A third order asymptotic test of bioequivalence in a multivariate parametric setting

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SUMMARY

Let $X_1, \ldots, X_n$ be a sample from a p-variate multivariate normal distribution with mean μ and unknown variance-covariance matrix Σ. For testing $H_0 : \mu'\mu \leq \delta_0$ versus $H_a : \mu'\mu > \delta_0$, exact statistical inference procedures seem generally to be unavailable, except in special cases. Witting (1976) suggested a simple asymptotic method to handle the problem but the order of accuracy of his method is unknown. Based on recent developments in likelihood asymptotic methods by Fraser & Reid (1995) building on Barndorff-Nielsen(1986) and an extensive literature, a new statistical inference procedure for this problem is derived. The proposed method is simple to use and has the order of accuracy $O(n^{-3/2})$.

Keywords: Ancillary direction; Observed level of significance; Scalar parameter; Tail probability; Third order inference.

1. INTRODUCTION

Let $(X_1, \ldots, X_n)$ be a sample from a p-variate multivariate normal distribution $N_p(\mu, \Sigma)$ with mean μ, and variance-covariance matrix Σ. A test of bioequivalence is defined as

$$H_0 : \mu \in \Gamma \quad \text{vs} \quad H_a : \mu \notin \Gamma \tag{1}$$

where Γ is some region. A special case of (1) is

$$H_0 : \mu'\mu \leq \delta \quad \text{vs} \quad H_a : \mu'\mu > \delta. \tag{2}$$

In medical studies, (2) is of special interest. For example, the problem of testing bioequivalence of two drugs in terms of bioavailability in blood. Let $(Z_1, \ldots, Z_n)$ and $(Y_1, \ldots, Y_n)$ be samples from $N_p(\mu_Z, \Sigma_Z)$ and $N_p(\mu_Y, \Sigma_Y)$ respectively. These two samples are often dependent samples. Researchers are interesting in testing

$$H_0 : ||\mu_Z - \mu_Y||^2 \leq \delta \quad \text{vs} \quad H_a : ||\mu_Z - \mu_Y||^2 > \delta$$

where $||w||^2$ is the square length of the vector w. Let $X = Z - Y$, then $(X_1, \ldots, X_n)$ is a sample from $N_p(\mu_X, \Sigma_X)$ where $\mu_X = \mu_Z - \mu_Y$. The hypothesis of interest can be rewritten as

$$H_0 : ||\mu_X||^2 \leq \delta \quad \text{vs} \quad H_a : ||\mu_X||^2 > \delta$$

or equivalently

$$H_0 : \mu'_X \mu_X \leq \delta \quad \text{vs} \quad H_a : \mu'_X \mu_X > \delta.$$

Consider the hypothesis in (2), and let $\delta = 0$. Then $T^2 = n\bar{X}'\hat{\Sigma}\bar{X}$ can be used as a test statistic which is known as the Hotelling T^2 statistic. The exact distributional form of this statistic is known (Anderson, 1975) and hence the exact observed level of significance for (2) can be obtained. Also, if $p = 1$ and Σ is known, then $\bar{X}'\bar{X}$ can be used as a test statistic which follows the noncentral chi-squared distribution with n degrees of freedom and non-centrality parameter δ (Anderson, 1975). Thus the exact observed level of significance for

(2) can be obtained. Nevertheless, except for the above cases, the exact observed level of significance is generally not available.

Witting (1976) showed that

$$\frac{\sqrt{n}(\bar{X}'\bar{X} - \mu'\mu)}{4\bar{X}'\hat{\Sigma}\bar{X}} \longrightarrow^{\mathcal{L}} N(0,1).$$

With this result, the observed level of significance can be approximated, but the order of accuracy of this approximation is uncertain.

In this paper, a new asymptotic method is proposed; the new method is derived from results in Fraser & Reid (1995). The advantage of the proposed method is its simplicity and its accuracy $O(n^{-3/2})$.

A brief review of third order inference is given in Section 2. The proposed method and its application to the bioequivalence testing problem is described in Section 3. Numerical examples are presented in Section 4. Some concluding remarks are recorded in Section 5.

2. THIRD ORDER INFERENCE

Let $y = (y_1, \ldots, y_n)$ be a sample obtained from a statistical model with density $f(y; \theta)$, where θ is a parameter of length k. Moreover, let $\psi = \psi(\theta)$ be a scalar parameter of interest. The type of inference we focus on is to obtain the left tail probability for testing the hypothesis $H_0 : \psi = \psi_0$.

Several simple approximations are widely used to obtain the left tail probabilities for a given ψ: for example, the normal approximation to the distribution of the maximum likelihood estimate of ψ, or the normal approximation to the distribution of the signed square root of the log likelihood ratio statistic. However, these simple approximations are often not very accurate. Some numerical comparisons are given in Wong (1993). Theoretically, these approximations have order of accuracy $O(n^{-1/2})$.

For a given ψ, let R be the signed square root of the log likelihood ratio statistic, which can be expressed as

$$R = sgn(\hat{\psi} - \psi)\{2[l(\hat{\theta}) - l(\hat{\theta}_\psi)]\}^{1/2} \qquad (3)$$

where $l(\theta)$ is the log likelihood function, $\hat{\theta}$ is the maximum likelihood estimate of θ, $\hat{\psi} = \psi(\hat{\theta})$, and $\hat{\theta}_\psi$ is the constrained maximum likelihood estimate of θ for a given ψ. Also let Q be a standardized maximum likelihood departure, and ϕ and Φ denote the standard normal density and distribution functions. Developed for particular classes of models, Lugannani & Rice (1980), and Barndorff-Nielsen (1986, 1991) derived

$$\Phi_1(R, Q) = \Phi(R) + \phi(R)\{R^{-1} - Q^{-1}\} \qquad (4)$$

$$\Phi_2(R, Q) = \Phi(R - R^{-1}\log(R/Q)) \qquad (5)$$

respectively, as formulas to approximate left tail probabilities for a given ψ. Results for different types of models are obtained by having specialized version of Q. These approximations generally have order of accuracy $O(n^{-3/2})$ with the appropriate Q. Reid (1996) gave a detail review of recent development in this area.

3. A NEW METHOD WITH APPLICATION TO BIOEQUIVALENCE TESTING

Most of the existing methods reviewed in Reid (1996) required the existence of a parameterization so that θ is expressed as (ψ, λ') where $\lambda = \lambda(\theta)$ is a nuisance parameter of length $(k-1)$. By differentiating the log likelihood function with respect to the ancillary direction, Fraser & Reid (1995) developed a general way to obtain the nominal parameterization such that (3) and (4) can be applied and the order of accuracy remained as $O(n^{-3/2})$.

Let

$$X_i = \begin{pmatrix} X_{1i} \\ \vdots \\ X_{pi} \end{pmatrix}, \quad \mu = \begin{pmatrix} \mu_1 \\ \vdots \\ \mu_p \end{pmatrix} \quad \text{and} \quad \Sigma^{-1} \begin{pmatrix} \sigma^{11} & \cdots & \sigma^{1p} \\ \vdots & & \vdots \\ \sigma^{p1} & \cdots & \sigma^{pp} \end{pmatrix}.$$

Note that Σ^{-1} is a symmetric matrix, i.e. $\sigma^{ij} = \sigma^{ji}$. If X_i be distributed as $N_p(\mu, \Sigma)$, then the density of X_i can be written as

$$f(X_i; \mu, \Sigma) = (2\pi)^{-p/2} [det(\Sigma^{-1})]^{1/2} \exp\{-\frac{1}{2}(X_i - \mu)'\Sigma^{-1}(X_i - \mu)\}. \tag{6}$$

By expanding (6), the density can be re-written as

$$(2\pi)^{-p/2} [det(\Sigma^{-1})]^{1/2} \exp\{-\frac{1}{2}\mu'\Sigma^{-1}\mu\} \times \tag{7}$$

$$\exp\left\{ \sum_{k=1}^{p}(-\frac{1}{2}y_{ki}^2)\sigma^{kk} + \sum_{k<l;k=1}^{p}(-y_{ki}y_{li})\sigma^{kl} + (\sum_{k=1}^{p}\mu_k\sigma^{k1})y_{1i} + \ldots + (\sum_{k=1}^{p}\mu_k\sigma^{kp})y_{pi} \right\}.$$

This is now expressed in an exponential family form with canonical parameter

$$(\sigma^{11}, \ldots, \sigma^{pp}, \sigma^{12}, \ldots, \sigma^{(p-1)p}, \sum_{k=1}^{p}\mu_k\sigma^{1k}, \ldots, \sum_{k=1}^{p}\mu_k\sigma^{pk}).$$

For a sample $(X_1, \ldots, X_n)$ from $N_p(\mu, \Sigma)$, the joint density can be expressed in an exponential family form with canonical parameter defined as above. The corresponding minimal sufficient statistic is

$$\left(\sum_{i=1}^{n}(-\frac{1}{2}y_{1i}^2), \ldots \sum_{i=1}^{n}(-\frac{1}{2}y_{pi}^2), \sum_{i=1}^{n}(-y_{1i}y_{2i}), \sum_{i=1}^{n}(-y_{(p-1)i}y_{pi}), \sum_{i=1}^{n}y_{1i}, \ldots, \sum_{i=1}^{n}y_{pi} \right).$$

For the problem of bioequivalence testing, the parameter of interest is $\mu'\mu$. In this case, an explicit form of the nuisance parameter seems hard to obtain. Thus the methods reviewed in Reid (1996) and also described in Fraser & Reid (1995) cannot be applied directly.

We will now described a method, which is an extension of the method in Fraser & Reid (1995), that does not require the explicit form of the nuisance parameter.

Note that the signed square root of the log likelihood ratio statistic does not depend on λ and is invariant to reparameterization, thus R remains unchanged as in equation (3). We now record details for the ingredients in the expression for Q.

The overall maximum likelihood value $\hat{\theta}$ is obtained by maximizing the log likelihood function $l(\theta)$. For a given ψ, the constrained maximum likelihood value $(\hat{\theta}_\psi, \hat{\alpha})$ is obtained by maximizing $l(\theta) + \alpha\{\psi(\theta) - \psi\}$. Let

$$\tilde{l}(\theta) = l(\theta) + \hat{\alpha}\{\psi(\theta) - \psi\} \tag{8}$$

be the Lagrangian in the calculations; it can be viewed as a tilted log likelihood function with maximum at $\hat{\theta}_\psi$. Then Q can be defined as

$$Q = sgn(\hat{\psi} - \psi)|\chi(\hat{\theta}) - \chi(\hat{\theta}_\psi)| \left\{ \frac{|\hat{j}_{(\theta\theta)}(\hat{\theta})|}{|\hat{\sigma}^2(\chi)||\tilde{j}_{(\theta\theta)}(\hat{\theta}_\psi)|} \right\}^{1/2} \tag{9}$$

where

$$
\begin{aligned}
\chi(\theta) &= \psi_\varphi(\hat{\theta}_\psi)\varphi(\theta) \\
\varphi(\theta) &= l_{;V}(\theta) \\
\hat{j}_{\theta\theta}(\hat{\theta}) &= -l_{\theta\theta}(\hat{\theta}) \\
|\hat{j}_{(\theta\theta)}(\hat{\theta})| &= |\hat{j}_{\theta\theta}(\hat{\theta})||\varphi_\theta(\hat{\theta})|^{-2} \\
\tilde{j}_{\theta\theta}(\hat{\theta}_\psi) &= -\tilde{l}_{\theta\theta}(\hat{\theta}_\psi) \\
|\tilde{j}_{(\theta\theta)}(\hat{\theta}_\psi)| &= |\tilde{j}_{\theta\theta}(\hat{\theta}_\psi)||\varphi_\theta(\hat{\theta}_\psi)|^{-2} \\
\tilde{j}^{\theta\theta}(\hat{\theta}_\psi) &= \tilde{j}_{\theta\theta}^{-1}(\hat{\theta}_\psi) \\
\hat{\sigma}^2(\chi) &= \psi_\theta(\hat{\theta}_\psi)\tilde{j}^{\theta\theta}(\hat{\theta}_\psi)\psi_\theta'(\hat{\theta}_\psi)
\end{aligned}
$$

and V is the ancillary direction defined as in Fraser & Reid (1995). We also use the notation

$$\varphi_\theta(\theta) = \frac{\partial \varphi(\theta)}{\partial \theta}$$

and similarly $l_{\theta\theta}(\theta), \psi_\theta(\theta)$ where subscripts denote differentiation. Using Q, as in equation (9), and R, as in equation (3), left tail probability for a given ψ can then be obtained by either equation (4) or equation (5). Following the argument in Fraser & Reid (1995), it can be shown that the order of accuracy remains $O(n^{-3/2})$. For details, see Fraser, Reid & Wu (1996).

With this setup, the observed level of significance for the test of bioequivalence can be approximated.

4. NUMERICAL EXAMPLES

Example 1: For $p = 1$ and $\Sigma = 1$, the exact observed level of significance for $\mu'\mu$ can be obtained from a noncentral chi-squared distribution. Table 1 recorded the approximated and the exact observed level of significance for various δ values.

Table 1: $n = 5$

δ	1			9		
$\bar{X}'\bar{X}$	9	16	25	16	25	36
$\Phi(R)$	0.9773	0.9987	1.0000	0.8413	0.9773	0.9987
$\Phi_1(R,Q)$	0.8163	0.9819	0.9993	0.6644	0.9318	0.9944
$\Phi_2(R,Q)$	0.7613	0.9765	0.9992	0.6531	0.9293	0.9942
Exact	0.8148	0.9809	0.9993	0.6621	0.9313	0.9944

The proposed methods gives good approximations in comparison with the first order method does not. Note that for this case, the equations for R and Q can be simplified tremendously. See further discussions and comparisons in Fraser, Wong & Wu (1997).

Example 2: For $p = 1$, using *Splus*, we generate five data points from a normal distribution with mean 2 and variance 1. The data are:

$$2.5189 \quad 0.2096 \quad 0.3357 \quad 2.6606 \quad 0.4453$$

In this case, we assume the variance to be unknown. Hence the exact results are unavailable. Table 2 records the approximate level of significance for various δ values using the proposed third order method and the ordinary likelihood ratio method $\Phi(R)$.

Table 2:

δ	0	0.5	1	2	8
$\Phi(R)$	0.9775	0.8432	0.6795	0.3592	0.0090
$\Phi_1(R, Q)$	0.9561	0.8042	0.6540	0.3796	0.0219

Note that, for $\delta = 0$, the observed value of significance can be obtained by using the simple t test with 4 degrees of freedom and the result is 0.9548; also note that this extreme parameter value corresponds to a singularity and we would thus not expect the asymptotics to apply. Even for such a small sample size, the proposed method gives reasonably good approximation whereas the first order method is less satisfactory.

Example 3: Data are taken from Johnson & Wichern (1982, p. 181-183). In this case, $n = 20$ and $p = 3$. $H_0 : \mu'\mu \le 2616$ vs $H_a : \mu'\mu > 2616$. The observed levels of significance from the first order method $\Phi(R)$, and the third order methods $\Phi_1(R, Q)$ and $\Phi_2(R, Q)$ are 0.07490, 0.06675 and 0.06676 respectively. The first order method and the proposed methods give different results. In this case, we do not have an exact result to compare to.

5. DISCUSSIONS

In this paper, a simple method is described to obtain the observed level of significance for the test of bioequivalence. Theoretically, the method has order of accuracy $O(n^{-3/2})$. The proposed method does not depend on the explicit form of the nuisance parameterization. All the calculations can easily be implemented into an algebraic computational program such as Maple or Mathematica. A version of this program has been developed, using Maple, by J. Wu.

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