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On Some Procedures Based on Fisher's Inverse Chi-Square Statistic

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ABSTRACT

We present approximations to the distribution of the weighted combination of independent and dependent P-values, $A=\sum_{i=1}^{m}\omega_i\left\{-2\log\left(P_i\right)\right\}$. In case that independence of P_i's is not assumed, it is argued that the quantity A is implicitly dominated by positive definite quadratic forms that induce a chi-square distribution. This gives way to the approximation of the associated degrees of freedom using Satterthwaite (1946) or Patnaik (1949) method. An approximation by Brown (1975) is used to estimate the covariance between the log transformed P-values. The performance of the approximations is compared using simulations. For both the independent and dependent cases, the approximations are shown to yield probability values close to the nominal level, even for arbitrary weights, ω_i's.

Keywords: P-Values; Weighting; Linear Combination; Correlation Coefficient; Estimated Degrees of Freedom

1. Introduction

Let $P_1,P_2,\cdots,P_m$ be m tail probabilities or probability values from continuous distributions. Associate null hypotheses $H_{0i}:\theta_i=0, i=1,\cdots,m,$ to these m probability values. Using the probability integral transform, we know that $P_i\sim\text{Uniform}(0,1)$ when H_{0i} is true. For $S_i=-2\log\left(P_i\right)$,

$$P\left(S_i>s\right)=P\left\{-2\log\left(P_i\right)>s\right\}$$
$$=P\left\{P_i<\exp\left(-s/2\right)\right\}=\exp\left(-s/2\right)$$

That is, $P\left(S_i<s\right)=1-\exp\left(-s/2\right)$, which is the cumulative distribution function of a chi-square variable with 2 degrees of freedom. That is, $S_i\sim\chi_2^2$, and the decision rule is to reject H_{0i} if $S_i>\chi^2_{2,1-\alpha}$. Define a combined statistic by

$$M=-2\log\left(\prod_{i=1}^{m}P_i\right)=\sum_{i=1}^{m}-2\log\left(P_i\right)=\sum_{i=1}^{m}S_i$$

For independent P_i's, the variable $M\sim\chi^2_{2m}$. The overall test procedure is to reject $H_0:\theta_1=\cdots=\theta_m=0$ if $M>\chi^2_{2m;1-\alpha}$. This is Fisher's Inverse Chi-square method. We notice that for the statistic M, all the P_i's are weighted equally, which may not be acceptable in some situations and therefore unequal weighting may be necessary. A number of authors have attempted to derive the distribution of a weighted form of M. For instance, let $W=\sum_{i=1}^{m}c_iW\left(\delta_i\right)$, where $W\left(\delta_i\right)$ has a non-central χ^2 distribution with non-centrality parameter δ_i. Solomon and Stephens [1] approximated the distribution of W by a random variable of the form $b_0\left(\chi^2_\upsilon\right)^{b_1}$ matching the first three moments. The disadvantage with this approximation is that there is no closed-form formula for computing the parameters. Buckley and Eagleson [2] approximation of the distribution of W involves approximating W using a variable that takes the form $T=b_0\chi^2_\nu+b_1$ and matching the first three cumulants of T and W. Zhang [3] showed that by equating the first three cumulants of W and $R=b_0\chi^2_\upsilon+b_1$, the distribution of W can be approximated by $P\left(W\le w\right)\approx P\left(R\le w\right)=P\left[\chi^2_\upsilon\le\left(w-b_1\right)/b_0\right]$. Zhang [3] also proposed a chi-square approximation to the distribution of W. Others authors have approximated the null distribution of W by intensive bootstrap [4-8].

In this article, we concentrate on linear combinations of S_i (a function of P_i's) that have a central chi-square distribution, and involve dependent and independent P_i's and arbitrary weights, ω_i's. For dependent P_i's, we use simulations to investigate the performance of the approach by Makambi [9] when it is assumed that there is homogeneity in correlation coefficients between any pair of the P_i's.

2. Distribution of Independent and Dependent Weighted χ^2's

Let's focus on the mixture

$$A = \sum_{i=1}^{m} \omega_i S_i,$$

where S_i has a central χ^2-distribution with 2 degrees of freedom and ω_i are arbitrary weights. For independent P_i's, Good [10] provided the following approximation:

$$P(A \le a) = 1 - \sum_{i=1}^{m} \Lambda_i \exp\left\{-\frac{a}{2\omega_i}\right\}$$

where $\Lambda_i = \omega_i^{m-1} \Big/ \left\{\prod_{j=1, j\ne i}\left(\omega_i - \omega_j\right)\right\}$, $\omega_i \ne \omega_j$. This approximation is usually regarded as the exact distribution of A. The approximation has been criticized because the calculations become ill-conditioned when any two weights, ω_i and $\omega_j, i \ne j,$ are equal. To avoid this problem, Bhoj [11] proposed the approximation

$$P(A \le a) = \sum_{i=1}^{m} \left\{\frac{\omega_i \cdot IG\left(1/\omega_i, a/2\omega_i\right)}{\Gamma\left(1/\omega_i\right)}\right\}$$

where IG denotes the incomplete gamma function. This approximation is also for independent probability values.

For an alternative and more general approximation to the distribution of A where independence of P_i's is not assumed, it may be argued that A is a quantity that is implicitly dominated by positive definite quadratic forms that induce a chi-square distribution. Thus by Satterthwaite [12] or Patnaik [13], we have

$$\nu \frac{A}{E(A)} \sim \chi^2_\nu$$

It follows that

$$\operatorname{var}\left\{\nu \frac{A}{E(A)}\right\} = \frac{\nu^2}{\left\{E(A)\right\}^2} \cdot \operatorname{var}(A) = 2\nu$$

Therefore, the degrees of freedom can be obtained by solving the above equation for ν, namely,

$$\nu = 2 \cdot \frac{\left\{E(A)\right\}^2}{\operatorname{var}(A)}$$

Now,

$$E(A) = \sum_{i=1}^{m} \omega_i E(S_i) = 2\sum_{i=1}^{m} \omega_i$$

and

$$\sigma_A^2 = \operatorname{var}(A) = \sum_{i=1}^{m} \omega_i^2 \operatorname{var}(S_i) + \sum_{i=1}^{m} \sum_{j \ne i=1} \omega_i \omega_j \operatorname{cov}(S_i, S_j)$$
$$= 4\sum_{i=1}^{m} \omega_i^2 + \sum_{i=1}^{m} \sum_{j \ne i=1} \omega_i \omega_j \operatorname{cov}(S_i, S_j)$$

where $\operatorname{cov}(S_i, S_j)$ denotes the covariance between S_i and S_j, for $i \ne j$. An estimate of the degrees of freedom, ν, is given by $\hat{\nu} = 8 \cdot \left(\sum_{i=1}^{m} \omega_i\right)^2 \Big/ \hat{\sigma}_A^2$ (see [9,14]).

We can now synthesize the m probability values $P_i, i = 1, \cdots, m,$ based on the decision rule

$$\text{Reject } H_0 \text{ if } A > 2 \cdot \frac{\chi^2_{\hat{\nu},1-\alpha}}{\hat{\nu}} \sum_{i=1}^{m} \omega_i$$

For normalized weights, that is, $\sum_{i=1}^{m} \omega_i = 1,$ the decision rule is:

$$\text{Reject } H_0 \text{ if } A > 2 \cdot \frac{\chi^2_{\hat{\nu},1-\alpha}}{\hat{\nu}},$$

with an estimate of the degrees of freedom ν given by $\hat{\nu}$. Notice that for independent S_i and S_j and normalized weights, Makambi [9] and Hou [14] utilize $\hat{\nu} = 2\Big/\sum_{i=1}^{m} \omega_i^2$. For $m = 2$ and 4, Hou [14] presented simulation results indicating that the approximation given above attains probability values close to the nominal level, similar to the Good [10] and Bhoj [11] approximations.

For $m = 4$ independent P-values, we use **Table 1** in Hou [14] to obtain **Table 1**, just for purposes of comparing the performance of the approaches. We notice that using $\hat{\nu}$ (column 5, **Table 1**) yields results that are close to both the exact method by Good [10] and the method by Bhoj [11].

To illustrate the application of the methods for independent probability values, we use data from Canner [15] on four selected multicenter trials involving aspirin and post-myocardial infarction patients carried out in Europe and the United States in the period 1970-1979. Two of these trials, referred to as UK-1 and UK-2 were carried out in the United Kingdom; the Coronary Drug Project Aspirin Study (CDPA); and the Persantine-Aspirin Reinfarction Study (PARIS) (**Table 2)**.

The P-values provided in column 4 of **Table 2** are for the log odds ratio as the outcome measure of interest. Using the P-values in **Table 2** and the weights from **Table 1** of [14], we obtain the values in **Tables 3**. We have also included results for normalized inverse variance weights determined from the data. The three approximations yield values that are close to each other, and are in good agreement with the exact method by

Good [10].

If S_i and S_j are non-independent, the expression for σ_A^2 contains a covariance term between S_i and S_j that has to be estimated. Let ρ_{ij} be the correlation between S_i and S_j *i.e.*, $\rho_{ij} = \text{corr}(S_i, S_j)$. An approximation of the variance of A is given by [16]

$$\sigma_A^2 = \begin{cases} 4\sum_{i=1}^{m}\omega_i^2 + \sum_{i=1}^{m}\sum_{j\neq i=1}^{m}\omega_i\omega_j\left(3.25\rho_{ij} + 0.75\rho_{ij}^2\right), & 0 \le \rho_{ij} \le 1 \\ 4\sum_{i=1}^{m}\omega_i^2 + \sum_{i=1}^{m}\sum_{j\neq i=1}^{m}\omega_i\omega_j\left(3.27\rho_{ij} + 0.71\rho_{ij}^2\right), & -0.5 \le \rho_{ij} \le 0 \end{cases}$$

3. A Procedure for Constant Correlation Coefficient

We require estimates of ρ_{ij} to implement the procedures above for dependent P_i's. Let's consider the case of homogeneous nonnegative correlation coefficients, that is, $\rho_{ij} = \rho$ for $0 \le \rho \le 1$. Let $S = (S_1, \cdots, S_m)'$ and define the quadratic form [9]

$$Q = \frac{\sum_{i=1}^{m}\left(S_i - \bar{S}\right)^2}{m-1}, \quad \bar{S} = \frac{\sum_{i=1}^{m} S_i}{m}$$

We can write $(m-1)Q = S'BS$, $B = I_m - \frac{1}{m}J_m$,

where I_m is identity matrix of order m and J_m is a square matrix of order m with every element equal to unity. It can be shown that $(m-1)E(Q) = tr(B\Sigma_S)$, where $\Sigma_S = \left(\sigma_{S_i,S_j}\right)_{i,j=1,\cdots,m}$; $\sigma_{S_i,S_i} = \text{var}(S_i) = 4$, and $tr(A)$ is the trace of the matrix A. For homogeneous $\rho_{ij} = \rho$, $0 \le \rho \le 1$, and using results from Brown [16] we have $\sigma_{S_i,S_j} = \text{cov}(S_i, S_j) = 3.25\rho + 0.75\rho^2$. We can show that

$E(Q) = tr(B\Sigma_S)/(m-1) = 4 - (0.75\rho^2 + 3.25\rho)$.

Solving the preceding equation for ρ yields the approximate admissible solution $\rho = -2.16667 + \left\{10.02778 - 4Q/3E(Q)\right\}^{1/2}$ with an estimate for ρ given by

$$\hat{\rho} = -2.16667 + \left\{10.02778 - 4Q/3\right\}^{1/2}, \ 0 \le Q \le 4 \quad (1)$$

We investigate how well this approximation works compared with the other approximations by simulating data from a m-variate normal distribution with covariance matrix $\Sigma = (\sigma_{ij})$, with $\sigma_{ii} = 1, i = 1, \cdots, m$, and $\sigma_{ij} = \rho, i \neq j = 1, \cdots, m$. Just as in Hou [14], we simulated

Table 1. $P(A \le a)$ for independent P_i's.

$(\omega_1,\omega_2,\omega_3,\omega_4)$	a	Good-Exact	Bhoj	M/H
(0.05, 0.15, 0.20, 0.60)	3.696	0.9000	0.9085	0.8955
	4.531	0.9500	0.9538	0.9510
	6.460	0.9900	0.9895	0.9923
(0.10, 0.20, 0.30, 0.40)	3.456	0.9000	0.9039	0.8986
	4.082	0.9500	0.9518	0.9505
	5.470	0.9900	0.9897	0.9911
(0.22, 0.23, 0.27, 0.28)	3.346	0.9000	0.9003	0.9000
	3.888	0.9500	0.9502	0.9500
	5.050	0.9900	0.9900	0.9901
(0.20, 0.25, 0.25, 0.30)	3.347	-	0.9000	0.8992
	3.892	-	0.9500	0.9500
	5.070	-	0.9900	0.9902
(0.20, 0.20, 0.20, 0.40)	3.373	-	0.9000	0.8945
	3.960	-	0.9500	0.9477
	5.330	-	0.9900	0.9912
(0.25, 0.25, 0.25, 0.25)	3.340	-	0.9000	0.9000
	3.877	-	0.9500	0.9500
	5.023	-	0.9900	0.9900

M/H is Makambi/Hou method using $\hat{\nu}$.

Table 2. Data on total mortality in six aspirin trials (Number of Deaths/Number of patients).

Study	Aspirin	Placebo	P-value
CDPA	44/758	64/771	0.029
UK--1	49/615	67/624	0.048
UK--2	102/832	126/850	0.063
PARIS	85/810	52/406	0.115

Table 3. $P(A \le a)$ for independent P_i's using Canner (1987) data for $m = 4$.

$(\omega_1,\omega_2,\omega_3,\omega_4)$	a	Good	Bhoj	M/H
(0.05, 0.15, 0.20, 0.60)	4.966	0.9652	0.9671	0.9674
(0.10, 0.20, 0.30, 0.40)	5.312	0.9880	0.9877	0.9891
(0.22, 0.23, 0.27, 0.28)	5.659	0.9959	0.9959	0.9960
(0.20, 0.25, 0.25, 0.30)	5.614	-	0.9954	0.9956
(0.20, 0.20, 0.20, 0.40)	5.467	-	0.9915	0.9927
(0.25, 0.25, 0.25, 0.25)	5.752	-	0.9966	0.9966
(0.19, 0.20, 0.22, 0.39)*	5.463	0.9919	0.9918	0.9929

*inverse variance weights determined from the data; M/H is Makambi/Hou method using $\hat{\nu}$.

10,000 multivariate normal samples and computed the corresponding values of A. For $m = 2$ and 4, we present values for $P(A \le a)$ at selected nominal levels and weights (**Tables 4-6**).

Table 4. Simulated estimates of $P(A \le a)$ at selected nominal levels for non-independent P_i's from bivariate normal distribution with $\mu = (0,0)'$ and covariance matrix $\Sigma = (\sigma_{ij})$, with $\sigma_{ii} = 1, i = 1,\cdots,m$, and $\sigma_{ij} = \rho, i \ne j = 1,\cdots,m : m = 2$.

		Simulated $P(A \le a)$					
		$\rho = 0.1$		$\rho = 0.5$		$\rho = 0.9$	
(ω_1, ω_2)	$1-\alpha$	H/M	Proposed*	H/M	Proposed*	M/H	Proposed*
(0.1, 0.9)	0.90	0.9062	0.9016	0.8969	0.9017	0.9007	0.8988
	0.95	0.9490	0.9510	0.9464	0.9462	0.9487	0.9480
	0.99	0.9898	0.9881	0.9888	0.9870	0.9880	0.9892
(0.3, 0.7)	0.90	0.8959	0.9054	0.9022	0.8983	0.9030	0.8968
	0.95	0.9486	0.9512	0.9530	0.9462	0.9521	0.9425
	0.99	0.9899	0.9885	0.9902	0.9848	0.9902	0.9837
(0.5, 0.5)	0.90	0.9041	0.9056	0.9032	0.8954	0.8964	0.9010
	0.95	0.9513	0.9540	0.9509	0.9400	0.9465	0.9458
	0.99	0.9900	0.9900	0.9890	0.9820	0.9902	0.9895

*ρ is estimated from Equation (1); M/H is Makambi/Hou method using $\hat{\nu}$.

Table 5. Simulated estimates of $P(A \le a)$ at selected nominal levels for non-independent P_i's from multivariate normal distribution with $\mu = (0,0,0,0)'$ and covariance matrix $\Sigma = (\sigma_{ij})$, with $\sigma_{ii} = 1, i = 1,\cdots,m$, and $\sigma_{ij} = \rho$, $i \ne j = 1,\cdots,m : m = 4$.

		Simulated $P(A \le a)$					
		$\rho = 0.1$		$\rho = 0.5$		$\rho = 0.9$	
$(\omega_1, \omega_2, \omega_3, \omega_4)$	$1-\alpha$	M/H	Proposed*	M/H	Proposed*	M/H	Proposed*
(0.05,0.15,0.20,0.60)	0.90	0.9023	0.9041	0.9011	0.8868	0.8990	0.8957
	0.95	0.9503	0.9492	0.9536	0.9325	0.9519	0.9417
	0.99	0.9885	0.9868	0.9913	0.9784	0.9902	0.9836
(0.10, 0.20,0.30,0.40)	0.90	0.9018	0.9006	0.9016	0.8776	0.9029	0.8966
	0.95	0.9502	0.9443	0.9516	0.9222	0.9530	0.9437
	0.99	0.9890	0.9862	0.9912	0.9680	0.9909	0.9796
(0.22,0.23,0.27,0.28)	0.90	0.8991	0.8960	0.9001	0.8695	0.8975	0.8885
	0.95	0.9498	0.9405	0.9503	0.9125	0.9493	0.9361
	0.99	0.9886	0.9830	0.9904	0.9620	0.9896	0.9750
(0.20,0.25,0.25,0.30)	0.90	0.8983	0.8972	0.9072	0.8769	0.9024	0.8928
	0.95	0.9482	0.9425	0.9533	0.9197	0.9511	0.9361
	0.99	0.9883	0.9842	0.9908	0.9652	0.9893	0.9753
(0.20,0.20,0.20,0.40)	0.90	0.8998	0.8964	0.8969	0.8759	0.8978	0.8910
	0.95	0.9488	0.9416	0.9483	0.9175	0.9516	0.9380
	0.99	0.9908	0.9855	0.9894	0.9653	0.9902	0.9772
(0.25,0.25,0.25,0.25)	0.90	0.8994	0.8989	0.8984	0.8704	0.8985	0.8967
	0.95	0.9496	0.9430	0.9498	0.9123	0.9496	0.9383
	0.99	0.9894	0.9848	0.9902	0.9616	0.9896	0.9762

*ρ is estimated from Equation (1); M/H is Makambi/Hou method using $\hat{\nu}$.

Table 6. Simulated estimates of $P(A \le a)$ (with weights, ω_i simulated from $\beta(2,2)$) at selected nominal levels for non-independent P_i's from bivariate normal distribution with $\mu = (0,0)'$ and covariance matrix $\Sigma = (\sigma_{ij})$, with $\sigma_{ii} = 1, i = 1,\cdots,m$, and $\sigma_{ij} = \rho, i \ne j = 1,\cdots,m : m = 2,4$.

		Simulated $P(A \le a)$			
		$m = 2$		$m = 4$	
ρ	$1-\alpha$	M/H	Proposed*	M/H	Proposed*
0.01	0.90	0.9000	0.8976	0.9030	0.9081
	0.95	0.9483	0.9496	0.9503	0.9512
	0.99	0.9888	0.9898	0.9899	0.9903
0.1	0.90	0.8983	0.8996	0.9021	0.8997
	0.95	0.9475	0.9508	0.9520	0.9440
	0.99	0.9899	0.9895	0.9899	0.9862
0.3	0.90	0.8973	0.8968	0.8999	0.8798
	0.95	0.9466	0.9480	0.9511	0.9319
	0.99	0.9881	0.9851	0.9903	0.9776
0.5	0.90	0.8975	0.8926	0.9011	0.8975
	0.95	0.9478	0.9487	0.9512	0.9446
	0.99	0.9890	0.9869	0.9910	0.9856
0.7	0.90	0.9015	0.8938	0.8986	0.8851
	0.95	0.9529	0.9478	0.9478	0.9254
	0.99	0.9899	0.9884	0.9887	0.9663
0.9	0.90	0.9025	0.8975	0.9039	0.8977
	0.95	0.9509	0.9458	0.9507	0.9446
	0.99	0.9887	0.9846	0.9899	0.9825
0.99	0.90	0.8950	0.8967	0.8997	0.8992
	0.95	0.9469	0.9462	0.9505	0.9496
	0.99	0.9895	0.9890	0.9887	0.9882

*ρ is estimated from Equation (1); M/H is Makambi/Hou method using $\hat{\nu}$.

For $m = 2$ (**Table 4**) the proposed method attains probability levels that are close to the nominal level, similar to the Makambi/Hou method.

For $m = 4$ (**Table 5**) the proposed estimate of the constant correlation coefficient ρ leads to attained probability level that are close to the nominal level, $1-\alpha$, for $\rho = 0.1$ and 0.9. However, for values of ρ close to 0.5, the estimate leads to underestimation of the probability level.

Now, instead of using pre-defined weights, we simulated weights from a beta distribution with parameters $\alpha = 2$ and $\beta = 2$. That is, for $b_i \sim \beta(2,2)$, $w_i = b_i \big/ \sum_{i=1}^m b_i$, $i = 1,\cdots,m$, such that $\sum_{i=1}^m w_i = 1$. Results are given in **Table 6** for selected nominal levels.

4. Conclusion

In this article, we have presented chi-square approximations to the distribution of Fisher's inverse chi-square statistic for independent and dependent P-values. It has also been shown that, for dependent P-values, the proposed estimate of the constant correlation coefficient ρ performs well by attaining probability levels close to the nominal level for correlation coefficients close to 0.1 and 0.9. We expect the proposed estimate to underestimate probability levels for relatively large numbers of studies, especially when ρ is close to 0.5. However, for values close to 0.1 and 0.9, the proposed estimate works quite well and can be recommended.

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