A general principle for shortening closed test procedures with applications

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Closed test procedures

Closed test procedures (with p-values)

- We want to test k hypotheses $H_1, \ldots, H_k$
- Consider the family of all intersection hypotheses

$$\mathcal{H} = \{ H_J = \cap_{j \in J} H_j \ : \ J \subseteq I = \{1, \ldots, k\}, H_J \neq \emptyset \}$$

- For all $H \in \mathcal{H}$ specify a test with p-value p_H
- Compute for all $H \in \mathcal{H}$ the "closed test"-adjusted p-value

$$q_H = \max_{H' \in \mathcal{H}, H' \subseteq H} p_{H'}$$

- Reject $H \in \mathcal{H}$ if and only if $q_H \leq \alpha$.

Closed test procedures ...

- *... strongly control the multiple type I error rate at level α:*

  Let θ_{true} be the true parameter value, $\quad H_{true} = \cap_{\theta_{true} \in H'} H'$,

$$P_{\theta_{true}}\Big(\bigcup_{\{\, H' : H' \ni \theta_{true} \,\}} \{q_{H'} \leq \alpha\}\Big) \leq \sup_{\theta \in H_{true}} P_\theta(p_{H_{true}} \leq \alpha) \leq \alpha$$

- *... can require the computation of p-values p_H for up to $2^k - 1$ intersection hypotheses, even if we are only interested in the k elementary hypotheses $H_1, \ldots, H_k$.*

Closed test procedures with shortcuts

- Several closed tests with shortcuts are available, e.g.:

  – Bonferroni-Holm and other step-down tests like e.g. Šidak, Dunnett, resampling tests (WESTFALL & YOUNG, 1993)

  – Step-up tests of HOCHBERG (1988), ROM (1990), DUNNETT & TAMHANE (1992), FINNER & ROTERS (1998)

  – Quasi-consonant intersection tests (HOMMEL, BRETZ & MAURER, 2007)

  $\Rightarrow$ General class of weighted Bonferroni-tests

Example - Bonferroni closed test procedure

- H_j ... the k elementary null hypotheses, $j \in I = \{1, \dots, k\}$
- $\mathcal{H} = \{ H_J : J \subseteq I \}, \quad |\mathcal{H}| = 2^k - 1$ (f.c.p.)
- p_j ... the p-value for H_j, $j \in I$
- For $H_J = \cap_{j \in J} H_j$ the Bonferroni-test p-values

$$p_{H_J} = \min(1, |J| \cdot \min_{j \in J} p_j), \qquad J \subseteq I$$

- Reject H_J iff $q_{H_J} = \max_{H' \in \mathcal{H}, H' \subseteq H_J} p_{H'} = \max_{J' \supseteq J} p_{H_{J'}} \leq \alpha$

Example - Bonferroni-Holm procedure

Let $\{i_1, \ldots, i_k\} \in I = \{1, 2, \ldots, k\}$ be such that

$$p_{i_1} \leq p_{i_2} \leq \ldots \leq p_{i_k}$$

Stepwise Procedure:

$$k\, p_{i_1} \leq \alpha \quad \overset{\text{yes}}{\longrightarrow} \quad (k-1)\, p_{i_2} \leq \alpha \quad \overset{\text{yes}}{\longrightarrow} \quad \cdots\cdots \quad \overset{\text{yes}}{\longrightarrow} \quad p_{i_k} \leq \alpha$$

Note: The p-values of only k different intersection hypotheses need to be computed:

$$k\, p_{i_1} = p_{H_{\{i_1,\ldots,i_k\}}}, \quad (k-1)\, p_{i_2} = p_{H_{\{i_2,\ldots,i_k\}}}, \quad \ldots\ldots, \quad p_{i_k} = p_{H_{i_k}}$$

General Principle

"How can we get rid of superfluous intersection tests?"

(Definition + Theorem)

Definition of a shortcut

A **shortcut** is a collection $\mathcal{K} = \{K_1, \ldots, K_s\} \subseteq \mathcal{H}$ of intersection hypotheses that can depend on the data and satisfies

(i) $|\mathcal{K}| < |\mathcal{H}|$

(ii) All closed test adjusted p-values can be determined from the smaller collection $\mathcal{K}$:

$$q_H = \max_{H' \in \mathcal{H},\ H' \subseteq H} p_{H'} = \max_{H' \in \mathcal{K},\ H' \subseteq H} p_{H'} \qquad (*)$$

(iii) The determination of $\mathcal{K}$ requires less computational efforts than the whole closed test procedure.

We call $|\mathcal{K}|$ the **size** of the shortcut $\mathcal{K}$.

Given the data, when is a collection of intersection hypotheses a shortcut?

Theorem: A collection $\mathcal{K} = \{K_1, \ldots, K_s\} \subseteq \mathcal{H}$ satisfies

$$q_H = \max_{H' \in \mathcal{K},\ H' \subseteq H} p_{H'} \quad \text{for all } H \in \mathcal{H} \qquad (*)$$

if and only if for all $H \in \mathcal{H}$ we can find $K \in \mathcal{K}$ such that

$$K \subseteq H \quad \text{and} \quad p_K \geq p_H \qquad (1)$$

Example - Bonferroni-Holm procedure

Proof of condition (1) for $\mathcal{K} = \{H_{\{i_1,\ldots,i_k\}}, H_{\{i_2,\ldots,i_k\}}, \ldots, H_{\{i_k\}}\}$

$$p_{i_1} \leq p_{i_2} \leq \cdots \leq p_{i_u} \leq p_{i_{u+1}} \leq \cdots \leq p_{i_t} \leq \cdots \leq p_{i_k}$$

$$i_1 \quad i_2 \quad \cdots \quad (i_u \quad i_{u+1}) \quad \cdots \quad (i_t) \quad \cdots \quad i_k$$

H_J

$H_J \supseteq H_{\{i_u,\ldots,i_k\}}$

$$i_1 \quad i_2 \quad \cdots \quad \boxed{i_u \quad i_{u+1} \quad \cdots \quad i_t \quad \cdots \quad i_k}$$

$H_{\{i_u,\ldots,i_k\}}$

$$p_{H_J} = |J|\, p_{i_u} \leq p_{H_{\{i_u,\ldots,i_k\}}} = |\{i_u,\ldots,i_k\}|\, p_{i_u}$$

Extensions:

- A similar argument applies to all quasi-consonant intersection tests. This covers most examples from the literature (HOMMEL, MAURER & BRETZ, 2007)
- In our paper we consider a somewhat more specific class of intersection tests which ...

  – ... is more explicit in terms of the quantities to be computed,

  – ... still covers most examples from the literature,

  – ... allows to derive a shortcut also in cases of logical constraints, e.g. for the all pairwise- comparison closed test procedure of HOMMEL & BERNHARD (1999).

A shortcut for flexible two stage closed tests

(BAUER & KIESER, 1999; KIESER, BAUER & LEHMACHER, 1999; HOMMEL, 2001)

(Closed test with non-consonant intersection tests)

Flexible two stage closed tests

Flexible two stage closed tests consist of **two sequential stages**. Observations are from two independent cohorts.

Planning stage:

- We start with k hypotheses H_j, $j \in I = \{1, \ldots, k\}$, which satisfy the f.c.p.
- We fix stage-1 test procedures for all H_J, $J \subseteq I$, e.g. Bonferroni intersection tests.
- We also fix a combination function $Q(x, y)$, such that

  $Q(x, y)$ is non-decreasing in x and y, and

  $Q(X, Y) \sim U(0, 1)$ for independent $X, Y \sim U(0, 1)$.

Flexible two stage closed tests

At stage 1:

- Compute $p_{H_J}^{(1)} = \min(1, |J| \min_{i \in J} p_i^{(1)})$ for all $J \subseteq I$
- Select $m \leq k$ hypotheses $\longrightarrow$ $I^{(2)} \subseteq I$, $|I^{(2)}| = m$

At stage 2: For all $J \subseteq I$ compute

$$p_{H_J}^{(2)} = \begin{cases} \min(1, |J \cap I^{(2)}| \min_{i \in J \cap I^{(2)}} p_i^{(2)}) & \text{if } J \cap I^{(2)} \neq \emptyset \\ 1 & \text{if } J \cap I^{(2)} = \emptyset \end{cases}$$

Closed test procedure without shortcut:

- We reject H_J iff $q_{H_J} = \max_{J' \supseteq J} Q(p_{H_{J'}}^{(1)}, p_{H_{J'}}^{(2)}) \leq \alpha$.

Shortcut for flexible two stage closed tests

- $i_1, \ldots, i_k \in I = \{1, \ldots, k\}$ ording of the first stage p-values
- $j_1, \ldots, j_m \in I^{(2)}$ ordering of the second stage p-values
- Let $J_{0,0} = I$
  and $J_{u,0} = I \setminus \{i_1, \ldots, i_u\}$, $u \leq k-1$,
  and $J_{0,v} = I \setminus \{j_1, \ldots, j_v\}$, $v \leq m-1$,
  and $J_{u,v} = I \setminus \{i_1, \ldots, i_u, j_1, \ldots, j_v\}$, $u \leq k-1$, $v \leq m-1$.

Proposition: The collection

$$\mathcal{K} = \{H_{J_{u,v}} : 0 \leq u \leq k-1,\ 0 \leq v \leq m-1,\ J_{u,v} \neq \emptyset\}$$

is a uniform shortcut for the flexible two stage closed test.

Proof: Verify condition (1) of the Theorem.

Example

$$I = \{1,2,3\},\ u \le k-1 = 2, \qquad p_1^{(1)} < p_2^{(1)} < p_3^{(1)}$$

$$I^{(2)} = \{1,2\},\ v \le m-1 = 1, \qquad p_2^{(2)} < p_1^{(2)}$$

	$v = 0$	$v = 1$
$u = 0$	$J_{0,0} = I = \{1,2,3\}$	$J_{0,1} = I \setminus \{2\} = \{1,3\}$
$u = 1$	$J_{1,0} = I \setminus \{1\} = \{2,3\}$	$J_{1,1} = I \setminus \{1;2\} = \{3\}$
$u = 2$	$J_{1,2} = I \setminus \{1,2\} = \{3\}$	$J_{2,1} = I \setminus \{1,2;2\} = \{3\}$

Example

$I = \{1,2,3\}$, $u \le k-1 = 2$, $\quad p_1^{(1)} < p_2^{(1)} < p_3^{(1)}$

$I^{(2)} = \{1,2\}$, $v \le m-1 = 1$, $\quad p_2^{(2)} < p_1^{(2)}$

	$v=0$	$v=1$
$u=0$	$J_{0,0} = I = \{1,2,3\}$	$J_{0,1} = I \setminus \{2\} = \{1,3\}$
$u=1$	$J_{1,0} = I \setminus \{1\} = \{2,3\}$	$J_{1,1} = I \setminus \{1;2\} = \{3\}$
$u=2$	$J_{1,2} = I \setminus \{1,2\} = \{3\}$	$J_{2,1} = I \setminus \{1,2;2\} = \{3\}$

Superfluous index sets: $\{1,2\}$, $\{1\}$, $\{2\}$

Size of the shortcut and extensions

Size of the shortcut:

- Some of the $H_{J_{u,v}}$'s are equal, some are empty. Which $H_{J_{u,v}}$ equal or are empty depends on the the orderings i_u and j_v.
- Size varies: $m \leq |\mathcal{K}| \leq m \cdot (k - \frac{m-1}{2}) \leq O(k^2)$

Extensions: We can extend the shortcut to situations where

- quasi-consonant intersection tests are used,
- hypotheses are added at the interim analysis,
- there are more than two sequential stages.

Summary

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- General and simple theory for shortcuts of closed test procedures.
- Shortcut for specific class of closed test procedures which covers many examples from the literature and can be extended to cases with logical constraints.
- Shortcut for flexible closed tests.
- The general and simple theory could be helpful for finding more new shortcuts and new short closed test procedures.

Selected references

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