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Noninformative Priors for the Ratio of the Lognormal Means with Equal Variances

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Abstract

We develop noninformative priors for the ratio of the lognormal means in equal variances case. The Jeffreys' prior and reference priors are derived. We find a first order matching prior and a second order matching prior. It turns out that Jeffreys' prior and all of the reference priors are first order matching priors and in particular, one-at-a-time reference prior is a second order matching prior. One-at-a-time reference prior meets very well the target coverage probabilities. We consider the bioequivalence problem. We calculate the posterior probabilities of the hypotheses and Bayes factors under Jeffreys' prior, reference prior and matching prior using a real-life example.

Keywords: Bioequivalence problem; equal variance; Jeffreys' prior; matching priors; ratio of the lognormal means; reference priors.

1. Introduction

Faced with a skewed distribution, one can transform the original data in a way that normalizes the distribution. The log-transformation is the most commonly used one. One estimation problem is to construct confidence intervals and to test for the lognormal mean. A common practice for such comparisons is to perform testing procedures on log-transformed outcome variables and to report the resulting p-values for the null hypothesis based on the original outcomes. For the Bayesian approach, see Moon *et al.* (2000) and Moon and Kim (2001). These proposed the methods which are based on the Bayes factor. Another estimation problem is for obtaining confidence intervals and tests for the ratio of means of two independent lognormal distributions. For example, in a bioequivalence

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trials, the relative potency of a new drug to that of a standard one is expressed in terms of the ratio of means, and analysts often need to construct a confidence interval for this ratio or to test the null hypothesis that the ratio is one (Berger and Hsu, 1996; Chow and Liu, 2000).

For our interest parameter, the ratio of lognormal means, we consider here noninformative priors. We consider Bayesian priors such that the resulting credible intervals for the ratio of the lognormal means have coverage probabilities equivalent to their frequentist counterparts. Although this matching can be justified only asymptotically, our simulation results indicate that this is indeed achieved for small or moderate sample sizes as well. The matching idea goes back to Welch and Peers (1963). Interest in such priors revived with the work of Stein (1985) and Tibshirani (1989). Among others, we may cite the work of Mukerjee and Dey (1993), Datta and Ghosh (1995a, 1995b), Datta and Ghosh (1995c, 1996), and Mukerjee and Ghosh (1997). On the other hand, Ghosh and Mukerjee (1992), and Berger and Bernardo (1989, 1992) extended Bernardo's (1979) reference prior approach, giving a general algorithm to derive a reference prior by splitting the parameters into several groups according to their order of inferential importance. This approach is very successful in various practical problems. Quite often reference priors satisfy the matching criterion described earlier.

In this paper, we develop noninformative priors when the variances of the log-transformed outcome variables are equal. In Section 2, we derive Fisher information matrix under orthogonal reparametrization. Then we develop the various noninformative priors. Specifically we derive the Jeffreys' prior and the reference priors for different groups of ordering for the parameters, and we develop first order and second order probability matching priors for our interesting parameter. Sufficient conditions for the propriety of posterior for a general class of priors are also given in this section. In Section 3, we provide the simulated frequentist coverage probabilities under the proposed priors. In Section 4, we consider the bioequivalence problem. Two different drugs or formulations of the same drugs are called *bioequivalent* if they are absorbed into the blood and become available at the drug action site at about the same rate and concentration. Bioequivalence of the two drugs is defined as the ratio of means is between the tolerance limit prespecified by a regulatory agency. We calculate the posterior probabilities of the hypotheses under Jeffreys' prior, reference prior and matching prior. Also we provide the Bayes factors. Two treatments AUC data are provided for equal variance case to illustrate our results.

2. Development of Noninformative Priors

Let $\boldsymbol{X}_1 = (X_{11}, \ldots, X_{1n_1})$ be a random sample of size n_1 from a lognormal population with parameters μ_1 and σ^2 and $\boldsymbol{X}_2 = (X_{21}, \ldots, X_{2n_2})$ be a random sample of size n_2 from a lognormal population with parameters μ_2 and σ^2. That is, $\log X_{1i}$ and $\log X_{2j}$ are independently and normally distributed with means μ_1 and μ_2 respectively and common variance σ^2. The parameter $\theta_1 = \mu_1 - \mu_2$ is of interest. Note that

$$\frac{\mathrm{E}(X_{1i})}{\mathrm{E}(X_{2j})} = \frac{\exp(\mu_1 + \frac{1}{2}\sigma^2)}{\exp(\mu_2 + \frac{1}{2}\sigma^2)} = \exp(\theta_1). \tag{2.1}$$

Thus the problem for the ratio of two means is equivalent to θ_1.

The pdf of $\boldsymbol{x}_1$, $\boldsymbol{x}_2$ is given by

$$f(\boldsymbol{x}_1, \boldsymbol{x}_2 : \mu_1, \mu_2, \sigma^2) \propto (\sigma^2)^{-\frac{n_1+n_2}{2}} \exp\left\{ -\frac{1}{2\sigma^2} \sum_{i=1}^{2} \sum_{j=1}^{n_i} (\log x_{ij} - \mu_i)^2 \right\}. \tag{2.2}$$

In order to find priors, it is convenient to introduce orthogonal parametrization (Cox and Reid, 1987). To this end, let

$$\theta_1 = \mu_1 - \mu_2,\ \theta_2 = \frac{n_1}{n_1+n_2}\mu_1 + \frac{n_2}{n_1+n_2}\mu_2 \text{ and } \theta_3 = \sigma^2. \tag{2.3}$$

With this parametrization, the likelihood has the alternate representation.

$$L(\theta_1, \theta_2, \theta_3) \propto \theta_3^{-\frac{n_1+n_2}{2}} \exp\left[-\frac{1}{2\theta_3} \left\{ \sum_{j=1}^{n_1} \left(\log x_{1j} - \frac{n_2}{n_1+n_2}\theta_1 - \theta_2\right)^2 \right.\right.$$
$$\left.\left. + \sum_{j=1}^{n_2} \left(\log x_{2j} + \frac{n_1}{n_1+n_2}\theta_1 - \theta_2\right)^2 \right\} \right]. \tag{2.4}$$

Based on (2.3), the Fisher information matrix is given by

$$\boldsymbol{I}(\boldsymbol{\theta}) = \mathrm{Diag}\left(\frac{n_1 n_2}{(n_1+n_2)\theta_3}, \frac{n_1+n_2}{\theta_3}, \frac{n_1+n_2}{2\theta_3^2} \right). \tag{2.5}$$

Thus θ_1 is orthogonal to (θ_2, θ_3) in the sense of Cox and Reid (1987).

We begin with Jeffreys' prior given by

$$\begin{aligned} \pi_J(\boldsymbol{\theta}) &\propto |\boldsymbol{I}(\boldsymbol{\theta})|^{\frac{1}{2}} \\ &\propto \theta_3^{-2}. \end{aligned} \tag{2.6}$$

This is a reference prior when all parameters are treated as equally important.

We consider now other reference priors. Let $\boldsymbol{\theta}_{(1)} = \{\theta_1\}$ and $\boldsymbol{\theta}_{(2)} = \{\theta_2, \theta_3\}$. Then the Fisher information matrix can be expressed as

$$\boldsymbol{I}(\boldsymbol{\theta}) = \mathrm{Diag}\big(h_1(\boldsymbol{\theta}), h_2(\boldsymbol{\theta})\big),$$

where $h_1(\boldsymbol{\theta}) = n_1 n_2/((n_1+n_2)\theta_3)$, $h_2(\boldsymbol{\theta}) = \mathrm{Diag}\big((n_1+n_2)/\theta_3, (n_1+n_2)/2\theta_3^2\big)$. Hence, from Theorem 1 of Datta and Ghosh (1995c) the two-group reference prior is given by

$$\pi_R(\boldsymbol{\theta}) \propto \theta_3^{-\frac{3}{2}}. \tag{2.7}$$

The one-at-a-time reference prior with the partition $\{\theta_1\}$, $\{\theta_2\}$, $\{\theta_3\}$ where θ_1 is the parameter of interest, while the remaining parameters are considered in any arbitrary order of importance. Writing the Fisher information matrix as

$$\boldsymbol{I}(\boldsymbol{\theta}) = \text{Diag}\big(h_1(\boldsymbol{\theta}), h_2(\boldsymbol{\theta}), h_3(\boldsymbol{\theta})\big),$$

where $h_1(\boldsymbol{\theta})$ is same as before, but $h_2(\boldsymbol{\theta}) = (n_1+n_2)/\theta_3$ and $h_3(\boldsymbol{\theta}) = (n_1+n_2)/(2\theta_3^2)$. Once again, an appeal to Theorem 1 of Datta and Ghosh (1995c) leads to the one-at-a-time reference prior as

$$\pi_R^*(\boldsymbol{\theta}) \propto \theta_3^{-1}. \tag{2.8}$$

Let $\boldsymbol{X} = (\boldsymbol{X}_1, \boldsymbol{X}_2)$. For a prior π, let $\theta_1^{1-\alpha}(\pi; \boldsymbol{X})$ denote the $(1-\alpha)^{th}$ percentile of the posterior distribution of θ_1, that is,

$$P^{\pi}\big[\theta_1 \le \theta_1^{1-\alpha}(\pi; \boldsymbol{X})|\boldsymbol{X}\big] = 1-\alpha, \tag{2.9}$$

where $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_t)^T$ and θ_1 is the parameter of interest. We want to find priors π for which

$$P\big[\theta_1 \le \theta_1^{1-\alpha}(\pi; \boldsymbol{X})|\boldsymbol{\theta}\big] = 1-\alpha+o(n^{-u}) \tag{2.10}$$

for some $u > 0$, as n goes to infinity. Priors π satisfying (2.10) are called matching priors. If $u = 1/2$, then π is referred to as a first order matching prior, while if $u = 1$, π is referred to as a second order matching prior.

From Tibshirani (1989), the class of first order probability matching priors is characterized by

$$\begin{aligned}\pi_F(\boldsymbol{\theta}) &\propto \boldsymbol{I}_{\theta_1\theta_1}(\boldsymbol{\theta})^{\frac{1}{2}} q(\theta_2, \theta_3) \\ &\propto \theta_3^{-\frac{1}{2}} q(\theta_2, \theta_3),\end{aligned} \tag{2.11}$$

where q is any arbitrary positive-valued function differentiable in its arguments. Jeffreys' prior as well as the other reference priors are all first order probability matching priors.

Clearly the class of prior given in (2.11) is quite large and it is important to narrow down this class of priors. To this end, we consider the class of second order probability matching priors as given Mukerjee and Ghosh (1997). Due to the orthogonality of θ_1 with (θ_2, θ_3), the class of second order probability matching priors is characterized by solving a partial differential equation

$$\frac{1}{6} q(\theta_2,\theta_3) \frac{\partial}{\partial\theta_1}\left(I_{11}^{-\frac{3}{2}} L_{1,1,1}\right) + \sum_{\nu=2}^{3}\sum_{s=2}^{3} \frac{\partial}{\partial\theta_\nu}\left\{I_{11}^{-\frac{1}{2}} L_{11s} I^{s\nu} q(\theta_2,\theta_3)\right\} = 0, \tag{2.12}$$

where $L_{1,1,1} = \mathrm{E}\Big[\big(\partial \log L/\partial\theta_1\big)^3\Big]$, $L_{11s} = \mathrm{E}\Big[\partial^3 \log L/\partial\theta_1^2\partial\theta_s\Big]$, $s = 2, 3$ and $I^{s\nu}$ is the $(s,\nu)^{th}$ element of $\boldsymbol{I}^{-1}(\boldsymbol{\theta})$, the inverse of the Fisher information matrix. Then (2.12) simplifies to

$$\frac{\partial}{\partial\theta_3}\left\{\theta_3^{\frac{1}{2}} q(\theta_2,\theta_3)\right\} = 0. \tag{2.13}$$

A general class of solutions to the above equation is given by

$$q(\theta_2, \theta_3) \propto \theta_3^{-\frac{1}{2}} g(\theta_2), \tag{2.14}$$

where g is a positive function, differential in its argument, but is otherwise arbitrary. Thus the resulting second order probability matching prior is

$$\pi_S(\boldsymbol{\theta}) \propto \theta_3^{-1} g(\theta_2). \tag{2.15}$$

We consider a particular second order matching prior when g is a constant in the above matching prior. This prior is given by θ_3^{-1} which is the same as $\pi_R^*(\boldsymbol{\theta})$.

Based on the above calculations, it follows that $\pi_J(\boldsymbol{\theta})$, $\pi_R(\boldsymbol{\theta})$ and $\pi_S(\boldsymbol{\theta})$ belong to a general class of priors of the form

$$\pi_a(\boldsymbol{\theta}) \propto \theta_3^{-a}. \tag{2.16}$$

In particular, the choices $a = 2$, $3/2$ and 1 lead respectively to π_J, π_R and π_S. In the original parameterization, the prior $\pi_a(\boldsymbol{\theta})$ reduces to

$$\pi_a(\mu_1, \mu_2, \sigma^2) \propto (\sigma^2)^{-a}. \tag{2.17}$$

We investigate the propriety of posteriors for a general class of priors which include the Jeffreys' prior, the reference prior and the second order matching prior. We consider the class of priors

$$\pi(\boldsymbol{\theta}) \propto \theta_3^{-a}, \tag{2.18}$$

where $a > 0$. The following general theorem provides the propriety of posteriors.

Theorem 2.1 *The posterior distribution of* $\boldsymbol{\theta}$ *under the prior* π, *(2.18), is proper if* $n_1 + n_2 + 2a - 3 > 0$.

The proof of this theorem is straightforward and is omitted. The marginal posterior of θ_1 under the prior (2.18) is given by

$$\pi(\theta_1 | \boldsymbol{x}_1, \boldsymbol{x}_2) \propto \left\{ S^2 + \frac{n_1 n_2}{n_1 + n_2} (\theta_1 - \bar{y}_1 + \bar{y}_2)^2 \right\}^{-\frac{n_1+n_2+2a-3}{2}}, \tag{2.19}$$

where $y_{ij} = \log x_{ij}$, $\bar{y}_i = 1/n_i \sum_{j=1}^{n_i} y_{ij}$ and $S^2 = \sum_{i=1}^{2} \sum_{j=1}^{n_i} (y_{ij} - \bar{y}_i)^2$, $j = 1, \ldots, n_i$, $i = 1, 2$.

3. Simulation Study

We evaluate the frequentist coverage probability by investigating the credible interval of the marginal posteriors density of θ_1 under the noninformative prior π given in (2.18) for several configurations (μ_1, μ_2, σ^2) and (n_1, n_2). That is to say, the frequentist coverage of a $(1-\alpha)^{th}$ posterior quantile should be close to $1 - \alpha$.

Table 3.1: Comparisons of Coverage Probability for Posterior Quantiles of θ_1 with Equal Variances

n_1	n_2	σ^2	0.05			0.95		
			π_J	π_R	π_S	π_J	π_R	π_S
5	5	0.5	0.073	0.062	0.050	0.929	0.940	0.950
		1	0.072	0.061	0.051	0.929	0.940	0.950
		10	0.073	0.063	0.051	0.928	0.940	0.951
5	10	0.5	0.061	0.054	0.048	0.940	0.945	0.951
		1	0.064	0.058	0.051	0.936	0.942	0.951
		10	0.061	0.055	0.049	0.935	0.943	0.949
10	10	0.5	0.063	0.057	0.053	0.941	0.945	0.952
		1	0.060	0.056	0.049	0.939	0.944	0.949
		10	0.059	0.055	0.050	0.936	0.941	0.946
10	20	0.5	0.056	0.052	0.050	0.945	0.948	0.951
		1	0.056	0.053	0.050	0.943	0.945	0.949
		10	0.056	0.052	0.048	0.946	0.948	0.951

For fixed (μ_1, μ_2, σ^2) and (n_1, n_2), we take 10,000 independent random samples of $(\boldsymbol{x}_1, \boldsymbol{x}_2)$ from the model (2.2).

The Table 3.1 gives numerical values of the frequentist coverage probabilities of 0 to 0.05 and 0 to 0.95 posterior quantiles under the Jeffreys', reference prior and second order matching prior.

In Table 3.1, we can observe that the second order matching prior π_S meets very well the target coverage probabilities. This is intuitively clear since π_S is a second order matching prior, but π_J, π_R are not. Also note that the results of table are not much sensitive to the change of the values of σ^2. Thus we recommend to use the second order matching prior for the Bayesian inference for the ratio of the lognormal means with equal variances.

4. Numerical Example in Bioequivalence Problems

In this section, we will illustrate our Bayesian method using a real-life example. AUC data from an experiment with simultaneous administration of a test formulation (x_1) and a reference formulation (x_2) in six male subjects (Alkalay *et al.*, 1980). The AUC data from this study are presented in Table 4.1 ($n_1 = n_2 = 6$). The sample means are 38.618 and 39.440, and the sample standard deviations are 25.112 and 26.394. After the log-transformation, the sample means are 3.499 and 3.508 and the sample standard deviations are 0.590 and 0.614.

The Shapiro-Wilk tests for the normality on the log-transformed data give a p-value of 0.191 for the test formulation group and a p-value of 0.185 for the reference formulation group, while the same tests on the original data give a p-value of 0.079 for the test

Table 4.1: AUC Data from an Experiment

x_1	19.96	20.37	52.42	21.37	82.98	34.61
x_2	19.91	21.30	55.49	19.73	85.33	34.88

formulation group and a p-value of 0.084 for the reference formulation group. Therefore, the log-transformation normalizes the data. The F-test for equal variances of the log-transformed data between the two groups gives a p-value of 0.932, and therefore the log-transformation stabilizes the variances.

We have two theories. Theory one says that two formulations are not bioequivalence, *i.e.*, $H_0 : \theta_1 \leq \kappa_L$ or $\theta_1 \geq \kappa_U$. Theory two says that two formulations are bioequivalence, *i.e.*, $H_a : \kappa_L < \theta_1 < \kappa_U$ (Berger and Hsu, 1996). Here θ_1 is that logarithm transformation be taken the ratio of the lognormal means.

The posterior probability of the null hypothesis is

$$P(H_0|\boldsymbol{x}_1, \boldsymbol{x}_2) = \frac{\int_{-\infty}^{\kappa_L} \pi(\theta_1|\boldsymbol{x}_1, \boldsymbol{x}_2)d\theta_1 + \int_{\kappa_U}^{\infty} \pi(\theta_1|\boldsymbol{x}_1, \boldsymbol{x}_2)d\theta_1}{\int_{-\infty}^{\infty} \pi(\theta_1|\boldsymbol{x}_1, \boldsymbol{x}_2)d\theta_1}, \tag{4.1}$$

and the posterior probability of the alternative hypothesis is

$$P(H_a|\boldsymbol{x}_1, \boldsymbol{x}_2) = \frac{\int_{\kappa_L}^{\kappa_U} \pi(\theta_1|\boldsymbol{x}_1, \boldsymbol{x}_2)d\theta_1}{\int_{-\infty}^{\infty} \pi(\theta_1|\boldsymbol{x}_1, \boldsymbol{x}_2)d\theta_1}, \tag{4.2}$$

where $\pi(\theta_1|\boldsymbol{x}_1, \boldsymbol{x}_2)$ is the marginal posterior of θ_1 is given in (2.19).

In this case, $n_1 = 6$, $n_2 = 6$, $\bar{y}_1 = 3.499$, $\bar{y}_2 = 3.508$ and $S^2 = 3.627$.

Table 4.2 provides the posterior probabilities of the null hypothesis H_0 and alternative hypothesis H_a corresponding to Jeffreys' prior (π_J), two group reference prior (π_R) and second order probability matching prior (π_S). Also Table 4.2 provides the Bayes factors for H_0 versus H_a.

If we use $\kappa_U = -\kappa_L = \log 1.25$, the Bayes factor gives the weak evidence for H_a for π_J. Hence two formulations are bioequivalence. But the Bayes factor gives the weak evidence for H_0 for π_R and π_S. Hence two formulations are bioinequivalence. This discrepancy in the conclusion may be due to the poor performance of π_J as we already noticed in Section 3.

Table 4.2: Posterior Probabilities and Bayes Factors with Equal Variances

	$\kappa_U = -\kappa_L = \log 1.25$		
	π_J	π_R	π_S
$P(H_0\|\boldsymbol{x}_1, \boldsymbol{x}_2)$	0.496	0.515	0.536
$P(H_a\|\boldsymbol{x}_1, \boldsymbol{x}_2)$	0.504	0.485	0.464
B_{12}	0.984	1.062	1.155

References

Alkalay, D., Wagner, W. E., Carlsen, S., Khemani, L., Volk, J., Bartlett, M. F. and LeSher, A. (1980). Bioavailability and kinetics of maprotiline. *Clinical Pharmacology and Therapeutics*, **27**, 697–703.

Berger, J. O. and Bernardo, J. M. (1989). Estimating a product of means: Bayesian analysis with reference priors. *Journal of the American Statistical Association*, **84**, 200–207.

Berger, J. O. and Bernardo, J. M. (1992). On the development of reference priors (with discussion). In *Bayesian Statistics 4* (J. M. Bernardo, et al., eds), 35–60, Oxford University Press, Oxford.

Berger, R. L. and Hsu, J. C. (1996). Bioequivalence trials, intersection-union tests and equivalence confidence sets. *Statistical Science*, **11**, 283–315.

Bernardo, J. M. (1979). Reference posterior distributions for Bayesian inference (with discussion). *Journal of the Royal Statistical Society*, Ser. B, **41**, 113–147.

Chow, S. C. and Liu, J. P. (2000). *Design and Analysis of Bioavailability and Bioequivalence Studies*, 2nd ed., Marcel Dekker, New York.

Cox, D. R. and Reid, N. (1987). Orthogonal parameters and approximate conditional inference (with discussion). *Journal of Royal Statistical Society*, Ser. B, **49**, 1–39.

Datta, G. S. and Ghosh, J. K. (1995a). On priors providing frequentist validity for Bayesian Iinference. *Biometrika*, **82**, 37–45.

Datta, G. S. and Ghosh, J. K. (1995b). Noninformative priors for maximal invariant parameter in group models. *Test*, **4**, 95–114.

Datta, G. S. and Ghosh, M. (1995c). Some remarks on noninformative priors. *Journal of the American Statistical Association*, **90**, 1357–1363.

Datta, G. S. and Ghosh, M. (1996). On the invariance of noninformative priors. *The Annals of Statistics*, **24**, 141–159.

Ghosh, J. K. and Mukerjee, R. (1992). Noninformative Ppriors (with discussion). In *Bayesian Statistics 4* (J. M. Bernardo, *et al.*, eds.) 195–210, Oxford University Press, Oxford.

Moon, K. A. and Kim, D. H. (2001). Bayesian testing for the equality of two lognormal populations with the fractional Bayes factor. *Journal of the Korean Data & Information Science Society*, **12**, 51–59.

Moon, K. A., Shin, I. H. and Kim, D. H. (2000). Bayesian testing for the equality of two lognormal populations. *Journal of the Korean Data & Information Science Society*, **11**, 269–277.

Mukerjee, R. and Dey, D. K. (1993). Frequentist validity of posterior quantiles in the presence of a nuisance parameter: higher order asymptotics. *Biometrika*, **80**, 499–505.

Mukerjee, R. and Ghosh, M. (1997). Second order probability matching priors. *Biometrika*, **84**, 970–975.

Stein, C. (1985). On the coverage probability of confidence sets based on a prior distribution. *Sequential Methods in Statistics*, **16**, 485–514.

Tibshirani, R. (1989). Noninformative priors for one parameter of many. *Biometrika*, **76**, 604–608.

Welch, B. L. and Peers, H. W. (1963). On formula for confidence points based on integrals of weighted likelihood. *Journal of the Royal Statistical Society*, Ser, B, **25**, 318–329.

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