Hochberg Multiple Test Procedure Under Negative Dependence

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Outline

Preliminaries

Conservative Simes Test

Multivariate Uniform Distribution Models

Error Rate Control for $n = 2$

Error Rate Control for $n \geq 3$

Error Rate Control Under Negative Quadrant Dependence

Simulation Results

Conclusions
Basic Setup

- Test hypotheses $H_1, H_2, \ldots, H_n$ based on their observed marginal $p$-values: $p_1, p_2, \ldots, p_n$.
- Label the ordered $p$-values: $p(1) \leq \cdots \leq p(n)$ and the corresponding hypotheses: $H(1), \ldots, H(n)$.
- Denote the corresponding random variables by $P(1) \leq \cdots \leq P(n)$.
- Familywise error rate (FWER) strong control (Hochberg & Tamhane 1987):

  $\text{FWER} = \Pr\{\text{Reject at least one true } H_i\} \leq \alpha,$

for all combinations of the true and false $H_i$'s.
Hochberg Procedure

- **Step-up Procedure**: Start by testing $H_{(n)}$. If at the $i$th step $p(n-i+1) \leq \alpha/i$ then stop & reject $H_{(n-i+1)}, \ldots, H_{(1)}$; else accept $H_{(n-i+1)}$ and continue testing.

\[
\begin{align*}
H_{(1)} & \leq H_{(2)} & \leq \cdots & \leq H_{(n-1)} & \leq H_{(n)} \\
p_{(1)} & \leq p_{(2)} & \leq \cdots & \leq p_{(n-1)} & \leq p_{(n)} \\
\frac{\alpha}{n} & \leq \frac{\alpha}{n-1} & \cdots & \leq \frac{\alpha}{2} & \leq \frac{\alpha}{1}
\end{align*}
\]

- Known to control FWER under independence and (certain types of) positive dependence among the $p$-values.
- Holm (1979) procedure operates exactly in reverse (step-down) manner and requires no dependence assumption (since it is based on the Bonferroni test), but is less powerful.
Closure Method

- Marcus, Peritz & Gabriel (1976).
- Test all nonempty intersection hypotheses \( H(I) = \bigcap_{i \in I} H_i \), using local \( \alpha \)-level tests where \( I \subseteq \{1, 2, \ldots, n\} \).
- Reject \( H(I) \) iff all \( H(J) \) for \( J \supseteq I \) are rejected, in particular, reject \( H_i \) iff all \( H(I) \) with \( i \in I \) are rejected.
- Strongly controls FWER \( \leq \alpha \).
- Ensures coherence (Gabriel 1969): If \( I \subseteq J \) then acceptance of \( H(J) \) implies acceptance of \( H(I) \).
- Stepwise shortcuts to closed MTPs exist under certain conditions.
- If the Bonferroni test is used as local \( \alpha \)-level test then the resulting shortcut is the Holm step-down procedure.
Closure Method: Example for $n = 3$
Simes Test

- Simes Test: Reject $H_0 = \bigcap_{i=1}^{n} H_i$ at level $\alpha$ if
  $$p(i) \leq \frac{i\alpha}{n} \text{ for some } i = 1, \ldots, n.$$  
- More powerful than the Bonferroni test.
- Based on the Simes identity: If the $P_i$'s are independent then under $H_0$:  
  $$\Pr \left( P(i) \leq \frac{i\alpha}{n} \text{ for some } i \right) = \alpha.$$  
- Simes test is conservative under (certain types of) positive dependence: Sarkar & Chang (1997) and Sarkar (1998).
Hommel Procedure Under Negative Dependence

- When the Simes test is used as a local $\alpha$-level test for all intersection hypotheses, the exact shortcut to the closure procedure is the Hommel (1988) multiple test procedure.
- So the Hommel procedure is more powerful than the Holm procedure.
- Since the Simes test controls $\alpha$ under independence/positive dependence but not under negative dependence, the Hommel procedure also controls/does not control FWER under the same conditions.
- Hochberg derived his procedure as a conservative shortcut to the exact shortcut to the closure procedure (i.e., Hommel procedure), so it also controls FWER under independence/positive dependence.
Hochberg Procedure Under Negative Dependence

- The common perception is that the Hochberg procedure may not control FWER under negative dependence.
- So practitioners are reluctant to use it if negative correlations are expected. They use the less powerful but more generally applicable Holm procedure.
- But the Hochberg procedure is conservative by construction.
- So, does it control FWER under also under negative dependence?
Conservative Simes Test

- Better to think of the Hochberg procedure as an exact stepwise shortcut to the closure procedure which uses a conservative Simes local $\alpha$-level test (Wei 1996).
- Conservative Simes test: Reject $H_0 = \bigcap_{i=1}^{n} H_i$ at level $\alpha$ if
  \[ p(i) \leq \frac{\alpha}{n - i + 1} \quad \text{for some } i = 1, \ldots, n. \]
- It is conservative because $\alpha/(n - i + 1) \leq i\alpha/n$ with equalities iff $i = 1$ and $i = n$.
- So the question of FWER control under negative dependence by the Hochberg procedure reduces to showing
  \[ \Pr \left( P(i) \leq \frac{\alpha}{n - i + 1} \quad \text{for some } i \right) \leq \alpha \]
  under negative dependence.
Conservative Simes Test

- For $n = 2$, the exact Simes test and the conservative Simes test are the same. So both are anti-conservative under negative dependence.
- Does the conservative Simes test remain conservative under negative dependence for $n > 2$?
Multivariate Uniform Distribution Models for $P$-Values

- Sarkar’s (1998) method, used by Block & Wang (2008) to show the anti-conservatism of the Simes test, does not work for the conservative Simes test since that method requires the critical constants $c_{n-i+1}$ used to compare with $p(i)$ to have the monotonicity property that $c_{n-i+1}/i$ must be nondecreasing in $i$.

- But for the conservative Simes test, $c_{n-i+1}/i = 1/i(n - i + 1)$ are decreasing (resp., increasing) in $i$ for $i \leq (n + 1)/2$ (resp., $i > (n + 1)/2$).

- To study the performance of the Simes/conservative Simes test under negative dependence we chose to use a multivariate uniform distribution for $P$-values.

- The distribution should be tractable enough to deal with ordered correlated multivariate uniform random variables.
Normal Model

- Let $X_1, \ldots, X_n$ be multivariate normal with $E(X_i) = 0$, $\text{Var}(X_i) = 1$ and $\text{Corr}(X_i, X_j) = \gamma_{ij}$ ($1 \leq i < j \leq n$).
- Define $P_i = \Phi(X_i)$ where $\Phi(\cdot)$ is the standard normal c.d.f.: one-sided marginal $P$-value.
- Then $P_i \sim U[0, 1]$ with $\rho_{ij} = \text{Corr}(P_i, P_j)$ a monotone and symmetric (around zero) function of $\gamma_{ij}$ ($1 \leq i < j \leq n$).

<table>
<thead>
<tr>
<th>$\gamma_{ij}$ = $\gamma$</th>
<th>0</th>
<th>0.1</th>
<th>0.3</th>
<th>0.5</th>
<th>0.7</th>
<th>0.9</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\rho_{ij}$ = $\rho$</td>
<td>0</td>
<td>0.0955</td>
<td>0.2876</td>
<td>0.4826</td>
<td>0.6829</td>
<td>0.8915</td>
<td>1</td>
</tr>
</tbody>
</table>

- This model is not analytically tractable.
Mixture Model

- $U_1, \ldots, U_n$ i.i.d. $U[0, \beta]$, $V_1, \ldots, V_n$ i.i.d. $U[\beta, 1]$, where $eta \in (0, 1)$ is fixed.
- Independent of the $U_i$'s and $V_i$'s, $W$ is Bernoulli with parameter $\beta$. Define
  
  $$X_i = U_i W + V_i (1 - W) \quad (1 \leq i \leq n).$$

- Let $Y_i$ be independent Bernoulli with parameters $\pi_i$ and define
  
  $$P_i = X_i Y_i + (1 - X_i)(1 - Y_i) \quad (1 \leq i \leq n).$$

  Then the $P_i$ are $U[0, 1]$ distributed with

  $$\text{Corr}(P_i, P_j) = \rho_{ij} = 3\beta (1-\beta)(2\pi_i-1)(2\pi_j-1) \quad (1 \leq i < j \leq n).$$

- Note that $-3/4 \leq \rho_{ij} \leq +3/4$ and $\rho_{ij} > 0 \Leftrightarrow \pi_i, \pi_j > 1/2$ or < 1/2.
- This model is also not analytically tractable.
Ferguson’s Model for $n = 2$

- Ferguson (1995) Theorem: Suppose $X$ is a continuous random variable with p.d.f. $g(x)$ on $x \in [0, 1]$. Let the joint p.d.f. of $(P_1, P_2)$ be given by

$$f(p_1, p_2) = \frac{1}{2} [g(|p_1 - p_2|) + g(1 - |1 - (p_1 + p_2)|)] \quad \text{for} \quad p_1, p_2 \in (0, 1).$$

Then $P_1, P_2$ are jointly distributed on the unit square with $U[0, 1]$ marginals and

$$\rho = \text{Corr}(P_1, P_2) = 1 - 6E(X^2) + 4E(X^3).$$
Ferguson’s Model for $n = 2$

- We chose

$$g(x) = \begin{cases} 
U[0, \theta] & \rho = (1 - \theta)(1 + \theta - \theta^2) > 0 \\
U[1 - \theta, 1] & \rho = -(1 - \theta)(1 + \theta - \theta^2) < 0.
\end{cases}$$

- If $\theta = 1$, i.e., $X \sim U[0, 1]$, then $\rho = 0$ for both models.
- If $\theta = 0$ then $\rho = +1$ if $g(x) = U[0, \theta]$ and $\rho = -1$ if $g(x) = U[1 - \theta, 1]$: point mass distributions with all mass at $(0, 0)$ and $(1, 1)$, respectively.
Ferguson’s Model for Bivariate Uniform Distribution

Left Panel: Positive correlation, Right Panel: Negative correlation
Ferguson’s Model for Multivariate Uniform Distribution

- Define the joint p.d.f. as

\[ f(p_1, \ldots, p_n) = \sum_{1 \leq i < j \leq n} w_{ij} f_{ij}(p_i, p_j) \]

for \( p_i, p_j \in [0, 1] \) where the \( w_{ij} \) are the mixing probabilities which sum to 1.

- We use \( g_{ij}(x) = U[0, \theta_{ij}] \) or \( g_{ij}(x) = U[1 - \theta_{ij}, 1] \) for +ve and −ve correlations, respectively.

- \( \text{Corr}(P_i, P_j) = \rho_{ij} \) are given by

\[ \rho_{ij} = \pm w_{ij} (1 - \theta_{ij})(1 + \theta_{ij} - \theta_{ij}^2). \]
Type I Error of the Simes Test for \( n = 2 \)

**Theorem:** For the Simes test, \( P = \Pr(\text{Type I Error}) \geq \alpha \) for all \( \rho \leq 0 \) under the Ferguson model with negative dependence.

\[
\max P = \frac{1}{2} \left( 1 + \alpha - \sqrt{1 - 2\alpha + \alpha^2/2} \right) > \alpha,
\]

and is achieved at \( \theta = \sqrt{1 - 2\alpha + \alpha^2/2}. \) \( \square \)

- For \( \alpha = 0.05 \), \( \max P = 0.0503 \) when \( \text{Corr}(P_1, P_2) = -0.053 \).

  For the bivariate normal model \( \max P = 0.0501 \) when \( \text{Corr}(P_1, P_2) = -0.184 \). These excesses are negligible.

- We can choose

\[
c_1 = 1, \quad c_2 = \left( 1 + \sqrt{\frac{1 - \alpha}{1 - 1.5\alpha}} \right)^{-1} < \frac{1}{2}
\]

to control \( \Pr(\text{Type I Error}) \leq \alpha \) for all \( \rho \leq 0 \) at a negligible loss of power.
Idea of the Proof for $n = 2$

$P = \begin{cases} 
\alpha & \text{(a): } 0 < \theta \leq 1 - 2\alpha \\
\alpha + \frac{(1-\theta-2\alpha)^2}{4\theta} & \text{(b): } 1 - 2\alpha < \theta \leq 1 - \frac{3}{2}\alpha \\
\alpha + \frac{1}{2}\alpha^2 - (1-\theta-\alpha)^2}{4\theta} & \text{(c): } 1 - \frac{3}{2}\alpha < \theta \leq 1 - \frac{1}{2}\alpha \\
\alpha + \frac{(1-\theta)^2}{4\theta} & \text{(d): } 1 - \frac{1}{2}\alpha < \theta < 1.
\end{cases}$
Type I Error of Conservative Simes Test for $n = 2$

Plot of type I error vs. $\text{Corr}(P_1, P_2)$ in the bivariate case for Ferguson’s model (solid curve) and Normal model (dashed curve) ($\alpha = 0.10$)
Type I Error of the Conservative Simes Test for $n \geq 3$

Proof of $\max P \leq \alpha$ for all negative correlations under the Ferguson model proceeds in two steps.

- First show that the result is true for $n = 3$. This is quite a laborious proof.
- Then use an induction argument to extend the result to all $n > 3$. 
Idea of the Proof for $n = 3$

The rejection region $\{p(3) \leq \alpha/1\} \cup \{p(2) \leq \alpha/2\} \cup \{p(1) \leq \alpha/3\}$ for $n = 3$: 

![Diagram](image-url)
Idea of the Proof for $n = 3$

- Slice the rejection region along the $p_3$-axis as shown above and find the probability of each two-dimensional slice using the results from the $n = 2$ case.
- This results in nine different expressions depending on the $\theta$ value for the bivariate distribution.
- Show that all nine expressions $\leq \alpha$. Hence their weighted sum (weighted by the probabilities of the slices) is $\leq \alpha$. 
Error Rate Control Under Negative Quadrant Dependence

**Theorem:** If \((P_1, \ldots, P_n)\) follow a multivariate uniform distribution which is a mixture of bivariate distributions \(f_{ij}(p_i, p_j)\) with mixing probabilities \(w_{ij} > 0\) where all pairs \((P_i, P_j)\) are negatively quadrant dependent then the conservative Simes test controls the type I error at level \(\alpha < 1/2\) for \(n \geq 4\). □

- **Negative Quadrant Dependence (Lehmann 1966):** Two random variables, \(X\) and \(Y\), are said to be negatively quadrant dependent if

  \[
  \Pr \{ (X \leq x) \cap (Y \leq y) \} \leq \Pr (X \leq x) \Pr (Y \leq y).
  \]

- The proof uses an upper bound on \(P(\text{Type I error})\) from Hochberg & Rom (1995).
Simulation Results

We performed simulations of type I error of the conservative Simes test for $n = 3, 5, 7$ for the following cases.

- **Equicorrelated normal model for**
  \[
  \gamma = -0.1/(n-1), -0.5/(n-1), -0.9/(n-1).
  \]

- **Mixture model with** $\beta = 0.1, 0.3, 0.5$ and each $\pi_i = 0.5 \pm \delta$ with $\delta = 0.1, 0.25, 0.4$ (more than half of the $\rho_{ij} < 0$).

- **Product-correlated normal model with the same correlation matrix as the mixture model.**

- **Ferguson model with the same correlation matrix as the mixture model:**
  - Uniform distribution: $g_{ij}(x) = U[0, \theta]$ or $g_{ij}(x) = U[1 - \theta, 1]$.
  - Beta distribution: $g_{ij}(x) = \text{Beta}(r, s)$.

- **All simulations show that the conservative Simes test and hence the Hochberg procedure remain conservative under negative dependence for $n \geq 3$.**
Conclusions

• Showed that the Simes test is anti-conservative under negative dependence using Ferguson’s model for \( n = 2 \). The amount of anti-conservatism is negligibly small.

• Showed that the critical constant \( c_2 \) of this test can be made slightly smaller than \( 1/2 \) to control \( P(\text{Type I error}) \) with negligible loss of power.

• Showed that the conservative Simes test remains conservative under negative dependence using Ferguson’s model for \( n \geq 3 \). The amount of conservatism increases with \( n \).

• Future research: Show that the conservative Simes test remains conservative under other negative dependence models, especially under the normal model.