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A Bayesian Analysis in Multivariate Bioassay and Multivariate Calibration+

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ABSTRACT

In the linear model which consider both the multivariate parallel-line bioassay and the multivariate linear calibration, this paper presents a Bayesian procedure which is an extension of Hunter and Lamboy(1981) and has several advantages compared with the non Bayesian techniques. Based on the methods of this article we discuss the effect of multivariate calibration and give a numerical example.

1. Introduction

Let us consider the following linear model;

$$Y_{ij}=\alpha+\beta_1 x_{ij}+\beta_2 Z_{ij}+\varepsilon_{ij},\ i=1,\ 2;\ j=1,\ 2,\cdots,n_i, \tag{1.1}$$

where Y_{ij} are observable p-dimensional random vectors, $p\times 1$ vectors α, β_1, β_2 are unknown parameters, the error terms ε_{ij}'s are i.i.d. $N_p(0, \Sigma)$(Σ is unknown) random vectors and Z_{ij}'s are defined as follows;

$$Z_{ij}=\begin{cases} 0, & \text{if} \quad i=1 \\ 1, & \text{if} \quad i=2. \end{cases}$$

Without loss of generality the controlled variables x_{ij}'s are chosen so that

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they have the property $\sum_{j=1}^{n_i} x_{ij}=0$, $i=1, 2$.

Model (1.1) is known as a multivariate bioassay model. The fundamental condition of similarity between test preparation($i=1$ case) and standard preparation($i=2$ case), a prerequisite of all dilution assays, requires $\beta_2=\beta_1\mu$. Under this condition the scalar μ is viewed as the potency of the test relative to the standard and (1.1) will be a parallel-line bioassy model. On test about $\beta_2=\beta_1\mu$ which we assume throughout this paper, refer to Srivastava(1986). We are concerned with inferences for μ. There are numerous non-Bayesian statistical studies concerning inferences on μ(see Srivastava(1986) and references therein). Very little Bayesian work is available for this problem. An exception is Buonaccorsi and Gatsonis(1988), who considered the $p=1$ case.

Moreover (1.1) is a multivariate linear calibration model if we take the key relation $\beta_2=\beta_1\mu$ and

$$x_{ij}=\begin{cases} x_{ij}, & i=1 \\ 0, & i=2. \end{cases}$$

Also in the calibration problem most work has concentrated on the estimation, including interval estimation, of μ. Brown(1982) gave Bayesian and non-Bayesian analysis for this problem. His Bayesian solutions obtained by assigning prior directly to the unknown μ are multivariate extensions of those of Hoadley(1970).

In this paper we present a Bayesian inference on μ and our approach will be based on ideas of Hunter and Lamboy(1981). In the multivariate bioassay setting our work is the first Bayesian treatment and in view of the multivariate calibration our work is different from that of Brown(1982) and possesses several advantages over that of Brown, among which is an ability to algebraically analyze the effect of multivariate calibration. The basic idea is that for any constant $p\times 1$ vector c, $c'\beta_2=c'\beta_1\mu$ holds so that μ can be expressed as the ratio of two linear combinations of regression coefficients, leading to the problem of finding the best choice of c in some sense.

In section 2 we derive the posterior density of $\mu=(c'\beta_2)/(c'\beta_1)$ by adopting an usual noninformative prior and choose c to minimize the posterior variance of μ. Also we study the effect of multivariate calibration by using the results of this section. Section 3 contains an example. In Section 4 we compare our approach with others and discuss some important issues.

2. Main Results

2-1. The Posterior Distribution of μ

In this subsection we derive the posterior density of μ and study the best choice of c. Model(1.1) can be rewritten as follows;

$$Y=XB+E \tag{2.1}$$

where $Y'=(y_{11}, y_{12},\cdots, y_{1n_1}, y_{21}, y_{22},\cdots,y_{2n_2})$,

$B'=(\alpha, \beta_1, \beta_2)$,

$E'=(\varepsilon_{11}, \varepsilon_{12},\cdots, \varepsilon_{1n_1}, \varepsilon_{21}, \varepsilon_{22},\cdots, \varepsilon_{2n_2})$, and

$$X'=\begin{pmatrix} 1 & 1\cdots 1 & 1\cdots 1 \\ x_{11} & x_{12}\cdots x_{1n_1} & x_{21}\cdots x_{2n_2} \\ 0 & 0\cdots 0 & 1\cdots 1 \end{pmatrix}.$$

If we use an invariant Jeffreys' prior

$$P(B \mid \text{data}) \propto |\Sigma|^{-(p+1)/2}$$

then familiar results(Box and Tiao(1973)) imply that the posterior distribution of B is

$$P(B \mid \text{data}) \propto |I_p+V^{-1}(B-\hat{B})'X'X(B-\hat{B})|^{-n/2} \tag{2.2}$$

where $\hat{B}=(\hat{\alpha}, \hat{\beta}_1, \hat{\beta}_2)'=(X'X)^{-1}X'Y$, $V=(Y-X\hat{B})'(Y-X\hat{B})$ and $n=n_1+n_2$. Implicitly defining A by

$$X'X=\begin{pmatrix} n & 0 & n_2 \\ 0 & A & 0 \\ n_2 & 0 & n_2 \end{pmatrix}, \quad \text{where } A=\sum_{i=1}^{2}\sum_{j=1}^{n_i} x_{ij}^2$$

the posterior distribution of β_1, β_2 is given by

$$P(\beta_1, \beta_2 \mid \text{data}) \propto$$
$$|I_p+V^{-1}(\beta_1-\hat{\beta}_1, \beta_2-\hat{\beta}_2)C_{22}^{-1}(\beta_1-\hat{\beta}_1, \beta_2-\hat{\beta}_2)'|^{-(n-1)/2} \tag{2.3}$$

where

$$C_{22}=\begin{pmatrix} A^{-1} & 0 \\ 0 & n/(n_1n_2) \end{pmatrix}.$$

From (2.3) we can obtain for any constant $p\times 1$ vector c,

$P(c'\beta_1, c'\beta_2 \mid \text{data})\propto$

$$\left\{1+(c'Vc)^{-1}\begin{pmatrix} c'\beta_1-c'\hat{\beta}_1 \\ c'\beta_2-c'\hat{\beta}_2 \end{pmatrix}' C_{22}^{-1}\begin{pmatrix} c'\beta_1-c'\hat{\beta}_1 \\ c'\beta_2-c'\hat{\beta}_2 \end{pmatrix}\right\}^{-(n-p)/2} \tag{2.4}$$

which is a bivariate t distribution with degrees of freedom $\nu=n-p-2$.(See Box and Tiao(1973).) From (2.4) we can obtain the generalized MLE of μ, namely, $\hat{\mu}=(c'\hat{\beta}_2)/(c'\hat{\beta}_1)$.

By the formula (2.6) in the Hunter and Lamboy (1981) and their corrigendum(1984), our final posterior density of μ is the following;

i) for even $\nu=n-p-2$ and $q=(\nu+2)/2$,

$$P(\mu \mid \text{data})=$$

$$\frac{k_1}{(q-1)k_2k_4^{(q-1)}}+\frac{k_1k_3^2}{(2q-1)k_2k_4^{(q-1)}}\sum_{m=0}^{q-2}\frac{(2k_2k_4)^m(2q-1)(2q-3)\cdots(2q-2m-1)}{(q-1)(q-2)\cdots(q-m-1)\Delta^{(m+1)}}$$

$$+\frac{2^q(2q-3)!!\,k_1k_3k_2^{(q-2)}}{(q-1)!\,\Delta^{(q-1/2)}}\tan^{-1}(k_3/\sqrt{\Delta}) \tag{2.5a}$$

ii) for odd ν and $q=(\nu+1)/2$

$$P(\mu \mid \text{data})=\frac{2k_1}{(2q-1)\,k_2k_4^{(q-1/2)}}+\frac{2k_1k_3^2}{(2q-1)\Delta k_2k_4^{(q-1/2)}}\times$$

$$\left\{1+\sum_{m=0}^{q-1}\frac{(8k_2k_4)^m(q-1)(q-2)\cdots(q-m)}{(2q-3)(2q-5)\cdots(2q-2m-1)\Delta^m}\right\} \tag{2.5b}$$

where $k_1=\{\Gamma((\nu+2)/2)\mid Q\mid^{-1/2}\}/\{\pi\Gamma(\nu/2)\}$

$$Q^{-1}=(c'Vc)^{-1}\begin{pmatrix} A & 0 \\ 0 & R \end{pmatrix}$$

$$k_2=(c'Vc)^{-1}(R\mu^2+A)$$

$$k_3=-2(c'Vc)^{-1}\,(R\mu c'\hat{\beta}_2+Ac'\hat{\beta}_1)$$

$$k_4=1+(c'Vc)^{-1}\,\{R(c'\hat{\beta}_2)^2+A(c'\hat{\beta}_1)^2\}$$

$$\Delta = 4k_2k_4 - k_3^2$$
$$(2q-3)!! = (2q-3)(2q-5)\cdots 1$$
$$R = n_1n_2/n.$$

When p=1, c will be a constant scalar and our approach will be reduced to the work of Hunter and Lamboy(1981).

2-2. Choice of c

For any constant p×1 vector c, $\mu = (c'\beta_2)/(c'\beta_1)$ holds so that the choice of suitable c is important. It is natural to choose c to minimize Var($(c'\beta_2)/(c'\beta_1)$ | data) but the non-existence of the conditional variance in this setting is the trouble. However, as Schukla(1972) mentioned, this trouble can be avoided by assuming $c'\beta_1 \neq 0$, so our development of this subsection is under the condition that the p-value is almost zero when testing $c'\beta_1 = 0$.

By forming a Taylor series expansion of $(c'\beta_2)/(c'\beta_1)$ about $(c'\hat{\beta}_1, c'\hat{\beta}_2)$ and dropping all terms of order higher than 2, we obtain

$$\text{Var}\left(\frac{c'\beta_2}{c'\beta_1} \mid \text{data}\right) \approx \frac{(\nu-2)^{-1}c'\text{Vc}(c'\hat{\beta}_2)^2}{(c'\hat{\beta}_1)^2}\left\{\frac{1}{(c'\hat{\beta}_2)^2 R} + \frac{A^{-1}}{(c'\hat{\beta}_1)^2}\right\}$$
$$= \frac{c'\text{Sc}}{(c'\hat{\beta}_1)^2}\left(\frac{n-3}{(\nu-2)R} + \hat{\mu}^2\frac{n-3}{\nu-2}A^{-1}\right) \tag{2.6}$$

where S=V/(n−3).

Recalling the relation $\beta_2 = \beta_1\mu$ it seems reasonable to assume that $\hat{\mu}$ does not vary much as c varies. On the other hand in the calibration case Var(μ | data) is approximated by $n_2^{-1}(c'\text{Sc})(c'\hat{\beta}_1)^{-2}$ for sufficiently large n_1(large calibration experiment case), assuming $A^{-1} \to 0$ as $n_1 \to \infty$. Therefore in our view we can roughly minimize Var(μ | data) by minimizing $(c'\text{Sc})(c'\hat{\beta}_1)^{-2}$. Applying the extended Cauchy-Schwarz inequality, $(c'\text{Sc})(c'\hat{\beta}_1)^{-2}$ has minimum $(\hat{\beta}_1'\text{S}^{-1}\hat{\beta}_2)^{-1}$ when $c' = \hat{\beta}_1'\text{S}^{-1}$ which is our choice of c.

We choose the c under some restricted circumstances but we can apply our method to the unrestricted cases with this chosen c. Replacing c' by $\hat{\beta}_1'\text{S}^{-1}$ in the generalized MLE $\hat{\mu} = (c'\hat{\beta}_2)/(c'\hat{\beta}_1)$ and (2.5), we can do point and interval estimation for μ.

2-3. Effect of Multivariate Calibration

In this subsection we will study how much we can improve the interval estimate of μ when we use the multivariate calibration compared with the univariate calibration. Park(1986) studied on this topic but he assumed all the nuisance parameters are known. When nuisance parameters are unknown it appears difficult to study this problem algebraically by non-Bayesian methods.

Take $c'=\beta_1'S^{-1}$. By (2.6)

$$\mathrm{Var}_m(\mu \mid \text{data}) \approx (\hat{\beta}_1'S^{-1}\hat{\beta}_1)^{-1}\left\{\frac{n-3}{(n-p-4)R}+\hat{\mu}_m^2\frac{n-3}{n-p-4}A^{-1}\right\} \tag{2.7}$$

where $\hat{\mu}_m=(\hat{\beta}_1'S^{-1}\hat{\beta}_1)^{-1}\hat{\beta}_1'S^{-1}\hat{\beta}_2$.

When $p=1$ (univariate calibration case),

$$\mathrm{Var}_u(\mu \mid \text{data})=\mathrm{Var}_u\left(\frac{\beta_{21}}{\beta_{11}} \mid \text{data}\right)\approx(\hat{\beta}_{11}^2 s_1^{-2})^{-1}\left\{\frac{n-3}{(n-5)R}+\hat{\mu}_u^2\frac{n-3}{n-5}A^{-1}\right\} \tag{2.8}$$

where $\hat{\mu}_u=\hat{\beta}_{21}/\hat{\beta}_{11}$, β_{11} and β_{21} are the first coordinates of β_1 and β_2 respectively, and s_1^2 is an unbiased estimator of σ_1^2, variance of the first coordinate of ε_{ij}. By arguments similar to those of subsection 2.2, we can approximate $\hat{\mu}_m \approx \hat{\mu}_u$. Let us restrict our problem to $p=2$ for the multivariate case and let

$$S=\begin{pmatrix} s_1^2 & rs_1s_2 \\ rs_1s_2 & s_2^2 \end{pmatrix}, \qquad \hat{\beta}_1=\begin{pmatrix} \hat{\beta}_{11} \\ \hat{\beta}_{12} \end{pmatrix}$$

where r is the sample correlation coefficient of y_1 and y_2. Then for sufficiently large n,

$$\frac{\mathrm{Var}_u(\mu \mid \text{data})}{\mathrm{Var}_m(\mu \mid \text{data})} \approx \frac{\hat{\beta}_1'S^{-1}\hat{\beta}_1}{\hat{\beta}_{11}^2 s_1^{-2}} = 1+(1-r^2)^{-1}\left(r-\frac{s_1\hat{\beta}_{12}}{s_2\hat{\beta}_{11}}\right)^2. \tag{2.9}$$

This result suggests that there is no need to add one more response variable (y_2) if r is close to $(s_1\hat{\beta}_{12})/(s_2\hat{\beta}_{11})$ or 1, though the effect of adding one more variable is great if r is near zero and far from $(s_1\hat{\beta}_{12})/(s_2\hat{\beta}_{11})$. See Park(1986) for a related discussion and example.

3. Example

In this section we use our approach to the data considered by Finney(1978, p.262 Table 13.2.1). For these data, we have n=24, p=2,

$$\hat{B}=\begin{pmatrix} 7.2167 & 48.3333 \\ 2.1875 & -2.1875 \\ -2.2167 & 3.7500 \end{pmatrix}$$

$$V=\begin{pmatrix} 106.854 & 81.471 \\ 81.471 & 223.021 \end{pmatrix}$$

$$c'=\begin{bmatrix} 0.8757 & -0.5847 \end{bmatrix}$$

Since $\nu=20$, we use the posterior p.d.f (2.5a) and calculate the values ℓ and u satisfying $\int_{\ell}^{u} P(\mu \mid \text{data})\, d\mu = 0.95$ numerically as $\ell = -1.48696$ and $u = -0.41196$.

Srivastava(1986) has obtained both exact and asymptotic confidence interval for μ through the multivariate versions of Fieller's theorem, and Finney(1978) has also done. Here is the list of the confidence intervals for comparison.

		lowerbound	upperbound	length
Srivastava (Fieller's theorem)	exact	-1.537508	-0.528973	1.008535
	asymptotic	-1.765346	-0.409624	1.355721
Finney		-1.653	-0.414	1.239
Park/Lee		-1.48696	-0.41196	1.07500

4. Discussion

Our approach has several advantages over that of Brown(1982). First we can investigate and interpret the effect of multivariate calibration as we have discussed in section 2.

Of course, with the noninformative prior on μ we can show that the posterior density of μ, when we apply the Brown's approach, goes to $N(\mu^*, (n_2\beta_1' \Sigma^{-1}\beta_1)^{-1})$ as $n_1 \to \infty$, where $\mu^* = (\beta_1' \Sigma^{-1}\beta_1)^{-1} \beta_1' \Sigma^{-1}\hat{\beta}_2$. This result enables us to investigate the multivariate calibration effect when n_1 is sufficiently large. However our method enables us to do this job without regard to the sample size.

Secondly under the noninformative prior we can obtain a proper posterior and express the density of μ explicitly while Brown(1982) cannot, except under the very special Student t prior density.

Finally in contrast with Brown(1982) our Bayesian approach deals with the multivariate bioassay and the multivariate calibration simultaneously.

Brown and Sundberg(1987) pointed out it might be more effective to use independent variables one at a time excluding the others than to use all the variables concerned with the linear model, even when more than one independent variables are to be predicted. We can demonstrate this phenomenon with two independent variables when n_1 is large and this is one of the reasons we consider only one independent variable in our multivariate calibration model.

As compared to non-Bayesian multivariate bioassay analysis(multivariate version of Fieller's theorem) our Bayesian approach enables the investigator to obtain a finite confidence interval and give an exact confidence level on the interval for any data set.

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