Accurate Critical Constants for the One-Sided Approximate Likelihood Ratio Test of a Normal Mean Vector When the Covariance Matrix Is Estimated

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1. Problem

- Compare a treatment group with a control group based on multiple endpoints.

- x_{ijk} = Measurement on the kth endpoint for the jth subject from the ith group ($i = 1$ treatment group, $i = 2$ control group; $j = 1, 2, \ldots, n_i; k = 1, 2, \ldots, p$).

- Assumptions:

  1. $\boldsymbol{x}_{ij} = (x_{ij1}, x_{ij2}, \ldots, x_{ijp})' \sim N_p(\boldsymbol{\mu}_i, \boldsymbol{\Sigma}_i)$ i.i.d. for $i = 1, 2; j = 1, 2, \ldots, n_i$. Here $\boldsymbol{\mu}_i = (\mu_{i1}, \mu_{i2}, \ldots, \mu_{ip})'$.

  2. $\boldsymbol{\Sigma}_1 = \boldsymbol{\Sigma}_2 = \boldsymbol{\Sigma}$.

  3. The treatment is expected to improve the mean response for at least one endpoint with no decrease in others.

2. One-Sided Hypothesis Testing Problem

- Let $\boldsymbol{\delta} = \boldsymbol{\mu}_1 - \boldsymbol{\mu}_2 = (\delta_1, \delta_2, \ldots, \delta_p)'$.

- The hypotheses are

$$H_0 : \boldsymbol{\delta} = \mathbf{0} \text{ vs. } H_1 : \boldsymbol{\delta} \in \mathcal{O}^+,$$

  where $\mathbf{0}$ is the null vector and

$$\mathcal{O}^+ = \{\boldsymbol{\delta} | \delta_k \geq 0 \text{ for } k = 1, 2, \ldots, m, \boldsymbol{\delta} \neq \mathbf{0}\}$$

  is the positive orthant.

- Hotelling's T^2-test is an omnibus test for detecting any deviation of $\boldsymbol{\delta}$ from $\mathbf{0}$. Hence it lacks power for testing H_1 :, where $\mathcal{O}^+$ is the positive orthant.

- There are other tests, e.g., O'Brien (1984).

- Global tests vs. Individual tests (e.g., Bonferroni).

3. Likelihood Ratio (LR) Tests

LR tests for known $\mathbf{\Sigma}$ derived by Kudô (1963).

- Let

$$\overline{\boldsymbol{x}}_{i\cdot} = (\overline{x}_{i\cdot 1}, \overline{x}_{i\cdot 2}, \ldots, \overline{x}_{i\cdot p})' \text{ and } \boldsymbol{y} = \overline{\boldsymbol{x}}_{1\cdot} - \overline{\boldsymbol{x}}_{2\cdot}.$$

  The LR statistic equals

$$\tilde{n}\left\{\boldsymbol{y}'\mathbf{\Sigma}^{-1}\boldsymbol{y} - \min_{\delta_k \geq 0}(\boldsymbol{y}-\boldsymbol{\delta})'\mathbf{\Sigma}^{-1}(\boldsymbol{y}-\boldsymbol{\delta})\right\}$$

  where

$$\tilde{n} = \frac{n_1 n_2}{n_1 + n_2}.$$

- Computation of the LR statistic involves finding the projection of $\boldsymbol{y}$ onto $\mathcal{O}^+$ using the Mahalnobis distance metric. A special case of this is Bartholomew's (1961) test for ordered alternatives.

- The null distribution of this statistic is not available in a closed form.

- Perlman (1969) extended Kudô's test to unknown $\mathbf{\Sigma}$. In this case the computation of the test statistic is more complicated, and the its null distribution depends on unknown $\mathbf{\Sigma}$.

3. Approximate Likelihood Ratio (ALR) Test

Proposed by Tang, Gnecco and Geller (1989). Assumes known $\boldsymbol{\Sigma}$. Steps are as follows:

- Make the transformation

$$\boldsymbol{u} = \sqrt{\tilde{n}}\boldsymbol{A}(\overline{\boldsymbol{x}}_{1\cdot} - \overline{\boldsymbol{x}}_{2\cdot})$$

  where $\boldsymbol{A}$ is a symmetric matrix s.t.

$$\boldsymbol{A}'\boldsymbol{A} = \boldsymbol{\Sigma}^{-1} \text{ and } \boldsymbol{A}\boldsymbol{\Sigma}\boldsymbol{A}' = \boldsymbol{I}.$$

- Under H_0, $\boldsymbol{u} \sim N_p(\boldsymbol{0}, \boldsymbol{I})$. $\boldsymbol{A}$ is not unique.

- In terms of this transformation, $\mathcal{O}^+$ is mapped to a polyhedral cone

$$\boldsymbol{A}(\boldsymbol{\delta}) = \{\boldsymbol{A}\boldsymbol{\delta} | \boldsymbol{\delta} \geq \boldsymbol{0}\}.$$

  To compute the LR test statistic, we need to compute the projection of $\boldsymbol{u}$ onto $\boldsymbol{A}(\boldsymbol{\delta})$. This is difficult. (One difficulty traded for another difficulty.)

- Approximate $\boldsymbol{A}(\boldsymbol{\delta})$ by $\mathcal{O}^+$. To make the approximation more accurate, choose $\boldsymbol{A}$ s.t. the center direction of $\boldsymbol{A}(\boldsymbol{\delta})$ coincides with the center direction of $\mathcal{O}^+$, which is the ray $(a, a, \ldots, a)'$ for $a \geq 0$.

- The LR statistic equals

$$g(\boldsymbol{u}) = \sum_{k=1}^{p} \{\max(u_k, 0)\}^2 .$$

- The null distribution of $g(\boldsymbol{u})$ is the $\overline{\chi}^2$ distribution with symmetric binomial weights, given by

$$\Pr\{g(\boldsymbol{u}) \leq c\} = \sum_{q=0}^{p} \left\{ \binom{p}{q} 2^{-p} \Pr\left(\chi_q^2 \leq c\right) \right\}$$

where $\chi_0^2 = 0$. This distribution is easy to compute.

- Tang et al. suggested that if $\boldsymbol{\Sigma}$ is unknown then use the pooled sample covariance matrix $\widehat{\boldsymbol{\Sigma}}$ with $\nu = n_1 + n_2 - 2$ d.f.

Simulation Estimates of Type I Error Probability Using $\bar{\chi}^2$ Approx.

($\alpha = .05$)

	p				
ν	2	4	6	8	10
10	0.0940	0.1835	0.3550	0.6285	0.9135
30	0.0646	0.0832	0.1066	0.1507	0.2015
50	0.0588	0.0660	0.0830	0.0997	0.1188

4. Distribution of the ALR Statistic When $\boldsymbol{\Sigma}$ Is Estimated

- Make the transformation

$$\boldsymbol{v} = \sqrt{\tilde{n}}\boldsymbol{B}(\overline{\boldsymbol{x}}_{1\cdot} - \overline{\boldsymbol{x}}_{2\cdot})$$

  where $\boldsymbol{B}$ is a symmetric matrix s.t.

$$\boldsymbol{B}'\boldsymbol{B} = \widehat{\boldsymbol{\Sigma}}^{-1} \text{ and } \boldsymbol{B}\widehat{\boldsymbol{\Sigma}}\boldsymbol{B}' = \boldsymbol{I}.$$

- The test statistic is

$$g(\boldsymbol{v}) = \sum_{k=1}^{p} \{\max(v_k, 0)\}^2.$$

- The choice of $\boldsymbol{B}$ is not unique, but if $\boldsymbol{B}$ is chosen to be the unique lower triangular matrix using the Cholesky decomposition then the distribution of $g(\boldsymbol{v})$ can be shown to be independent of $\boldsymbol{\Sigma}$.

- The c.d.f. of $g(\boldsymbol{v})$ is intractable.
- Even the distribution of $\Sigma_{k=1}^{q} v_k^2$ is intractable except when $q = 1$, in which case, $v_1^2 \sim t_\nu^2$ and when $q = p$, in which case,

$$\sum_{k=1}^{p} v_k^2 = \boldsymbol{v}'\boldsymbol{v} \sim T_{p,\nu}^2 \sim \left(\frac{\nu p}{\nu - p + 1}\right) F_{p,\nu-p+1},$$

  where $T_{p,\nu}^2$ is Hotelling's T^2.
- In analogy with the $\overline{\chi}^2$ distribution, we propose to approximate the c.d.f. of $g(\boldsymbol{v})$ by

$$\Pr\{g(\boldsymbol{v}) \le c\} \approx \sum_{q=0}^{p} \binom{p}{q} 2^{-p} \Pr\left\{\left(\frac{\nu q}{\nu - p + 1}\right) F_{q,\nu-p+1} \le c\right\}$$

  where $F_{0,\nu-p+1} = 0$. Denote this mixture of scaled F r.v.'s by $\overline{F}_{p,\nu-p+1}$.

- The approximation is exact for $p = 1, \nu < \infty$ and for $p > 1, \nu = \infty$.

- Their first moments match.

  Proof: Write

$$g(\boldsymbol{v}) = \sum_{k=1}^{p} w_k^2 = \boldsymbol{w}'\boldsymbol{w},$$

where $\boldsymbol{w} = (w_1, w_2, \ldots, w_p)'$ and

$$w_k = \begin{cases} v_k & \text{if } v_k > 0 \ \text{ with probability } \frac{1}{2} \\ 0 & \text{if } v_k \le 0 \ \text{ with probability } \frac{1}{2}. \end{cases}$$

Then,

$$\begin{aligned} E\{g(\boldsymbol{v})\} = E(\sum_{k=1}^{p} w_k^2) &= \frac{1}{2}E(\boldsymbol{v}'\boldsymbol{v}) \\ &= \frac{1}{2}E(T_{p,\nu}^2) \\ &= \frac{\nu p}{2(\nu - p - 1)}. \end{aligned}$$

Next,

$$\begin{aligned} E(\overline{F}_{p,\nu-p+1}) &= E\left[\frac{\nu y}{\nu - p + 1}E\{F_{y,\nu-p+1}\}\right] \quad (y \sim \text{Bin}(p, 1/2)) \\ &= E\left[\frac{\nu y}{\nu - p + 1} \times \frac{\nu - p + 1}{\nu - p - 1}\right] \\ &= \frac{\nu p}{2(\nu - p - 1)}. \end{aligned}$$

- The second moments match approx.:

$$\mathrm{Var}(\overline{F}_{p,\nu-p+1}) = p\left(\frac{\nu}{\nu-p-1}\right)^2\left\{\frac{1}{4}+\frac{2\nu-p-1}{2(\nu-p-3)}\right\}$$

and

$$\begin{aligned}\mathrm{Var}(g(\boldsymbol{v})) \;\approx\; & p\left(\frac{\nu}{\nu-p-1}\right)^2\left[\left(\frac{\nu-p-1}{\nu-2}\right)^2\left\{\frac{1}{4}+\frac{\nu-1}{2(\nu-4)}\right\}\right. \\ & \left.+\frac{\nu-1}{2(\nu-p-3)}\right].\end{aligned}$$

- In all cases that we checked $\mathrm{Var}(g(\boldsymbol{v})) \le \mathrm{Var}(\overline{F}_{p,\nu-p+1})$.

5. Critical Constants and Type I Error Probabilities for $\overline{F}$ Approx.

Critical Constants for ALR Test Using $\overline{F}$ Approx. ($\alpha = .05$)

ν	p								
	2	3	4	5	6	7	8	9	10
10	6.18	9.65	14.40	21.61	33.87	58.48	123.6	432.4	11,125
30	4.75	6.41	8.05	9.74	11.52	13.43	15.50	17.76	20.26
50	4.53	5.99	7.36	8.70	10.05	11.43	12.84	14.29	15.81
∞	4.23	5.44	6.50	7.48	8.41	9.29	10.16	10.99	11.81

Simulation Estimates of Type I Error Probability of the ALR Test Using the $\overline{F}$ Approx. for $\mathbf{\Sigma}_1 = \mathbf{\Sigma}_2$ ($\alpha = .05$)

ν	p				
	2	4	6	8	10
10	0.0497	0.0449	0.0464	0.0505	0.0503
30	0.0513	0.0482	0.0476	0.0447	0.0444
50	0.0507	0.0479	0.0510	0.0464	0.0445

All simulations based on 10,000 runs.

6. Extension to the Case $\boldsymbol{\Sigma}_1 \neq \boldsymbol{\Sigma}_2$

Notation: Define $\boldsymbol{\Sigma} = \frac{n_2\boldsymbol{\Sigma}_1 + n_1\boldsymbol{\Sigma}_2}{n_1+n_2}$. Then

$$\frac{1}{\tilde{n}}\boldsymbol{\Sigma} = \frac{1}{n_1}\boldsymbol{\Sigma}_1 + \frac{1}{n_2}\boldsymbol{\Sigma}_2 \quad \Rightarrow \boldsymbol{\Omega} = \boldsymbol{\Omega}_1 + \boldsymbol{\Omega}_2.$$

- Make the transformation

$$\boldsymbol{v} = \boldsymbol{D}(\overline{\boldsymbol{x}}_{1\cdot} - \overline{\boldsymbol{x}}_{2\cdot}) = \boldsymbol{D}\boldsymbol{y}$$

  where $\boldsymbol{D}$ is a symmetric matrix s.t.

$$\boldsymbol{D}'\boldsymbol{D} = \widehat{\boldsymbol{\Omega}}^{-1} \text{ and } \boldsymbol{D}\widehat{\boldsymbol{\Omega}}\boldsymbol{D}' = \boldsymbol{I}.$$

- The test statistic is

$$g(\boldsymbol{v}) = \sum_{k=1}^{p} \{\max(v_k, 0)\}^2 .$$

- The distribution of $\boldsymbol{v}'\boldsymbol{v} = \boldsymbol{y}'\boldsymbol{D}'\boldsymbol{D}\boldsymbol{y} = \boldsymbol{y}'\widehat{\boldsymbol{\Omega}}^{-1}\boldsymbol{y}$ can be approximated by Hotelling's $T^2_{p,\nu}$ where ν can be estimated by the moment matching (Welch-Satterthwaite) method as follows (Yao, 1965).

$$\frac{1}{\nu} = \frac{1}{(\boldsymbol{y}'\widehat{\boldsymbol{\Omega}}^{-1}\boldsymbol{y})^2}\left[\frac{(\boldsymbol{y}'\widehat{\boldsymbol{\Omega}}^{-1}\widehat{\boldsymbol{\Omega}}_1\widehat{\boldsymbol{\Omega}}^{-1}\boldsymbol{y})^2}{n_1 - 1} + \frac{(\boldsymbol{y}'\widehat{\boldsymbol{\Omega}}^{-1}\widehat{\boldsymbol{\Omega}}_2\widehat{\boldsymbol{\Omega}}^{-1}\boldsymbol{y})^2}{n_2 - 1}\right].$$

- Use this estimated value of ν in the $\overline{F}_{p,\nu-p+1}$ approximation.

Simulations

Type I error rate of the ALR test using the proposed approx. was simulated for the following choices of $\mathbf{\Sigma}_1$ and $\mathbf{\Sigma}_2$.

For Control group:

$$(\mathbf{\Sigma}_2)_{ii} = 1, (\mathbf{\Sigma}_2)_{ij} = \rho_2 \ \ (1 \leq i \neq j \leq p).$$

For Treatment group:

$$(\mathbf{\Sigma}_1)_{ii} = \sigma_1^2 \ \ (1 \leq i \leq p/2), (\mathbf{\Sigma}_1)_{ii} = \sigma_2^2 \ \ (p/2 + 1 \leq i \leq p),$$

and all correlations equal to ρ_1.

All simulations based on 10,000 runs.

Simulation Estimates of Type I Error Probability of the ALR Test

Using the $\overline{F}$ Approx. for $\boldsymbol{\Sigma}_1 \neq \boldsymbol{\Sigma}_2$ ($\alpha = .05$)

σ_1^2	σ_2^2	ρ_1	ρ_2	$n_1 = n_2 = 50$		$n_1 = n_2 = 30$		$n_1 = n_2 = 20$	
				$p = 4$	$p = 8$	$p = 4$	$p = 8$	$p = 4$	$p = 8$
4	4	0	0	.0506	.0487	.0536	.0486	.0535	.0562*
4	2	0	0	.0501	.0500	.0530	.0468	.0463	.0509
4	4	0.5	0	.0486	.0500	.0481	.0453	.0478	.0512
4	2	0.5	0	.0512	.0460	.0466	.0460	.0493	.0444
4	4	0	0.5	.0458	.0477	.0500	.0501	.0500	.0575*
4	2	0	0.5	.0449	.0476	.0479	.0474	.0479	.0546*
4	4	0.5	0.5	.0479	.0482	.0469	.0525	.0572*	.0538
4	2	0.5	0.5	.0473	.0490	.0499	.0450	.0509	.0463

For $n_1, n_2 \leq 20$, the type I error probability exceeds .05 in several cases.