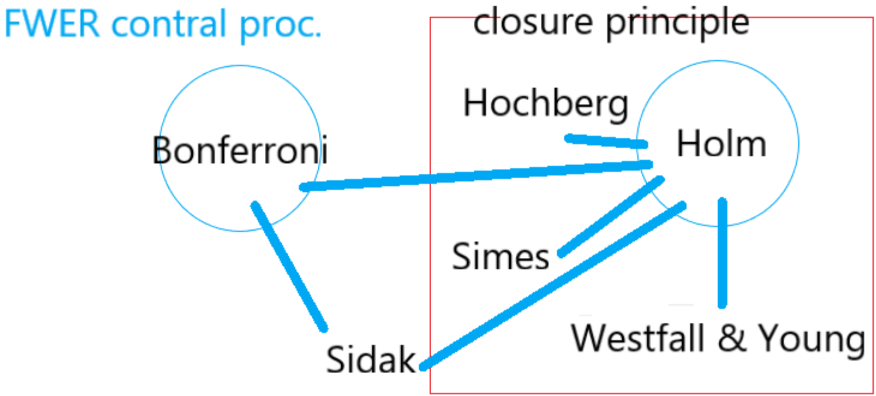
Adjusted p-Values and the FWER

- Adjusted p-Values

  Let $\boldsymbol{x}$ indicate all the data available for testing the family of hypotheses H_{01}, H_{02},. . . , H_{0N} , and let $\text{FWER}_\alpha(\boldsymbol{x})$ be a FWER level-α test procedure based on α.

$$\tilde{p}_i(\boldsymbol{x}) = \inf_\alpha \{H_{0i} \text{ rejected by } \text{FWER}_\alpha(\boldsymbol{x})\}$$

FWER control methods



Bonferroni procedure

- Reject those null hypotheses H_{0i} for which

$$p_i \le \alpha/N.$$

- FWER control property: Let I_0 index the true null hypotheses, having N_0 members. Then

$$\mathrm{FWER} = \mathrm{P}\left\{\bigcup_{i\in I_0}(p_i \le \frac{\alpha}{N})\right\} \le \sum_{i\in I_0} \mathrm{P}\left\{p_i \le \frac{\alpha}{N}\right\} = N_0 \frac{\alpha}{N} \le \alpha.$$

- family-wise adjusted p-value:

$$\tilde{p}_i = \{N p_i\}_1,$$

where $\{x\}_1 = \min(x, 1)$.

$\check{S}id\acute{a}k$ procedure

- Reject those null hypotheses H_{0i} for which

$$p_i \leq 1 - (1-\alpha)^{1/N}.$$

  It is noted that $\alpha/N \leq 1 - (1-\alpha)^{1/N}$.

- FWER control property: Let I_0 index the true null hypotheses, having N_0 members. Then

$$\mathrm{FWER} = \mathrm{P}\left\{\bigcup_{i \in I_0} (p_i \leq \frac{\alpha}{N})\right\} = 1 - \mathrm{P}\left\{\bigcap_{i \in I_0} (p_i \geq \frac{\alpha}{N})\right\} 1 - (1-\alpha)^{N_0/N} \leq \alpha$$

  if p-values $p_1, \ldots, p_N$ are statistically independent.

- family-wise adjusted p-value:

$$\tilde{p}_i = 1 - (1-p_i)^N$$

Holm's procedure

- Let the ordered p-values be denoted by $p_{(1)} \le p_{(2)} \le p_{(3)} \le \cdots \le p_{(N)}$.

$$\text{Reject } H_{0(i)} \text{ if } p_{(j)} \le \frac{\alpha}{N-j+1} \qquad \text{for } j = 1, 2, \ldots, i.$$

- FWER control property: Let I_0 index the true null hypotheses, having N_0 members. Let $i_0 = N - N_0 + 1$ and $\widehat{i}$ be the stopping index for Holm's procedure. Then,

$$\begin{aligned} A = \left\{ p_{(i)} > \frac{\alpha}{N_0} \text{ for all } (i) \in I_0 \right\} \quad &\Longrightarrow \quad \left\{ p_{(i_0)} > \frac{\alpha}{N_0} = \frac{\alpha}{N+1-i_0} \right\} \\ &\Longrightarrow \quad \{\widehat{i} < i_0\} \Longrightarrow \left\{ p_{(\widehat{i})} < \frac{\alpha}{N_0} \right\} = B \end{aligned}$$

It is noted that the Bonferroni bound implies $\mathrm{P}(A) \ge 1 - \alpha$ and B

implies none of the true H_{0i} have been rejected.

- family-wise adjusted p-value: $\tilde{p}_{(i)} = \max_{j \le i} \left\{ (N-j+1)p_{(j)} \right\}_1$

A Global Test

- Let I be a subset of the indices $\{1, 2, \cdots, N\}$,

$$\mathcal{I} = \bigcap_I H_{0(i)}$$

- A global test: suppose a level α non-randomized test function $\phi_I(\boldsymbol{x})$.

  When rejecting $\mathcal{I}$, $\phi_I(\boldsymbol{x}) = 1$; otherwise, $\phi_I(\boldsymbol{x}) = 0$.

- Control the error rate:

$$\Pr_{\mathcal{I}} \{\phi_I(\boldsymbol{x}) = 1\} \leq \alpha$$

- Example: Bonferroni's global test

$$\min_{i \in I} p_i \leq \frac{\alpha}{|I|}.$$

Closure Principle

- Let $\Pr\limits_{\mathcal{I}} \{\phi_I(\boldsymbol{x}) = 1\} \leq \alpha$ for all I. Let the simultaneous test function $\Phi_I(\boldsymbol{x}) = \min_{I' \supseteq I} \phi_{I'}(\boldsymbol{x})$.

$$\text{reject } \mathcal{I} \Longleftrightarrow \Phi_I(\boldsymbol{x}) = 1$$

equivalently or

$$\Phi_I(\boldsymbol{x}) = 1 \Longleftrightarrow \text{ reject all } I' \text{ containing } I \text{ at level } \alpha.$$

Closure Principle-Example

Consider the cases of 4 hypotheses. Suppose the underlined hypotheses are rejected at α level.

$$\underline{H_{1234}}$$

$$\underline{H_{123}} \quad \underline{H_{124}} \quad \underline{H_{134}} \quad H_{234}$$

$$\underline{H_{12}} \quad \underline{H_{13}} \quad \underline{H_{14}} \quad H_{23} \quad H_{24} \quad H_{34}$$

$$\underline{H_{1}} \quad \underline{H_{2}} \quad H_{3} \quad H_{4}$$

In this example, only H_1 is rejected.

Closure Principle- FWER control property

Let $I \subseteq I_0$, the set of all the true H_{0i}. Then

$$\mathrm{FWER} = \Pr_{\mathcal{I}} \{\Phi_I(\boldsymbol{x}) = 1 \text{ for any } I \subseteq I_0\} \leq \Pr_{\mathcal{I}_0} \{\phi_{\mathcal{I}_0}(\boldsymbol{x}) = 1\} \leq \alpha.$$

Holm's procedure (Again!)

- Let $\Phi_I(x)$ be Bonferroni's global test:

$$\min_{i \in I} p_i \leq \frac{\alpha}{|I|}.$$

- By using the closure principle, we have (a) $p_{(i)} \leq \alpha/(n-i+1)$ (b) if it rejects $H_{0,(i)}$, it also rejects $H_{0,(1)}, \ldots, H_{0,(i-1)}$.
- For example, the case of 3 hypothesis $\{H_{01}, H_{02}, H_{03}\}$

$H_{0,\{1,2,3\}} : \min_{i \in \{1,2,3\}} p_i < \alpha/3$

$H_{0,\{1,3\}} : \min_{i \in \{1,3\}} p_i < \alpha/2$, $H_{0,\{1,2\}} : \min_{i \in \{1,3\}} p_i < \alpha/2$

$H_{0,\{1\}} : \min_{i \in \{1\}} p_i < \alpha/1$

Simes' processure

- Let the ordered p-values be denoted by $p_{(1)} \leq p_{(2)} \leq p_{(3)} \leq \cdots \leq p_{(N)}$.

$$\text{Reject } H_{0(i)} \text{ if } \frac{p_{(j)}}{j} \leq \frac{\alpha}{N-j+1} \qquad \text{for } j = 1, 2, \ldots, i.$$

- FWER control property: Let I_0 index the true null hypotheses, having N_0 members. Let $i_0 = N - N_0 + 1$ and $\widehat{i}$ be the stopping index for Holm's procedure. Then,

$$A = \left\{ p_{(i)} > \frac{\alpha i}{N_0} \text{ for all } (i) \in I_0 \right\} \implies \left\{ p_{(i_0)} > \frac{\alpha i_0}{N_0} = \frac{\alpha i_0}{N+1-i_0} \right\}$$
$$\implies \{\widehat{i} < i_0\} \implies \left\{ p_{(\widehat{i})} < \frac{\alpha i_0}{N_0} \right\} = B$$

It is noted that if p_i's are independent, the Simes' inequality implies

$\mathrm{P}(A) \geq 1 - \alpha$ and B implies none of the true H_{0i} have been rejected.

- family-wise adjusted p-value: $\tilde{p}_{(i)} = \max_{j \leq i} \{(N-j+1)p_{(j)}/j\}_1$

Hochberg processure

- Let the ordered p-values be denoted by $p_{(1)} \leq p_{(2)} \leq p_{(3)} \leq \cdots \leq p_{(N)}$.

  Reject $H_{0(i)}$ if there is an index j such that $i \leq j$ and $p_{(j)} \leq \alpha/(N-j+1)$.
- FWER control property: Let i_0 be the index given by $i_0 = \sup\{k : (k) \in I \text{ and } k \leq j\}$

$$
\begin{aligned}
p_{(i_0)} \leq p_{(j)} \leq \frac{\alpha}{N-j+1} \quad &\leq \quad \frac{\alpha}{1+|\{(j+1),\ldots,(N)\}\bigcap I|} \\
&\leq \quad \frac{\alpha}{|\{(i_0),\ldots,(N)\}\bigcap I|} \leq \frac{|\{(1),\ldots,(i_0))\}\bigcap I|}{|I|}\alpha \leq \frac{i_0}{|I|}\alpha
\end{aligned}
$$

  Note that we reject Hochberg's H_{0i}, we also reject Simes'.
- family-wise adjusted p-value: $\tilde{p}_{(i)} = \min_{j \geq i} \{(N-j+1)p_{(j)}\}_1$

Step-Down vs Step Up procedures

We can write Holm's and Hochberg's procedures side-by-side:

Procedure *Holm*

$j = 0$
while $p_{(j+1)} \leq \alpha/(n-j)$ **do**
  $j = j + 1$
end
Reject $H_{(1)}$, ..., $H_{(j)}$

Procedure *Hochberg*

$j = n$
while $p_{(j)} > \alpha/(n-j+1)$ **do**
  $j = j - 1$
end
Reject $H_{(1)}$, ..., $H_{(j)}$

The two procedures have the same thresholds, i.e., $p_{(j)}$ is compared to $\alpha/(n-j+1)$. However,

- Holm's scans forward, and stops as soon as a p-value fails to clear its threshold. This pessimistic approach is called a **step-down** procedure (think stepping downwards on the χ^2-statistics).
- Hochberg's scans backwards, and stops as soon as a p-value succeeds in passing its threshold. This optimistic approach is called a **step-up** procedure (think stepping upwards on the χ^2-statistics).

(source: 2017 Wager, S. and Candes, E.)

Permutation Algorithms

The Bonferroni bound holds true regardless of the dependence structure of the data. If we want to know the structure...

Permutation Algorithms

Under the complete null hypothesis H_0 that all of the H_{0i} are true.

- The order p-values: $p_{(1)} \leq p_{(2)} \leq \cdots \leq p_{(N)}$
- Let $p_{(j)} = p_{r_j},\ j = 1, 2, \ldots, N$
- Define $R_j = \{r_j, r_{j+1}, \ldots, r_N\}$ and

$$\pi(j) = \mathrm{Pr}_0 \left\{ \min_{k \in R_j} (P_k) \leq p_{(j)} \right\},$$

where $(P_1, P_2, \cdots, P_N)$ indicates a hypothetical realization of the unordered p-values $(p_1, p_2, \cdots, p_3)$ obtained under $\boldsymbol{H}_0$.

- The *Westfall-Young step-down min-p* adjusted p-values

$$\tilde{p}_{(i)} = \max_{j \le i}\{\pi(j)\}$$

- Connect with Holm's procedure, Bool's inequality implies

$$\pi(j) \le \sum_{k \in R_j} \mathsf{Pr}_0 \left\{ P_k \le p_{(j)} \right\} = (N - j + 1) p_{(j)}$$

- The Westfall-Young adjusted p-values are smaller than Holms values ($\tilde{p}_{(i)} = \max_{j \le i}\{(N - j + 1)p_{(j)}\}_1$).

max-T

- The min-p procedure can be difficult to implement.
- Let $t_{(1)} \geq t_{(2)} \geq \cdots \geq t_{(N)}$
- With $t_{(j)} = t_{r_j}$
- Also let $(T_1, T_2, \cdots, T_N)$ represent a hypothetical unordered realization obtained under $\boldsymbol{H}_0$.
- Define

$$\pi(j) = \text{Pr}\left\{ \max_{k \in R_j}(T_k) \leq t_{(j)} \right\}$$

Example: prostate data

Goal: To discover genes whose expression levels differ between the prostate and normal subjects.

- $N = 6033$ genes
- 50 normal control subjects and 52 prostate cancer patients
- Data matrix

	the normal contral (1,2,...,50)	the cancer patients (51,53,...,102)
gene: N=6033	x_{ij} = level for gene i on patient j,	

- If $\boldsymbol{j}^* = (j_1^*, j_2^*, \ldots, j_n^*)$ is a randomly selected permutation of $(1, 2, \ldots, n)$ then X^* has entries

$$x_{ij}^* = x_{iJ^*(j)} \qquad \text{for } j = 1, 2, \ldots, n \text{ and } i = 1, 2, \ldots, N$$

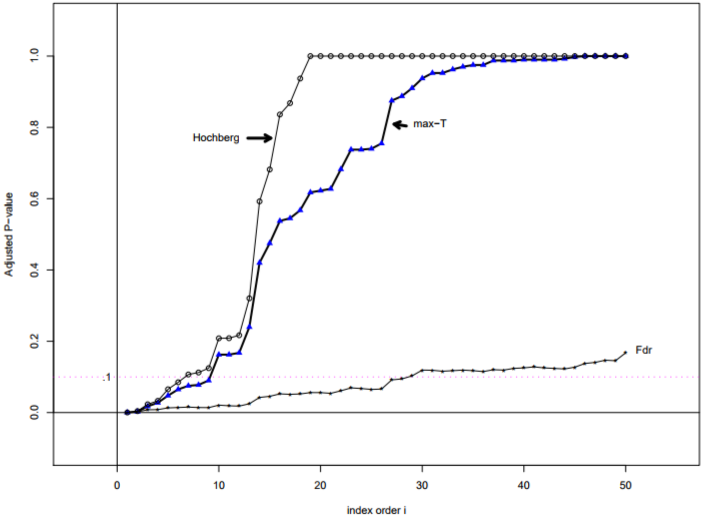
- Still considering the first 50 columns as controls and the last 52 as cancer patients. it yields a 6033-vector of apermutation t-values

$$\boldsymbol{T}^* = (T_1^*, T_2^*, \ldots, T_N^*)'$$

- Define

$$\hat{\pi}(j) = \#\left\{\max_{k \in R_j}(T_k^*) > t_{(j)}\right\} / B$$

where B repeat the permutation process times.


Adjusted P-value
index order i
Hochberg
max-T
Fdr
.1
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50

- The estimated false sidcovery rates:

$$\overline{\mathsf{Fdr}}_{(i)} = N \cdot [1 - \Phi(z_{(i)})] \;/\; \#\{z_j \leq z_{(j)}\}$$

  where $z_{(1)} \leq z_{(2)} \leq \cdots \leq z_{(N)}$ and Φ are the standard normal cdf.

- For i=20 ,
  - Fdr: $\overline{\mathsf{Fdr}}_{(20)} = 0.056$
  - max-T: $\tilde{p}_{(20)} = 0.62$
  - Hochberg: $\tilde{p}_{(20)} = 1$

k-FWER

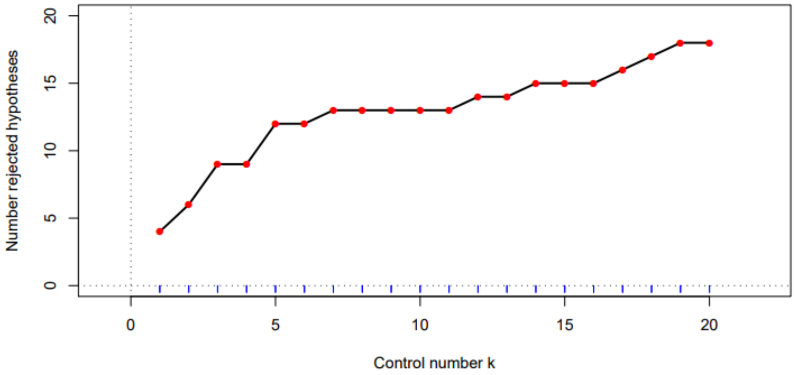
Theorem

The procedure that rejects only those null hypotheses H_{0i} for which

$$p_i \leq k\alpha/N$$

controls k-FWER at level α,

$$\Pr\{k \text{ or more true } H_{0i} \text{ rejected}\} \leq \alpha.$$


Number rejected hypotheses
0
5
10
15
20
Control number k