

HOCHBERG PROCEDURE UNDER NEGATIVE DEPENDENCE

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Abstract: The Hochberg (1988) procedure is commonly used in practice to test multiple hypotheses based on their p -values. It is a conservative step-up shortcut to the closed procedure (Marcus, Peritz and Gabriel (1976)) based on the Simes (1986) test. The Simes test is anti-conservative if the test statistics are negatively dependent in a certain sense. So practitioners are reluctant to use the Hochberg procedure under this condition and prefer to use the less powerful Holm (1979) procedure, which requires no dependence assumptions. But the Hochberg procedure is conservative by construction, so we may conjecture that it will remain so under certain types of negative dependence. In this paper we show that a slightly modified version of the Hochberg procedure controls the familywise type I error rate (FWER) if the p -values follow a multivariate uniform distribution which is a mixture of bivariate components each of which is negative quadrant dependent (NQD) (Lehmann (1966)) or positive dependent through stochastic ordering (PDS) (Block, Savits and Shaked (1985)). By negative dependence we will mean this distribution model, in particular, that its negatively dependent bivariate components are NQD. Simulations suggest that conservatism of the Hochberg procedure is likely to be true for more general negatively dependent distributions.

Key words and phrases: Familywise type I error rate, multiple comparisons, multivariate uniform distribution, negative/positive quadrant dependence, negative/positive dependence through stochastic ordering, simes test.

1. Introduction

Consider the problem of testing $n \geq 2$ null hypotheses, H_1, \dots, H_n , based on their observed p -values, p_1, \dots, p_n . Denote the corresponding random variables (r.v.'s) by P_1, \dots, P_n . We restrict to multiple test procedures which satisfy the following strong type I FWER control requirement (Hochberg and Tamhane (1987)):

$$\text{FWER} = \Pr(\text{Reject at least one true } H_i) \leq \alpha, \quad (1.1)$$

for a given $\alpha \in (0, 1)$ under any combination of the true and false H_i 's.

The Holm (1979) procedure for this problem is a step-down shortcut to the closed procedure (Marcus, Peritz and Gabriel (1976)) based on the Bonferroni

test, that is used as the local α -level test for every nonempty intersection hypothesis $H(I) = \bigcap_{i \in I} H_i$ for $I \subseteq \{1, \dots, n\}$. The Simes (1986) test is more powerful than the Bonferroni test and so its use as a local test in the closed procedure results in a more powerful multiple test procedure, the Hommel (1988) procedure.

The Hochberg (1988) procedure is a conservative shortcut to the Hommel procedure, but is uniformly more powerful than the Holm procedure. Its testing algorithm is as simple as that of the Holm procedure: Denote by $p_{(1,n)} \leq \dots \leq p_{(n,n)}$ the ordered p -values, by $P_{(1,n)} \leq \dots \leq P_{(n,n)}$ the corresponding r.v.'s, and by $H_{(1,n)}, \dots, H_{(n,n)}$ the corresponding null hypotheses. At step 1, if $p_{(n,n)} \leq \alpha$ then reject all hypotheses and stop testing; otherwise retain $H_{(n,n)}$ and go to step 2. In general, at step $i = 1, \dots, n - 1$, if $p_{(n-i+1,n)} \leq \alpha/i$ then reject $H_{(n-i+1,n)}, \dots, H_{(1,n)}$ and stop testing; otherwise retain $H_{(n-i+1,n)}$ and go to step $i + 1$. At step n , reject $H_{(1,n)}$ if $p_{(1,n)} \leq \alpha/n$, else accept $H_{(1,n)}$ and stop testing. The Hochberg procedure is more commonly used in practice than the Hommel procedure because of its simplicity even though it is slightly less powerful (Dunnett and Tamhane (1993)).

The Bonferroni test does not make any assumptions on the joint distribution of the test statistics. While the Simes test is derived under the independence assumption. Sarkar (1998) has shown that the Simes test is conservative if the test statistics associated with the p -values have a multivariate totally positive of order 2 (MTP₂) distribution (Karlin and Rinott (1980)). Hochberg and Rom (1995) previously proved this result for the bivariate case. The special case of the bivariate normal distribution was studied by Samuel-Cahn (1996), who showed that the Simes test is conservative if the correlation coefficient of the distribution is positive, and anti-conservative if it is negative. Block, Savits and Wang (2008) extended the latter result to the class of negatively dependent distributions satisfying the so-called N condition introduced in Block, Savits and Shaked (1982). They further extended the result to the more general class, known as negatively dependent through stochastic ordering (NDS) class of distributions.

These results cast doubt on the validity of the Hochberg procedure under negative dependence. So practitioners prefer to use the less powerful Holm procedure, which is valid without any dependence assumptions, being based on the Bonferroni test. However, the Hochberg procedure is conservative by construction and so we may conjecture that it will remain so under certain types of negative dependence. Such a finding would make it more widely applicable. The goal of the present paper is to explore this conjecture.

We can restrict attention to one-sided hypotheses since the Simes test has

been shown to be valid under either positive or negative dependent test statistics for two-sided hypotheses by Sarkar (1998) and Block et al. (2013). Under one-sided null hypotheses $H_i : \theta_i \leq \theta_{i0}$, we have $\Pr(P_i \leq p_i) \leq p_i$ ($1 \leq i \leq n$). If monotone likelihood ratio (MLR) tests are used to test these hypotheses then, according to the Karlin-Rubin theorem (see Theorem 8.3.17 in Casella and Berger (2002)), the maximum type I error is achieved at $\theta_i = \theta_{i0}$, where $\Pr(P_i \leq p_i) = p_i$ ($1 \leq i \leq n$). Thus we may assume that the P_i 's are uniformly distributed on $[0, 1]$ (denoted by $P_i \sim U[0, 1]$) under the respective H_i 's ($1 \leq i \leq n$). The main result of the paper in Theorem 1 can be shown to be valid under the more general assumption that $\Pr(P_i \leq p_i) \leq p_i$ ($1 \leq i \leq n$).

The Hochberg procedure itself cannot be shown to be conservative under negative dependence. This is known for $n = 2$ since the Simes test is anti-conservative in this case; we show that it is also true for $n = 3$. Therefore we need to modify the critical constants of the Hochberg procedure for $n = 2$ and 3 which makes it slightly conservative. We refer to the resulting procedure as the modified Hochberg (*m-Hochberg*) procedure. The main result of the paper is that the m-Hochberg procedure is conservative under negative dependence.

The outline of the paper is as follows. Section 2 gives the steps leading up to the m-Hochberg procedure. We begin with the Simes test and the Hommel procedure which is based on it. The Hochberg procedure is obtained as an exact stepwise shortcut to a closed procedure that is based on a conservative Simes test (*c-Simes test*), presented next. To control the FWER of the Hochberg procedure under negative dependence a slightly modified conservative Simes test (*mc-Simes test*) must be used as a local test of intersection hypotheses in a closed procedure, the resulting step-up shortcut being the m-Hochberg procedure. Section 3 states the main result of the paper and the lemmas needed to prove it; the proofs of the lemmas and the main result are given in Appendix A. Section 4 presents simulation results that indicate that the Hochberg procedure is conservative under several negatively dependent distributions. Section 5 provides a discussion of tests of the NQD assumption and some concluding remarks. Besides the proof of the main result, all the supplementary materials are included in the Appendix. Appendix B describes three multivariate uniform distributions that can be used to model the joint distribution of the P -values. Appendix C gives definitions of some concepts of positive and negative dependence. Appendix D gives three counterexamples to show why some results cannot be extended to a wider class of dependent distributions.

2. Modified Hochberg Procedure

We begin with a generalized Simes test defined by Gou and Tamhane (2014). It rejects $H_0 = \bigcap_{i=1}^n H_i$ at level α if

$$p_{(n-i+1,n)} \leq c_{ni}\alpha \quad \text{for at least one } i = 1, \dots, n. \quad (2.1)$$

Suppose this test is used as an α -level local test of every intersection hypothesis $H(I) = \bigcap_{i \in I} H_i$ of a closed testing procedure, and that its critical constants (modulo a common multiplying factor α) are laid out in the form of a lower triangular matrix, referred to as the *critical matrix*,

$$\begin{bmatrix} c_{11} & & & & \\ c_{21} & c_{22} & & & \\ c_{31} & c_{32} & c_{33} & & \\ \vdots & \vdots & \vdots & \ddots & \\ c_{n1} & c_{n2} & \cdots & \cdots & c_{nn} \end{bmatrix}.$$

Liu (1996) showed that if every column of this matrix has equal entries then that closed procedure has a step-up shortcut with its critical constants given by the last row of the matrix. (Similarly, if every row has equal entries then the closed procedure has a step-down shortcut with its critical constants given by the first column.)

The Simes test uses $c_{ji} = (j - i + 1)/j$ for $1 \leq i \leq j \leq n$, which control the α level exactly under independence. The critical matrix for the Simes test does not have either constant rows or constant columns and so the closed procedure based on it does not have a simple step-up or step-down shortcut, that procedure being the Hommel (1988) procedure.

The c-Simes test uses constant column entries $c_{ji} = c_i = 1/i$ for $1 \leq i \leq j \leq n$. Since $1/i \leq (j - i + 1)/j$, with equalities if and only if $i = 1$ and $i = j$, it is clear that the c-Simes test is conservative compared to the Simes test for $n > 2$; for $n = 2$ the two tests are identical. The Hochberg procedure is the exact step-up shortcut to the closed procedure based on the c-Simes test. In fact, it is most easily derived in this way rather than as a conservative shortcut to the Hommel procedure.

Unfortunately, the c-Simes test does not control the type I error for $n = 2$ and $n = 3$ under negative dependence. Since local tests of intersection hypotheses of all cardinalities $n \geq 1$ must be of level α in order that the resulting closed procedure controls the FWER requirement (1.1), we need to modify the critical constants c_2 and c_3 of the c-Simes test. In Lemma 4 we show that these modified

critical constants are

$$c_2 = \frac{1}{2} - \frac{\alpha}{2} \quad \text{and} \quad c_3 = \frac{1}{3} - \frac{\alpha}{36}. \quad (2.2)$$

The other critical constants are the same as those of the c-Simes test, namely, $c_i = 1/i$. We refer to the resulting test as the mc-Simes test and the exact step-up shortcut to the closed procedure based on this test as the m-Hochberg procedure. The m-Hochberg procedure operates in the same way as the Hochberg procedure, except that it uses the slightly more conservative critical constants c_2 and c_3 given by (2.2) at steps 2 and 3, respectively. In Section 3 we show that the mc-Simes test is conservative under negative dependence,

$$\Pr(P_{(n-i+1,n)} \leq c_i \alpha \text{ for at least one } i = 1, \dots, n) \leq \alpha, \quad (2.3)$$

where c_2 and c_3 are given by (2.2) and all other $c_i = 1/i$. Hence it follows that the m-Hochberg procedure controls the FWER (1.1).

3. Main Result

Our main result is based on the assumption that the joint multivariate uniform distribution of (P_1, \dots, P_n) under $H_0 = \bigcap_{i=1}^n H_i$ is given by the bivariate mixture model,

$$f(p_1, \dots, p_n) = \sum_{1 \leq i < j \leq n} w_{ij} f_{ij}(p_i, p_j), \quad (3.1)$$

where $f_{ij}(p_i, p_j)$ is the bivariate p.d.f. of (P_i, P_j) , and $w_{ij} > 0$ are the mixing probabilities that sum to 1. The choice of $f_{ij}(p_i, p_j)$ can be arbitrary.

Theorem 1. *The mc-Simes test satisfies (2.3) for $\alpha < 2(1 + \sqrt{94})/31 \approx 0.69$ for all $n \geq 2$ under the mixture model (3.1), where each bivariate marginal distribution $f_{ij}(p_i, p_j)$ is either positively dependent through stochastic ordering (PDS) or negative quadrant dependent (NQD). Hence the m-Hochberg procedure satisfies (1.1) under the same class of distributions.*

Because of (3.1), we only need to consider whether each $f_{ij}(p_i, p_j)$ is positively dependent or negatively dependent. In practice, some (P_i, P_j) pairs are positively dependent while others are negatively dependent. In (3.3) we show that the type I error of the mc-Simes test is a weighted sum of the type I error probabilities computed under the respective bivariate components of the mixture distribution. Thus we need to show that each of these bivariate type I error probabilities is $\leq \alpha$ under either positive dependence or negative dependence. Block, Savits and Wang (2008) in their Theorem 2 have extended Sarkar's (1998) result about the conservatism of the Simes test (and hence also of the mc-Simes test)

from MTP_2 to PDS distributions. This result does not extend to the larger class of PQD distributions, as shown by a counterexample in Appendix D. Hence from now on we assume that any positively dependent bivariate component belongs to the PDS class of distributions. Thus we only need to consider the case of negatively dependent bivariate components.

For NDS distributions, Block, Savits and Wang (2008) showed that the Simes test is anti-conservative by using a method of Sarkar (1998). This method requires that the critical constants of the test satisfy that the ratios c_{n-i+1}/i are non-decreasing in i . This property is satisfied by the Simes critical constants since $c_{n-i+1} = i/n$ and so c_{n-i+1}/i is constant $= 1/n$. As the c-Simes critical constants, $c_{n-i+1}/i = 1/[i(n-i+1)]$, are decreasing in i for $i \leq (n+1)/2$ and increasing in i for $i > (n+1)/2$, we cannot apply Sarkar's method.

The proof of the main result is achieved through a series of lemmas. From now on we restrict to generalized Simes tests with a critical matrix having constant column entries c_i .

Lemma 1. *If the type I error probability of a generalized Simes test is*

$$P[n; C_n | \alpha] \equiv \Pr \left(\bigcup_{i=1}^n \{P_{(n-i+1:n)} \leq c_i \alpha\} \right), \quad (3.2)$$

where $C_n = \{c_1, \dots, c_n\}$, then under (3.1),

$$P[n; C_n | \alpha] = \sum_{1 \leq i < j \leq n} w_{ij} P_{ij}[n; C_n | \alpha], \quad (3.3)$$

where $P_{ij}[n; C_n | \alpha]$ is the same probability as in (3.2), but calculated under f_{ij} .

We have an induction formula for $P_{ij}[n; C_n | \alpha]$.

Lemma 2. *Under (3.1), we have*

$$P_{ij}[n; C_n | \alpha] = c_n \alpha + \sum_{k=1}^n \alpha (c_{k-1} - c_k) P_{ij}[n-1; C_n \setminus \{c_k\} | \alpha], \quad (3.4)$$

where $c_0 = 1/\alpha$ and $C_n \setminus \{c_k\} = \{c_1, \dots, c_{k-1}, c_{k+1}, \dots, c_n\}$.

Lemma 3. *If the critical constants are $c_i = 1/i$ ($1 \leq i \leq n$) then*

$$P[n-1; C_{n-1} | \alpha] \leq \alpha \implies P[n; C_n | \alpha] \leq \alpha.$$

Remark 1. This lemma uses the c-Simes test critical constants, $c_i = 1/i$ ($1 \leq i \leq n$). In Lemma 4 we show that we need to choose $c_2 < 1/2$ and $c_3 < 1/3$ in order to control $P_{ij}[n; C_n | \alpha] \leq \alpha$ under all bivariate NQD distributions. Thus, for $n = 2$ and 3 , $c_i = 1/i$ is not satisfied and Lemma 3 does not apply. In

Lemma 5 we show that for $n = 4$, the inequality is satisfied under the NQD assumption for $c_4 = 1/4$ if $\alpha < 0.69$. Thus we can then apply Lemma 3 and conclude that, because the modified values of c_2 and c_3 are more conservative than $1/2$ and $1/3$, respectively, the inequality is satisfied for all $n \geq 2$.

Lemma 4. *For $n = 2$, if the distribution of (P_1, P_2) is NQD then*

$$P[2; C_2|\alpha] \leq 2c_2\alpha + c_1^2\alpha^2. \quad (3.5)$$

With $c_1 = 1$, the mc-Simes test satisfies (2.3) if c_2 is given by (2.2). For $n = 3$, if the distribution of (P_1, P_2, P_3) is NQD then

$$P[3; C_3|\alpha] \leq 3c_3\alpha + c_2(3c_2 - 4c_3)\alpha^2 + c_1(c_1^2 - c_2^2 - c_1c_3)\alpha^3. \quad (3.6)$$

With $c_1 = 1$ and $c_2 = (1 - \alpha)/2$, the mc-Simes test satisfies (2.3) if

$$c_3 = \left(\frac{1 - \alpha}{3}\right) \left[\frac{1 + (\alpha/4) + \alpha^2 - (\alpha^3/4)}{1 - (2\alpha/3) + (\alpha^2/3)}\right]. \quad (3.7)$$

For practical application we recommend a slightly more conservative but simpler lower bound on c_3 given by (2.2). This bound is valid when $\alpha < (22 - \sqrt{367})/9 \approx 0.31$. For $\alpha = 0.05$, we get $c_2 = 0.475$ from (2.2) and $c_3 = 0.3322$ from (3.7). If we use (2.2) then we get $c_3 = 0.3319$.

Lemma 5. *For $n = 4$, if the distribution of (P_1, P_2, P_3, P_4) is NQD and $c_1 = 1, c_2 = 1/2 - \alpha/2, c_3 = 1/3 - \alpha/36$ and $c_4 = 1/4$ then*

$$P[4; C_4|\alpha] \leq \alpha - \frac{1}{6}\alpha^2 + \frac{1}{18}\alpha^3 + \frac{31}{72}\alpha^4.$$

This upper bound is $< \alpha$ if $\alpha < 2(1 + \sqrt{94})/31 \approx 0.69$ and so $P[4; C_4|\alpha] < \alpha$.

4. Simulation Study

We performed simulations of the type I error rate of the c-Simes test under the three distribution models given in Appendix B, for $n = 3, 5$ and 7 , using MATLAB. Since the mc-Simes test is more conservative than the c-Simes test, it controls the type I error if the c-Simes test does. We chose the parameters of the three distribution models so that they had the same correlations among the P_i 's. Toward this end, we chose the BU model as the reference model, then chose the parameters of the other two models to match with the BU model correlations. Each simulation consisted of 10^9 replications, which gives four decimal place accuracy. Simulation results for the equicorrelated normal model are given in Table 1. Simulation results for the other models are given in Table 2.

4.1. Distribution models

The multivariate uniform distribution models used for simulation are ex-

plained in Appendix B.

Bernoulli-Uniform (BU) Model: Here we chose $\pi_i = 0.5 - \delta$ for $i \leq m$ and $\pi_i = 0.5 + \delta$ for $i > m$, where $m = \lfloor n/2 \rfloor$ and $\delta = 0.1, 0.25, 0.4$; thus $\pi_i = 0.4$ or $0.6, 0.25$ or 0.75 , and 0.1 or 0.9 . We took β to be $0.1, 0.3$ and 0.5 (the correlations given by (B.4) are symmetric around $\beta = 0.5$, so we need not consider $\beta > 0.5$). From (B.4) we get $\rho_{ij} = \pm\rho = \pm 12\beta(1 - \beta)\delta^2$ ($1 \leq i < j \leq n$), positive if $i, j \leq m$ or $i, j > m$, and negative if $i \leq m$ and $j > m$. Thus $m(n - m)$ of the ρ_{ij} are < 0 and the remaining $\binom{n}{2} - m(n - m)$ of the ρ_{ij} are > 0 . Table 2 gives the values of $\pm\rho$ for different combinations of β and δ .

Multivariate Normal (MVN) Model: For this model we studied product correlation and equal correlation. The parameters of the product correlation model were chosen to match the correlations for the BU model. Specifically, $\text{Corr}(Z_i, Z_j) = \gamma_{ij} = \lambda_i \lambda_j$ where $\lambda_i \in (-1, 1)$. We set $\lambda_i = -\lambda$ for $i \leq m$ and $\lambda_i = +\lambda$ for $i > m$, where $m = \lfloor n/2 \rfloor$ so that $\gamma_{ij} = \gamma = \lambda^2$ if $i, j \leq m$ or $i, j > m$ and $\gamma_{ij} = -\gamma = -\lambda^2$ if $i \leq m$ and $j > m$. Then we numerically solved for γ from the equation $h(\gamma) = \rho$, where $h(\cdot)$ is defined in (B.1). The γ -values for the product correlation model are listed in Table 2. For the equal correlation model we chose $\gamma = -0.1/(n - 1), -0.5/(n - 1)$ and $-0.9/(n - 1)$, representing small to large negative correlations, where $-1/(n - 1)$ is the maximum negative correlation for given n .

Ferguson Model: To match the pairwise correlations $\rho_{ij} = \pm\rho$ given in Table 2 we chose the positive dependence Ferguson distribution with $g_{ij}(x) = U[0, \theta]$ if $i, j \leq m$ or $i, j > m$ and the negative dependence Ferguson distribution with $g_{ij}(x) = U[1 - \theta, 1]$ if $i \leq m$ and $j > m$. Then we chose θ to solve $\rho = w_{ij}(1 - \theta)(1 + \theta - \theta^2)$, where $w_{ij} = 1/\binom{n}{2}$. A solution in θ does not exist to this equation if $(1 - \theta)(1 + \theta - \theta^2) > 1/\binom{n}{2}$. These cases are marked as N/A in Table 2. To see whether the type I error control is still maintained if the distribution $g_{ij}(x)$ is other than the uniform distribution, we chose the beta distribution on $[0, 1]$ with parameters (r, s) (denoted by $B(r, s)$). We chose (r, s) to match the mean and correlation of the Ferguson distribution with that obtained using $g_{ij}(x) = U[0, \theta]$ if $i, j \leq m$ or $i, j > m$ if ρ is positive, and $g_{ij}(x) = U[1 - \theta, 1]$ if $i \leq m$ and $j > m$ if ρ is negative. The k th moment of the $B(r, s)$ distribution is given by $E(X^k) = (\Gamma(r + k)\Gamma(r + s))/(\Gamma(r)\Gamma(r + s + k))$. Using this formula we get the following expressions for its mean and correlation: $E[B(r, s)] = r/(r + s)$ and $\rho = 1 - (2r(r + 1)(r + 3s + 2))/((r + s)(r + s + 1)(r + s + 2))$. Equating $E[B(r, s)]$ to $\theta/2$ or $1 - \theta/2$, and ρ to $(1 - \theta)(1 + \theta - \theta^2)$ or to $-(1 - \theta)(1 + \theta - \theta^2)$ we get solutions to the resulting equations. For $\rho > 0$:

Table 1. Simulated type I error (%) of the c-Simes test for equicorrelated MVN model.

n	$\text{Corr}(Z_i, Z_j) = \gamma$	$\text{Corr}(P_i, P_j) = \rho$	Type I Error (%)
3	-0.0500	-0.0478	4.957
	-0.2500	-0.2394	4.994
	-0.4500	-0.4334	5.000
5	-0.0250	-0.0239	4.923
	-0.1250	-0.1194	4.967
	-0.2250	-0.2153	4.988
7	-0.0167	-0.0159	4.909
	-0.0833	-0.0796	4.949
	-0.1500	-0.1434	4.973

$$r = \frac{3\sqrt{1-\theta}}{2} \left(\sqrt{1-\theta} + \sqrt{1-\frac{5\theta}{9}} \right) \quad \text{and} \quad s = \frac{2-\theta}{\theta} r$$

and for $\rho < 0$:

$$s = \frac{3\sqrt{1-\theta}}{2} \left(\sqrt{1-\theta} + \sqrt{1-\frac{5\theta}{9}} \right) \quad \text{and} \quad r = \frac{2-\theta}{\theta} s.$$

Here $r < s$ for $\rho > 0$ and $r > s$ for $\rho < 0$. In Table 2, (r, s) has $r < s$. We use the $B(r, s)$ distribution for $g(x)$ to obtain $\rho > 0$, and the $B(s, r)$ distribution for $g(x)$ to obtain $\rho < 0$, for any given pair (r, s) .

4.2. Simulation results

From Tables 1 and 2 we see that the type I error is controlled at the 5% level in all cases studied. The dependence of the type I error on the correlation is most clearly seen in Table 1 for the equicorrelated normal model since all correlations are equal and negative in each case. We see that for each n , as the common correlation decreases, the type I error increases, approaching 5% for $n = 3$ with common correlation $\gamma = -0.45$. Even across different values of n , the type I error generally increases as γ decreases.

5. Discussion

Positive dependence is more common in practice than negative dependence. For example in clinical trial applications, multiple efficacy endpoints are generally positively correlated. However, regulatory agencies require them to be not too highly correlated since otherwise they would be proxies of each other. Thus some independent efficacy endpoints end up with small negative correlations due to sampling errors. A situation where efficacy endpoints may be negatively cor-

Table 2. Simulated type I error (%) of the c-Simes test for BU, MVN and bivariate mixture models.

n	BU Model Parameters		Normal Model Parameter	Beta Model Parameters		Corr. ρ	Type I Error (%)			
	β	δ	$\pm\gamma$	r	s		Product-Corr. Normal	BU	Ferguson Uniform	Ferguson Beta
3	0.1	0.1	± 0.0113	0.2279	0.2427	± 0.0108	4.940	4.855	4.954	4.778
	0.3	0.1	± 0.0264	0.3843	0.4429	± 0.0252	4.941	4.929	4.951	4.857
	0.5	0.1	± 0.0314	0.4293	0.5076	± 0.0300	4.941	4.941	4.951	4.873
	0.1	0.25	± 0.0707	0.7297	1.0431	± 0.0675	4.942	4.838	4.950	4.933
	0.3	0.25	± 0.1647	1.3249	2.9646	± 0.1575	4.944	4.927	4.948	4.953
	0.5	0.25	± 0.1960	1.5159	4.0053	± 0.1875	4.944	4.945	4.947	4.954
	0.1	0.4	± 0.1807	1.4220	3.4564	± 0.1728	4.944	4.815	4.947	4.954
	0.3	0.4	± 0.4191	N/A	N/A	± 0.4032	4.944	4.929	N/A	N/A
	0.5	0.4	± 0.4974	N/A	N/A	± 0.4800	4.942	4.952	N/A	N/A
5	0.1	0.1	± 0.0113	0.4825	0.5887	± 0.0108	4.908	4.742	4.912	4.871
	0.3	0.1	± 0.0264	0.8464	1.3116	± 0.0252	4.908	4.887	4.911	4.905
	0.5	0.1	± 0.0314	0.9548	1.5994	± 0.0300	4.908	4.908	4.911	4.908
	0.1	0.25	± 0.0707	1.7630	5.9142	± 0.0675	4.909	4.728	4.908	4.915
	0.3	0.25	± 0.1647	N/A	N/A	± 0.1575	4.910	4.887	N/A	N/A
	0.5	0.25	± 0.1960	N/A	N/A	± 0.1875	4.910	4.912	N/A	N/A
	0.1	0.4	± 0.1807	N/A	N/A	± 0.1728	4.910	4.719	N/A	N/A
	0.3	0.4	± 0.4191	N/A	N/A	± 0.4032	4.903	4.890	N/A	N/A
	0.5	0.4	± 0.4974	N/A	N/A	± 0.4800	4.897	4.919	N/A	N/A
7	0.1	0.1	± 0.0113	0.7878	1.1717	± 0.0108	4.898	4.713	4.899	4.895
	0.3	0.1	± 0.0264	1.4449	3.5832	± 0.0252	4.899	4.874	4.898	4.900
	0.5	0.1	± 0.0314	1.6624	5.0409	± 0.0300	4.899	4.895	4.897	4.900
	0.1	0.25	± 0.0707	N/A	N/A	± 0.0675	4.899	4.702	N/A	N/A
	0.3	0.25	± 0.1647	N/A	N/A	± 0.1575	4.898	4.874	N/A	N/A
	0.5	0.25	± 0.1960	N/A	N/A	± 0.1875	4.897	4.899	N/A	N/A
	0.1	0.4	± 0.1807	N/A	N/A	± 0.1728	4.898	4.697	N/A	N/A
	0.3	0.4	± 0.4191	N/A	N/A	± 0.4032	4.885	4.876	N/A	N/A
	0.5	0.4	± 0.4974	N/A	N/A	± 0.4800	4.878	4.905	N/A	N/A

related is when one of the endpoints is a censoring event such as death, which censors the occurrence of other morbidity outcomes such as number of hospitalizations or strokes or heart attacks. Thus increase in the number of deaths tends to decrease these outcomes. Another example in diabetes the efficacy measures such as A1c and fasting serum glucose level and body weight are negatively correlated, i.e., drops in sugar levels are accompanied by gains in body weight; see <http://www.health.com/health/gallery/0,,20545602,00.html>. The efficacy and safety endpoints are often negatively correlated because if a drug is administered at a higher dose it is more effective, but also has possible adverse side-effects.

To conclude, we have analytically shown that the mc-Simes test and hence

the m-Hochberg procedure continues to be conservative under the class of bivariate mixture models where each bivariate component is either PDS or NQD. We have verified this result by simulation for other selected distributions for the less conservative c-Simes test, on which the original Hochberg procedure is based. Therefore the use of the Hochberg procedure can be advocated for negatively correlated test statistics for many cases of practical interest. An important interesting topic for future research is to extend the results of this paper to the class of MVN distributions defined in Appendix B.

Appendix

A. Proof of the Main Result

Proof of Lemma 1

Proof. Let $\mathcal{R} = \bigcup_{i=1}^n \{P_{(i:n)} \leq c_{n-i+1}\alpha\}$ denote the rejection region of the mc-Simes test. Then

$$\begin{aligned} P[n; C_n | \alpha] &= \int \cdots \int_{\mathcal{R}} f(p_1, \dots, p_n) dp_1 \cdots dp_n \\ &= \int \cdots \int_{\mathcal{R}} \sum_{1 \leq i < j \leq n} w_{ij} f_{ij}(p_i, p_j) dp_1 \cdots dp_n \\ &= \sum_{1 \leq i < j \leq n} w_{ij} \int \cdots \int_{\mathcal{R}} f_{ij}(p_i, p_j) dp_1 \cdots dp_n \\ &= \sum_{1 \leq i < j \leq n} w_{ij} P_{ij}[n; C_n | \alpha]. \end{aligned}$$

In the following, for the most part we use the critical constants $c_i = 1/i$, although some results are true for more general critical constants c_i 's satisfying $1 = c_1 > \cdots > c_n$.

Proof of Lemma 2

Proof. For $n = 2$, the formula (3.4) is true under independence, as follows. First from Figure 1, by direct computation we get

$$\begin{aligned} P[2; C_2 | \alpha] &= \Pr(\{P_{(2,2)} \leq c_1\alpha\} \cup \{P_{(1,2)} \leq c_2\alpha\}) \\ &= \Pr(P_1 \leq c_1\alpha, P_2 \leq c_1\alpha) + 2\Pr(c_1\alpha \leq P_1 \leq 1, P_2 \leq c_2\alpha) \\ &= 2c_2\alpha(1 - c_1\alpha) + c_1^2\alpha^2. \end{aligned}$$

Next we check that using (3.4) we get the same expression:

$$P[2; C_2 | \alpha] = c_2\alpha + \sum_{k=1}^2 \alpha(c_{k-1} - c_k)P[1; C_2 \setminus \{c_k\} | \alpha]$$

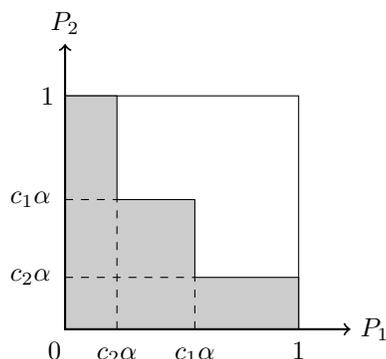


Figure 1. Rejection region of the generalized Simes test for $n = 2$.

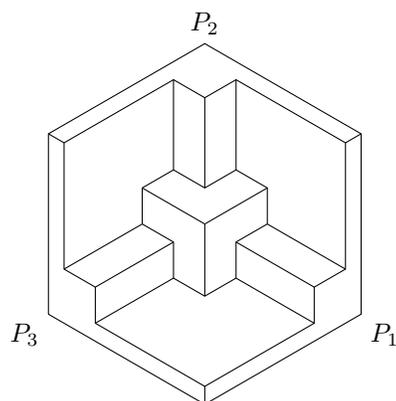


Figure 2. Rejection region $\{P_{(3:3)} \leq c_1\alpha\} \cup \{P_{(2:3)} \leq c_2\alpha\} \cup \{P_{(1:3)} \leq c_3\alpha\}$.

$$\begin{aligned}
 &= c_2\alpha + \alpha(c_0 - c_1) \Pr(P_1 \leq c_2\alpha) + \alpha(c_1 - c_2) \Pr(P_1 \leq c_1\alpha) \\
 &= c_2\alpha + (1 - c_1\alpha)c_2\alpha + (c_1 - c_2)c_1\alpha^2 \\
 &= 2c_2\alpha(1 - c_1\alpha) + c_1^2\alpha^2.
 \end{aligned}$$

If $c_1 = 1, c_2 = 1/2$ then $P[2; C_2|\alpha] = \alpha$, as expected.

For $n = 3$, the rejection region is shown in Figure 2 and the four slices of this rejection region obtained by conditioning on P_3 are shown in Figure 3.

If (P_1, P_2, P_3) follows the bivariate mixture model (3.1), then P_k for $k \neq i, j$ is independent of (P_i, P_j) and is $U[0, 1]$. So by conditioning on P_k , we can evaluate the type I error probability in terms of $f_{ij}(p_i, p_j)$. For example, if $(i, j) = (1, 2)$ and $k = 3$, by conditioning on P_3 to each of the four slices of the rejection region shown in Figure 3, we can write

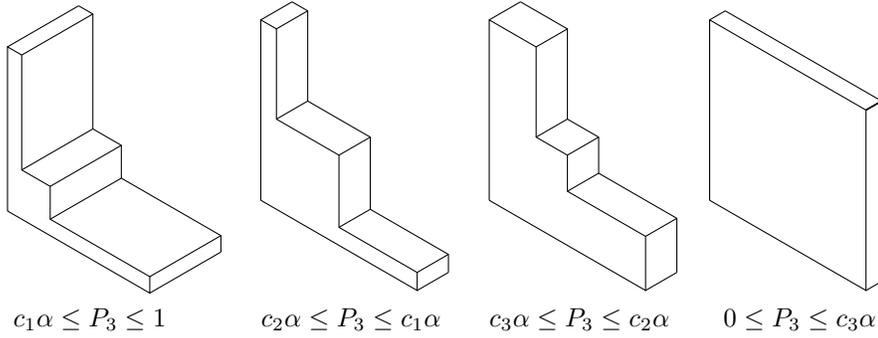


Figure 3. Slices of the rejection region in Figure 2 along the P_3 -axis.

$$\begin{aligned}
 P_{12} [3; C_3 | \alpha] &= \Pr (\{P_{(3:3)} \leq c_1 \alpha\} \cup \{P_{(2:3)} \leq c_2 \alpha\} \cup \{P_{(1:3)} \leq c_3 \alpha\}) \\
 &= (1 - c_1 \alpha) \Pr (\{P_{(2:2)} \leq c_2 \alpha\} \cup \{P_{(1:2)} \leq c_3 \alpha\}) \\
 &\quad + (c_1 \alpha - c_2 \alpha) \Pr (\{P_{(2:2)} \leq c_1 \alpha\} \cup \{P_{(1:2)} \leq c_3 \alpha\}) \\
 &\quad + (c_2 \alpha - c_3 \alpha) \Pr (\{P_{(2:2)} \leq c_1 \alpha\} \cup \{P_{(1:2)} \leq c_2 \alpha\}) \\
 &\quad + (c_3 \alpha - 0) \times 1.
 \end{aligned} \tag{A.1}$$

This probability depends on the joint distribution f_{12} of (P_1, P_2) since each of the bivariate probability terms in the above expression involve the order statistics $P_{(1:2)}$ and $P_{(2:2)}$ of (P_1, P_2) ; as such we denote this probability by P_{12} . The bivariate probability of the slice for $0 \leq P_3 \leq c_3 \alpha$ is 1 because in that slice, (P_1, P_2) lies in the unit square. The terms in (A.1) can be rearranged to obtain

$$P_{12} [3; C_3 | \alpha] = c_3 \alpha + \sum_{k=1}^3 \alpha (c_{k-1} - c_k) P_{12} [2; C_3 \setminus \{c_k\} | \alpha],$$

where $c_0 = 1/\alpha$.

Slicing the rejection region by conditioning on one of the P_i 's for different ranges of its values, and writing the type I error probability in terms of the remaining P_j 's can be applied in higher dimensions. As a further example, for $n = 4$ the expression for any bivariate distribution f_{ij} can be written as

$$\begin{aligned}
 P_{ij} [4; C_4 | \alpha] &= \Pr (\{P_{(4:4)} \leq \alpha\} \cup \{P_{(3:4)} \leq c_2 \alpha\} \cup \{P_{(2:4)} \leq c_3 \alpha\} \cup \{P_{(1:4)} \leq c_4 \alpha\}) \\
 &= (1 - c_1 \alpha) \Pr (\{P_{(3:3)} \leq c_2 \alpha\} \cup \{P_{(2:3)} \leq c_3 \alpha\} \cup \{P_{(1:3)} \leq c_4 \alpha\}) \\
 &\quad + (c_1 \alpha - c_2 \alpha) \Pr (\{P_{(3:3)} \leq c_1 \alpha\} \cup \{P_{(2:3)} \leq c_3 \alpha\} \cup \{P_{(1:3)} \leq c_4 \alpha\}) \\
 &\quad + (c_2 \alpha - c_3 \alpha) \Pr (\{P_{(3:3)} \leq c_1 \alpha\} \cup \{P_{(2:3)} \leq c_2 \alpha\} \cup \{P_{(1:3)} \leq c_4 \alpha\}) \\
 &\quad + (c_3 \alpha - c_4 \alpha) \Pr (\{P_{(3:3)} \leq c_1 \alpha\} \cup \{P_{(2:3)} \leq c_2 \alpha\} \cup \{P_{(1:3)} \leq c_3 \alpha\}) \\
 &\quad + (c_4 \alpha - 0) \times 1,
 \end{aligned} \tag{A.2}$$

which is obtained by conditioning on, say, P_ℓ , and where $P_{(1:3)} \leq P_{(2:3)} \leq P_{(3:3)}$ are the order statistics of (P_i, P_j, P_k) for $i \neq j \neq k \neq \ell$. Upon further conditioning on P_k , each of the trivariate probability terms can be written in terms of the order statistics of (P_i, P_j) . We denote the above expression by P_{ij} and rearrange it to obtain

$$P_{ij} [4; C_4 | \alpha] = c_4 \alpha + \sum_{k=1}^4 \alpha (c_{k-1} - c_k) P_{ij} [3; C_4 \setminus \{c_k\} | \alpha],$$

where $c_0 = 1/\alpha$. Generalizing this derivation to any n completes the proof of the lemma.

Proof of Lemma 3

Proof. Let $C_n = \{1, 1/2, \dots, 1/n\}$ and $C_{n-1} = \{1, 1/2, \dots, 1/(n-1)\}$. Assume the induction hypothesis. Then we get

$$\begin{aligned} P_{ij} [n-1; C_n \setminus \{1\} | \alpha] &= P_{ij} \left[n-1; \left\{ \frac{1}{2}, \frac{1}{3}, \dots, \frac{1}{n-1}, \frac{1}{n} \right\} \middle| \alpha \right] \\ &\leq P_{ij} \left[n-1; \left\{ \frac{n-1}{n}, \frac{n-1}{2n}, \dots, \frac{n-1}{n(n-2)}, \frac{1}{n} \right\} \middle| \alpha \right] \\ &= P_{ij} \left[n-1; \left\{ 1, \frac{1}{2}, \dots, \frac{1}{n-2}, \frac{1}{n-1} \right\} \middle| \left(\frac{n-1}{n} \right) \alpha \right] \\ &\leq \binom{n-1}{n} \alpha. \end{aligned}$$

The first inequality holds since $1/i \leq (n-1)/[n(i-1)]$ for $2 \leq i \leq n$, the second equality holds since $P_{ij} [n; \{dc_1, \dots, dc_n\} | \alpha] = P_{ij} [n; \{c_1, \dots, c_n\} | d\alpha]$ for any constant $d > 0$ such that $d\alpha \leq 1$. The last inequality holds because of the induction hypothesis.

For $k \geq 2$, $P_{ij} [n-1; C_n \setminus \{c_k\} | \alpha] \leq P_{ij} [n-1; C_{n-1} | \alpha] \leq \alpha$ since the first $k-1$ elements of $C_n \setminus \{c_k\}$ and C_{n-1} are the same and $c_\ell < c_{\ell-1}$ for $\ell = k+1, \dots, n$. We then have

$$\begin{aligned} P_{ij} [n; C_n | \alpha] &= c_n \alpha + \sum_{k=1}^n \alpha (c_{k-1} - c_k) P_{ij} [n-1; C_n \setminus \{c_k\} | \alpha] \\ &= \frac{\alpha}{n} + \alpha (c_0 - c_1) P [n-1; C_n \setminus \{c_1\} | \alpha] \\ &\quad + \sum_{k=2}^n \alpha \left(\frac{1}{k-1} - \frac{1}{k} \right) P_{ij} \left[n-1; C_n \setminus \left\{ \frac{1}{k} \right\} \middle| \alpha \right] \\ &\leq \frac{\alpha}{n} + \alpha (1 - \alpha) \binom{n-1}{n} + \sum_{k=2}^n \alpha^2 \left(\frac{1}{k-1} - \frac{1}{k} \right) \end{aligned}$$

$$\begin{aligned}
& \text{(since } \alpha(c_0 - c_1) = \alpha\left(\frac{1}{\alpha} - 1\right) = 1 - \alpha) \\
& = \alpha \left[\frac{1}{n} + (1 - \alpha) \frac{n-1}{n} + \sum_{k=2}^n \alpha \left(\frac{1}{k-1} - \frac{1}{k} \right) \right] \\
& = \alpha \left[\frac{1}{n} + \left(\frac{n-1}{n} \right) - \alpha \left(\frac{n-1}{n} \right) + \alpha \left(1 - \frac{1}{n} \right) \right] \\
& = \alpha.
\end{aligned}$$

Proof of Lemma 4

Proof. First consider $n = 2$ with rejection region as shown in Figure 1. The Bonferroni upper bound on the type I error of the generalized Simes test can be obtained by adding the probabilities of the three overlapping subregions of this rejection region:

$$\begin{aligned}
\Pr(\text{Reject } H_0) &= \Pr\{\{P_{(2,2)} \leq c_1\alpha\} \cup \{P_{(1,2)} \leq c_2\alpha\}\} \\
&\leq \Pr\{P_1 \leq c_2\alpha\} + \Pr\{P_2 \leq c_2\alpha\} + \Pr\{\{P_1 \leq c_1\alpha\} \cap \{P_2 \leq c_1\alpha\}\} \\
&= 2c_2\alpha + \Pr\{\{P_1 \leq c_1\alpha\} \cap \{P_2 \leq c_1\alpha\}\} \\
&\leq 2c_2\alpha + c_1^2\alpha^2,
\end{aligned}$$

where the last step follows from the NQD property of (P_1, P_2) . If we set $c_1 = 1$ and set the above upper bound to α then we get the equation $2c_2\alpha + \alpha^2 = \alpha$, which gives $c_2 = (1 - \alpha)/2$.

Next consider $n = 3$. Each of the probability terms in (A.1) is a bivariate probability to which we can apply the upper bound (3.6) to get

$$\begin{aligned}
\Pr(\text{Reject } H_0) &\leq (1 - c_1\alpha)(2c_3\alpha + c_2^2\alpha^2) + (c_1\alpha - c_2\alpha)(2c_3\alpha + c_1^2\alpha^2) \\
&\quad + (c_2\alpha - c_3\alpha)(2c_2\alpha + c_1^2\alpha^2) + c_3\alpha \\
&= 3c_3\alpha + \alpha^2c_2(3c_2 - 4c_3) + \alpha^3c_1(c_1^2 - c_2^2 - c_1c_3). \quad (\text{A.3})
\end{aligned}$$

By substituting $c_1 = 1$, $c_2 = 1/2$, and $c_3 = 1/3$, this upper bound is $\alpha + 1/12\alpha^2 + 5/12\alpha^3 > \alpha$, so the c -Simes test cannot be shown to control the type I error for $n = 3$ under all NQD distributions.

Putting $c_1 = 1$ and $c_2 = 1/2 - \alpha/2$ in the upper bound, setting it equal to α and solving for c_3 , we get

$$c_3 = \left(\frac{1 - \alpha}{3} \right) \left[\frac{1 + \alpha/4 + \alpha^2 - \alpha^3/4}{1 - (2\alpha)/3 + \alpha^2/3} \right].$$

This value of c_3 , along with $c_1 = 1$, $c_2 = 1/2 - \alpha/2$, controls the type I error of the mc -Simes test under the NQD assumption. A slightly more conservative but simpler lower bound is $c_3 = 1/3 - \alpha/36$ when $\alpha < (22 - \sqrt{367})/9 \approx 0.31$.

Proof of Lemma 5

Proof. Each of the terms in (A.2) is a trivariate probability to which the upper bound in (A.3) can be applied. Substituting $c_i = 1/i$ we get

$$\begin{aligned} \Pr(\text{Reject } H_0) &\leq (1 - \alpha) \left(\frac{3}{4}\alpha + \frac{1}{144}\alpha^3 \right) + \frac{\alpha}{2} \left(\frac{3}{4}\alpha + \frac{23}{36}\alpha^3 \right) \\ &\quad + \frac{\alpha}{6} \left(\frac{3}{4}\alpha + \frac{1}{4}\alpha^2 + \frac{1}{2}\alpha^3 \right) + \frac{\alpha}{12} \left(\alpha + \frac{1}{12}\alpha^2 + \frac{5}{12}\alpha^3 \right) + \frac{\alpha}{4} \\ &= \alpha - \frac{1}{6}\alpha^2 + \frac{1}{18}\alpha^3 + \frac{31}{72}\alpha^4. \end{aligned}$$

It is easy to check that if $\alpha < (2(1 + \sqrt{94}))/31 \approx 0.69$ then $-1/6\alpha^2 + 1/18\alpha^3 + 31/72\alpha^4 < 0$, so $\Pr(\text{Reject } H_0) < \alpha$.

Proof of Theorem 1

Proof. From (3.3), it is sufficient to show that $P_{ij}[n; C_n|\alpha] \leq \alpha$. We have disposed of the case where $f_{ij}(p_i, p_j)$ is a PDS distribution, so it remains to deal with the case where $f_{ij}(p_i, p_j)$ is an NQD distribution. We have shown that this inequality holds for $n = 2$ and 3 if $c_1 = 1$, and c_2 and c_3 are modified as in (2.2). In Lemma (5) we have shown that this inequality holds for $n = 4$ and $c_4 = 1/4$. Then by applying the induction result of Lemma 3, the inequality holds for all n . Hence

$$\Pr(\text{Reject } H_0) = \sum_{1 \leq i < j \leq n} w_{ij} P_{ij}[n; C_n|\alpha] \leq \sum_{1 \leq i < j \leq n} w_{ij} \alpha = \alpha.$$

B. Multivariate Uniform Distributions

We say the joint distribution of (P_1, \dots, P_n) is multivariate uniform if all of its marginals are $U[0, 1]$. In this section we introduce three models which allow for negative as well as positive dependencies among the P_i 's. The first two are fully multivariate while the third model is a mixture of bivariate uniform distributions. The third model allows us to use induction to prove (2.3). For the first two models we could not obtain analytical proofs, so we used simulations.

B.1. Multivariate normal (MVN) model

Let Z_1, \dots, Z_n have a multivariate normal distribution with $E(Z_i) = 0$, $\text{Var}(Z_i) = 1$, and $\text{Corr}(Z_i, Z_j) = \gamma_{ij}$ ($1 \leq i < j \leq n$). We take $P_i = \Phi(Z_i)$ where $\Phi(\cdot)$ is the standard normal c.d.f. The P_i 's are marginally $U[0, 1]$ and $\text{Corr}(P_i, P_j) = \rho_{ij}$ is given by

$$\rho_{ij} = \frac{E(P_i P_j) - E(P_i)E(P_j)}{\sqrt{\text{Var}(P_i)\text{Var}(P_j)}}$$

Table 3. Correlation* between a pair of normal test statistics and their P -values.

γ	0	0.1	0.3	0.5	0.7	0.9	1
$\rho = h(\gamma)$	0	0.0955	0.2876	0.4826	0.6829	0.8915	1

* For negative correlations the same relationship holds except for change of sign.

$$\begin{aligned}
&= \frac{\int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \Phi(z_i) \Phi(z_j) \phi(z_i, z_j | \gamma_{ij}) dz_i dz_j - (1/2)^2}{(1/12)} \\
&= 12 \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \Phi(z_i) \Phi(z_j) \phi(z_i, z_j | \gamma_{ij}) dz_i dz_j - 3 \\
&= h(\gamma_{ij}) \quad (\text{say}), \tag{B.1}
\end{aligned}$$

where $\phi(\cdot, \cdot | \gamma)$ is the standard bivariate normal p.d.f. with correlation coefficient γ . It is easy to see that $h(\gamma_{ij})$ is a monotone, anti-symmetric function of γ_{ij} with $h(-\gamma_{ij}) = -h(\gamma_{ij})$. Specifically, $\text{sign}(\rho_{ij}) = \text{sign}(\gamma_{ij})$. Table 3 gives selected values of $\gamma_{ij} = \gamma$ and $\rho_{ij} = \rho = h(\gamma)$.

B.2. Bernoulli-uniform (BU) model

This model is an extension of the model proposed by Samuel-Cahn (1996). Let X_1, \dots, X_n be i.i.d. $U[0, \beta]$, and Y_1, \dots, Y_n be i.i.d. $U[\beta, 1]$ r.v.'s with the X_i 's and the Y_i 's mutually independent and where $\beta \in (0, 1)$ is fixed. Let Z be a Bernoulli r.v. with success probability β independent of both the X_i 's and the Y_i 's, and

$$U_i = X_i Z + Y_i(1 - Z), \quad i = 1, \dots, n. \tag{B.2}$$

Then the $U_i \sim U[0, 1]$. Next let the V_i 's be independent Bernoulli r.v.'s, also independent of the U_i 's, with success probabilities π_i ($1 \leq i \leq n$), and let

$$P_i = U_i V_i + (1 - U_i)(1 - V_i), \quad i = 1, \dots, n. \tag{B.3}$$

Then it is not difficult to show that the P_i 's have a multivariate uniform distribution on $[0, 1]^n$ with

$$\text{Corr}(P_i, P_j) = \rho_{ij} = 3\beta(1 - \beta)(2\pi_i - 1)(2\pi_j - 1), \quad i, j = 1, \dots, n, i \neq j. \tag{B.4}$$

Here all ρ_{ij} are between $-3/4$ and $3/4$. Both bounds are attained when $\beta = 1/2$. The lower bound is attained when $(\pi_i, \pi_j) = (1, 0)$ or $(0, 1)$ and the upper bound is attained when $(\pi_i, \pi_j) = (1, 1)$ or $(0, 0)$. Furthermore, $\rho_{ij} > 0$ if both π_i and π_j are $> 1/2$ or $< 1/2$ and $\rho_{ij} \leq 0$ otherwise.

B.3. Ferguson distribution

Ferguson (1995) proposed a new bivariate uniform distribution and extended

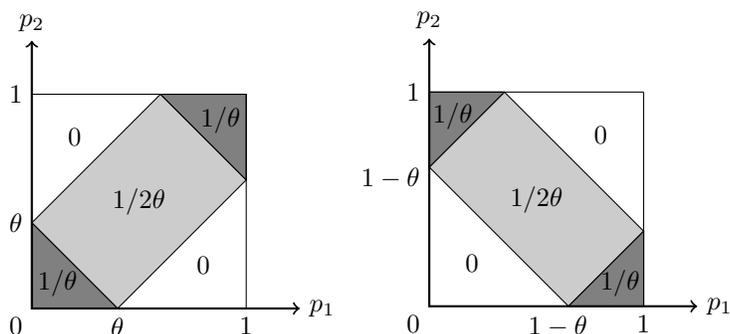


Figure 4. Region of support and corresponding p.d.f.'s for Ferguson's bivariate uniform distribution model (B.5) with $g(x) = U[0, \theta]$ resulting in positive correlation (left panel) and $g(x) = U[1 - \theta, 1]$ resulting in negative correlation (right panel).

it to the multivariate setting by using the bivariate mixture model (3.1). Let X be any continuous r.v. with p.d.f. $g(x)$ on an interval $I \subseteq [0, 1]$, and let the p.d.f. of (P_1, P_2) be given by

$$f(p_1, p_2) = \frac{1}{2}[g(|p_1 - p_2|) + g(1 - |1 - (p_1 + p_2)|)] \text{ for } p_1, p_2 \in [0, 1]. \quad (\text{B.5})$$

Then (P_1, P_2) has a bivariate uniform distribution on the unit square $[0, 1]^2$. Further, $\text{Corr}(P_1, P_2)$ equals

$$\rho = 1 - 6E(X^2) + 4E(X^3). \quad (\text{B.6})$$

A convenient choice for $g(x)$ is $U[0, \theta]$ or $U[1 - \theta, 1]$, where $\theta \in [0, 1]$. The former choice yields a positive correlation while the latter yields a negative correlation. Using (B.6) it is easy to see that

$$\rho = \begin{cases} (1 - \theta)(1 + \theta - \theta^2) & \text{if } g(x) = U[0, \theta], \\ -(1 - \theta)(1 + \theta - \theta^2) & \text{if } g(x) = U[1 - \theta, 1]. \end{cases} \quad (\text{B.7})$$

The regions of support and the corresponding p.d.f.'s $f(p_1, p_2)$ are shown in Figure 4. Note that if $\theta = 1$, which corresponds to $X \sim U[0, 1]$, then $\rho = 0$, while if $\theta = 0$ then $\rho = +1$ if $g(x) = U[0, \theta]$, and $\rho = -1$ if $g(x) = U[1 - \theta, 1]$, which are point mass distributions on $(0, 0)$ and $(1, 1)$, respectively. We use the mixture distribution in (3.1) with $f_{ij}(p_i, p_j)$ given by (B.5) where $g_{ij}(x) = U[0, \theta_{ij}]$ or $g_{ij}(x) = U[1 - \theta_{ij}, 1]$. The resulting mixture distribution (3.1) has $\rho_{ij} = \text{Corr}(P_i, P_j) = w_{ij}\rho_{ij}$ where ρ_{ij} is given by (B.7) with $\theta = \theta_{ij}$.

C. Concepts of Positive and Negative Dependence

There are many different concepts of positive and negative dependence; see

Joe (1997) for a review. We will mainly use two concepts here. The first is *positive or negative quadrant dependence (PQD or NQD)*, introduced by Lehmann (1966).

Definition 1. *Random variables X_1 and X_2 are said to be PQD if they satisfy the inequality*

$$\Pr \{(X_1 \leq x_1) \cap (X_2 \leq x_2)\} \geq \Pr(X_1 \leq x_1) \Pr(X_2 \leq x_2) \quad \text{for all } x_1, x_2. \quad (\text{C.1})$$

If the above inequality is reversed then X_1 and X_2 are said to be NQD.

The second dependence concept is that of *positive or negative dependence through stochastic ordering (PDS or NDS)* introduced by Block, Savits and Shaked (1985).

Definition 2. *Let $\psi(\cdot, \dots, \cdot)$ be a function of $n - 1$ arguments that is increasing in each of its arguments. A random vector (X_1, \dots, X_n) is said to be PDS if*

$$E[\psi(X_1, \dots, X_{i-1}, X_{i+1}, \dots, X_n) | X_i = x_i]$$

is increasing in x_i for all $i = 1, \dots, n$. If this expected value is decreasing in x_i for all $i = 1, \dots, n$, then (X_1, \dots, X_n) is said to be NDS.

It can be shown that $\text{PDS} \implies \text{PQD}$; similarly $\text{NDS} \implies \text{NQD}$. Thus PDS and NDS are subsets of PQD and NQD classes of distributions, respectively, and MTP_2 is a subset of the PDS class of distributions.

Of the three distributional models of Appendix B, the MVN and the Ferguson distributions are PQD if the correlation coefficient for each bivariate component is positive and NQD if it is negative. However, the bivariate BU model is not necessarily PQD (if $\rho > 0$) nor NQD (if $\rho < 0$). Proofs of these results are given in Gou and Tamhane (2015).

D. Counterexamples

In this section we give three counterexamples. Counterexample 1 gives an NQD distribution for which the upper bound (3.5) on the probability of type I error of the c-Simes test based on the critical constants $c_i = 1/i$ for $n = 2$ is sharp, so c_2 needs to be adjusted downwards as given in (2.2). Counterexample 2 gives an NQD distribution for which the exact probability of type I error of the c-Simes test based on the critical constants $c_i = 1/i$ for $n = 3$ exceeds α ; so c_3 needs to be adjusted downwards as given in (2.2). Finally Counterexample 3 gives a PQD distribution for which the exact probability of type I error of the mc-Simes test exceeds α and so we cannot extend the Block, Savits and Wang (2008)'s result of the conservatism of the c-Simes test from PDS to PQD distributions.

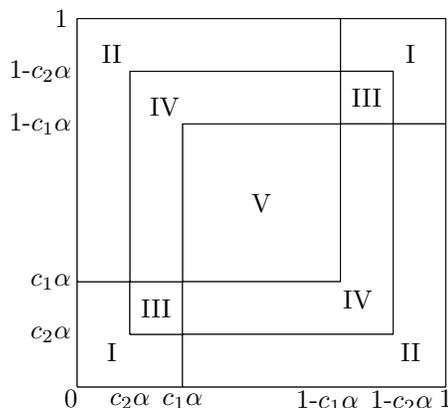


Figure 5. The region defined in (D.1).

Counterexample 1

Consider a density function $f(x_1, x_2)$ for $(x_1, x_2) \in [0, 1]^2$, that is symmetric about the diagonal $x_1 + x_2 = 1$, where

$$f(x_1, x_2) = \begin{cases} 0 & 0 \leq x_1 < \alpha, 0 \leq x_2 < \alpha/2 \text{ and} \\ & 0 \leq x_1 < \alpha/2, \alpha/2 \leq x_2 < \alpha \text{ (Region I),} \\ \frac{1}{1-\alpha} & 0 \leq x_1 < \alpha/2, \alpha \leq x_2 < 1-x_1 \text{ and} \\ & 0 \leq x_2 < \alpha/2, \alpha \leq x_1 < 1-x_2 \text{ (Region II),} \\ 4 & \alpha/2 \leq x_1, x_2 < \alpha \text{ (Region III),} \\ 1 - \frac{\alpha(1-\alpha/2)}{(1-\alpha)(1-3\alpha/2)} & \alpha/2 \leq x_1 < \alpha, \alpha \leq x_2 < 1-x_1 \text{ and} \\ & \alpha/2 \leq x_2 < \alpha, \alpha \leq x_1 < 1-x_2 \text{ (Region IV),} \\ \frac{1}{1-2\alpha} - \frac{2\alpha(1-\alpha/2)}{(1-\alpha)(1-3\alpha/2)} & \alpha \leq x_1, x_2 < 1-\alpha, x_1+x_2 < 1 \text{ (Region V).} \end{cases} \tag{D.1}$$

Figure 5 shows the different regions on which $f(x_1, x_2)$ is defined; in this figure $c_1 = 1, c_2 = 1/2$. It is easy to check that both marginals are uniform.

Straightforward but lengthy calculations (given in Gou and Tamhane (2015)) show that this distribution is NQD. Under this distribution $\Pr(\text{Reject } H_0) = \alpha + \alpha^2$, which is the upper bound (3.5) for $c_1 = 1, c_2 = 1/2$. Thus the upper bound is sharp and is $> \alpha$.

Counterexample 2

For $n = 3$, the distribution in (D.1) gives an upper bound, $< \alpha$, as the

following calculation shows.

Substituting $c_1 = 1$, $c_2 = 1/2$, and $c_3 = 1/3$ in (A.1), we get

$$\begin{aligned} \Pr(\{P_{(2:2)} \leq c_2\alpha\} \cup \{P_{(1:2)} \leq c_3\alpha\}) &= \frac{2}{3}\alpha, \\ \Pr(\{P_{(2:2)} \leq c_1\alpha\} \cup \{P_{(1:2)} \leq c_3\alpha\}) &= \frac{2}{3}\alpha + \alpha^2, \\ \Pr(\{P_{(2:2)} \leq c_1\alpha\} \cup \{P_{(1:2)} \leq c_2\alpha\}) &= \alpha + \alpha^2. \end{aligned}$$

Thus the probability of type I error is

$$\begin{aligned} P[3; C_3|\alpha] &= (1 - \alpha) \times \frac{2}{3}\alpha + \left(\alpha - \frac{1}{2}\alpha\right) \left(\frac{2}{3}\alpha + \alpha^2\right) \\ &\quad + \left(\frac{1}{2}\alpha - \frac{1}{3}\alpha\right) (\alpha + \alpha^2) + \left(\frac{1}{3}\alpha - 0\right) \times 1 \\ &= \alpha - \frac{1}{6}\alpha^2 + \frac{2}{3}\alpha^3, \end{aligned}$$

which is less than α if $\alpha < 1/4$. Hence the distribution (D.1) is not sufficient to show that type I error is uncontrolled in the trivariate case.

However, we can modify (D.1) to achieve a sharp upper bound that is $> \alpha$. In (A.3), the first term is of $O(1)$ while the other three terms are $O(\alpha)$, and thus of lower order. Therefore we need to construct a bivariate distribution which reaches the upper bound for the bivariate probability in the first term, for $c_1 = 1/2$ and $c_2 = 1/3$. We proceed as before. The regions of definition of the distribution are those shown in Figure 5, but with $c_1 = 1/2, c_2 = 1/3$. The corresponding density function is

$$f(x_1, x_2) = \begin{cases} 0 & 0 \leq x_1 < \alpha/2, 0 \leq x_2 < \alpha/3 \text{ and} \\ & 0 \leq x_1 < \alpha/3, \alpha/3 \leq x_2 < \alpha/2 \text{ (Region I),} \\ \frac{1}{1 - \alpha/2} & 0 \leq x_1 < \alpha/3, \alpha/2 \leq x_2 < 1 - x_1 \text{ and} \\ & 0 \leq x_2 < \alpha/3, \alpha/2 \leq x_1 < 1 - x_2 \text{ (Region II),} \\ 9 & \alpha/3 \leq x_1, x_2 < \alpha/2 \text{ (Region III),} \\ 1 - \frac{\alpha(1 - \alpha/3)}{(1 - \alpha/2)(1 - 5\alpha/6)} & \alpha/3 \leq x_1 < \alpha/2, \alpha/2 \leq x_2 < 1 - x_1 \text{ and} \\ & \alpha/3 \leq x_2 < \alpha/2, \alpha/2 \leq x_1 < 1 - x_2 \text{ (Region IV),} \\ \frac{1 - 7\alpha/3 + 7\alpha^2/4 - \alpha^3/4}{(1 - \alpha)(1 - 5\alpha/6)(1 - \alpha/2)} & \alpha/2 \leq x_1, x_2 < 1 - \alpha/2, x_1 + x_2 < 1 \text{ (Region V).} \end{cases} \tag{D.2}$$

This distribution can be shown to be NQD. Furthermore, here it can be

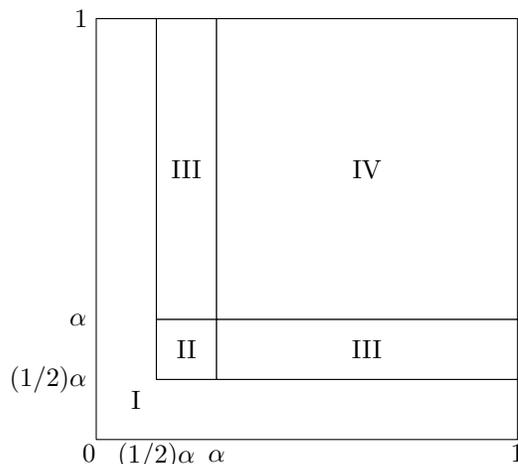


Figure 6. The region defined in (D.3).

shown that the exact type I error of the c -Simes test is $\alpha + \alpha^2/12 + 5\alpha^3/108 + o(\alpha^3) > \alpha$. The details of the calculations can be obtained from Gou and Tamhane (2015).

Counterexample 3

Consider a bivariate density function $f(x_1, x_2)$, regions shown in Figure 6, given by

$$f(x_1, x_2) = \begin{cases} 1 & 0 \leq x_1, x_2 \leq \alpha/2 \text{ and } \alpha/2 \leq x_1 \leq 1, 0 \leq x_2 \leq \alpha/2 \\ & \text{and } 0 \leq x_1 \leq \alpha/2, \alpha/2 \leq x_2 \leq 1 \text{ (Region I),} \\ \frac{2}{\alpha} - 1 & \alpha/2 \leq x_1, x_2 \leq \alpha \text{ (Region II),} \\ 0 & \alpha \leq x_1 \leq 1, \alpha/2 \leq x_2 \leq \alpha \text{ and} \\ & \alpha/2 \leq x_1 \leq \alpha, \alpha \leq x_2 \leq 1 \text{ (Region III),} \\ \frac{1 - \alpha/2}{1 - \alpha} & \alpha \leq x_1, x_2 \leq 1 \text{ (Region IV).} \end{cases} \quad (\text{D.3})$$

It is easy to check that both marginals are uniform. We show that it is PQD, that $\Pr(X_1 \leq x_1, X_2 \leq x_2) \geq x_1 x_2$ on $[0, 1]^2$. This inequality is obviously true when (x_1, x_2) is in Region I or Region II. When (x_1, x_2) is in Region III, without loss of generality, we can assume that $x_1 \in [\alpha, 1]$ and $x_2 \in [\alpha/2, \alpha]$. Then we have

$$\Pr(X_1 \leq x_1, X_2 \leq x_2) = \left(\frac{2}{\alpha} - 1\right) \cdot \frac{\alpha}{2} \cdot \left(x_2 - \frac{\alpha}{2}\right) + 1 \cdot \frac{\alpha}{2} \cdot x_1 + 1 \cdot \frac{\alpha}{2} \cdot \left(x_2 - \frac{\alpha}{2}\right)$$

$$= \frac{\alpha}{2}x_1 + x_2 - \frac{\alpha}{2}.$$

Since $x_1 \leq 1$ and $x_2 \geq \alpha/2$, we have

$$\Pr(X_1 \leq x_1, X_2 \leq x_2) - x_1x_2 = -(x_1 - 1) \left(x_2 - \frac{\alpha}{2}\right) \geq 0.$$

When (x_1, x_2) is in Region IV with $x_1, x_2 \in [\alpha, 1]$, we have

$$\begin{aligned} & \Pr(X_1 \leq x_1, X_2 \leq x_2) \\ &= \frac{1 - \alpha/2}{1 - \alpha} \cdot (x_1 - \alpha)(x_2 - \alpha) + \left(\frac{2}{\alpha} - 1\right) \cdot \frac{\alpha^2}{4} + 1 \cdot \frac{\alpha}{2} \cdot \left(x_1 + x_2 - \frac{\alpha}{2}\right) \\ &= x_1x_2 - \frac{\alpha}{2}(x_1 + x_2) + \frac{\alpha}{2} + \frac{\alpha^2}{2} + \frac{\alpha/2}{1 - \alpha}(x_1 - \alpha)(x_2 - \alpha) \\ &= x_1x_2 + \frac{(x_1 - 1)(x_2 - 1)}{2(1 - \alpha)} \geq x_1x_2 \end{aligned}$$

since $x_1, x_2 \leq 1$.

Finally, we have

$$\begin{aligned} \Pr(\text{Reject } H_0) &= 1 \cdot \frac{\alpha}{2} \cdot \left(1 + 1 - \frac{\alpha}{2}\right) + \left(\frac{2}{\alpha} - 1\right) \cdot \frac{\alpha^2}{4} \\ &= \frac{3}{2}\alpha - \frac{\alpha^2}{2} > \alpha, \end{aligned}$$

when $\alpha < 1$. If $\alpha = 0.05$ then this probability is 0.07375. We conclude that a PQD distribution does not always satisfy Simes inequality.

This counterexample uses $c_2 = 1/2$. If we use the more conservative value $c_2 = 1/2 - \alpha/2$ derived in Lemma 4, the above probability is $3\alpha/2 - 3\alpha^2/2 + \alpha^3/2 - \alpha^4/4$, which is slightly smaller (for $\alpha = 0.05$ this probability equals 0.07131) but still $> \alpha$ since the leading term in this expression is $3\alpha/2$.

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