Hochberg Multiple Test Procedure Under Negative Dependence

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Outline

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 ith 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.

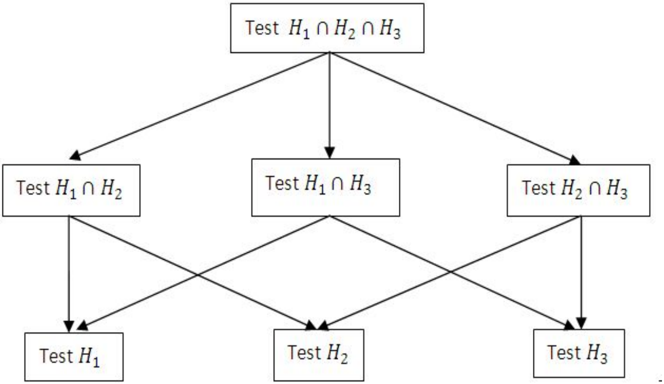
$$
\begin{array}{ccccccccc}
H_{(1)} & & H_{(2)} & & \cdots & & H_{(n-1)} & & H_{(n)} \\
p_{(1)} & \leq & p_{(2)} & \leq & \cdots & \leq & p_{(n-1)} & \leq & p_{(n)} \\
\frac{\alpha}{n} & & \frac{\alpha}{n-1} & & \cdots & & \frac{\alpha}{2} & & \frac{\alpha}{1}
\end{array}
$$

- 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 α-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 α-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 α 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:

$$\text{Pr}\left(P_{(i)} \leq \frac{i\alpha}{n} \text{ for some } i\right) = \alpha.$$

- Simes test is conservative under (certain types of) positive dependence: Sarkar & Chang (1997) and Sarkar (1998).
- Simes test is anti-conservative under (certain types of) negative dependence: Hochberg & Rom (1995), Samuel-Cahn (1996), Block, Savits & Wang (2008).

Hommel Procedure Under Negative Dependence

- When the Simes test is used as a local α-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 α 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 α-level test (Wei 1996).
- Conservative Simes test: Reject $H_0 = \bigcap_{i=1}^{n} H_i$ at level α if

$$p_{(i)} \leq \frac{\alpha}{n-i+1} \text{ for some } i = 1, \ldots, n.$$

- 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

$$\Pr\left(P_{(i)} \leq \frac{\alpha}{n-i+1} \text{ for some } i\right) \leq \alpha$$

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 γ_{ij} $(1 \leq i < j \leq n)$.

$\gamma_{ij} = \gamma$	0	0.1	0.3	0.5	0.7	0.9	1
$\rho_{ij} = \rho$	0	0.0955	0.2876	0.4826	0.6829	0.8915	1

- This model is not analytically tractable.

Mixture Model

- $U_1, \dots, U_n$ i.i.d. $U[0, \beta]$, $V_1, \dots, V_n$ i.i.d. $U[\beta, 1]$, where $\beta \in (0, 1)$ is fixed.
- Independent of the U_i's and V_i's, W is Bernoulli with parameter β. Define

$$X_i = U_i W + V_i(1 - W) \; (1 \leq i \leq n).$$

- Let Y_i be independent Bernoulli with parameters π_i and define

$$P_i = X_i Y_i + (1 - X_i)(1 - Y_i) \; (1 \leq i \leq n).$$

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

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

- 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

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

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

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

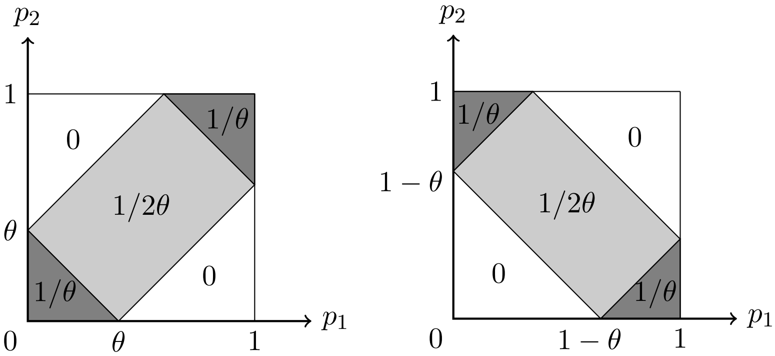
Ferguson's Model for $n = 2$

- 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.
- 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.

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

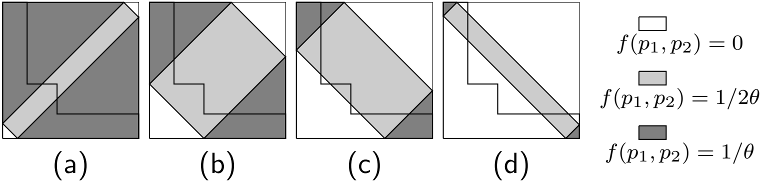
and is achieved at $\theta = \sqrt{1 - 2\alpha + \alpha^2/2}$. □

- For $\alpha = 0.05$, $\max P = 0.0503$ when Corr$(P_1, P_2) = -0.053$. For the bivariate normal model $\max P = 0.0501$ when Corr$(P_1, P_2) = -0.184$. These excesses are negligible.
- We can choose

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

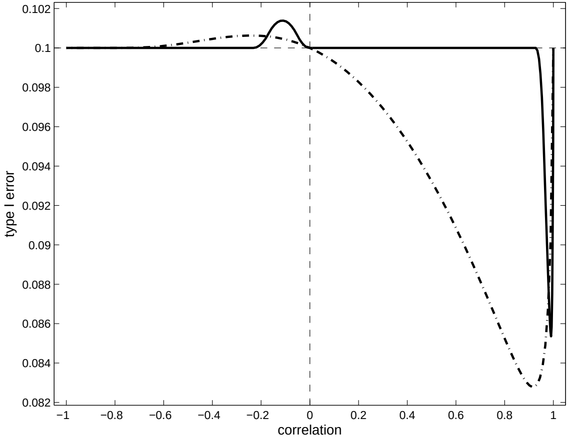
to control $\Pr(\text{Type I Error}) \leq \alpha$ for all $\rho \leq 0$ at a negligible loss of power.

Idea of the Proof for $n = 2$



$$P = \begin{cases} \alpha & \text{(a): } 0 < \theta \le 1 - 2\alpha \\ \alpha + \frac{(1-\theta-2\alpha)^2}{4\theta} & \text{(b): } 1 - 2\alpha < \theta \le 1 - \frac{3}{2}\alpha \\ \alpha + \frac{\frac{1}{2}\alpha^2 - (1-\theta-\alpha)^2}{4\theta} & \text{(c): } 1 - \frac{3}{2}\alpha < \theta \le 1 - \frac{1}{2}\alpha \\ \alpha + \frac{(1-\theta)^2}{4\theta} & \text{(d): } 1 - \frac{1}{2}\alpha < \theta < 1. \end{cases}$$

Type I Error of Conservative Simes Test for $n = 2$



Plot of type I error vs. Corr(P_1, P_2) in the bivariate case for Ferguson's model (solid curve) and Normal model (dashed curve) $(\alpha = 0.10)$

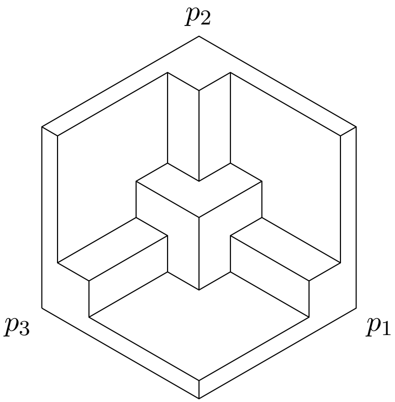
Type I Error of the Conservative Simes Test for $n \geq 3$

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

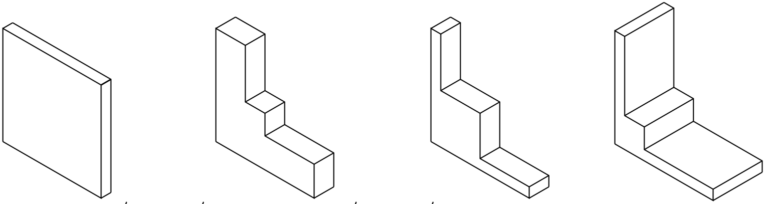
- First show that the result is true for $n = 3$. This is quite a laborious proof.
- Then use an induction argument to extend the result to all $n > 3$.

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 $n = 3$:



Idea of the Proof for $n = 3$



$0 \le p_3 \le \alpha/3$ $\alpha/3 \le p_3 \le \alpha/2$ $\alpha/2 \le p_3 \le \alpha$ $\alpha \le p_3 \le 1$

- 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 θ value for the bivariate distribution.
- Show that all nine expressions $\le \alpha$. Hence their weighted sum (weighted by the probabilities of the slices) is $\le \alpha$.

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(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.