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Bootstrap and MLS methods-based individual bioequivalence assessment

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Abstract— It is a one-sided hypothesis testing process for assessing bioequivalence. Bootstrap and modified large-sample(MLS) methods are considered to study individual bioequivalence(IBE), type I error and power of hypothesis tests are simulated and compared with FDA(2001). The results show that modified large-sample method is equivalent to the method of FDA(2001) .

Keywords—individual bioequivalence; bootstrap; Bayesian bootstrap; modified large-sample

I. Introduction

THE aim of bioequivalence(BE) studies is to assess the equivalence of two pharmaceutical drug of the same active drug substance(Wijnand [1]). BE generally have three types including average bioequivalence (ABE), population bioequivalence (PBE) and individual bioequivalence(IBE). ABE focuses only on the difference of average measure between test drug(T) and reference drug(R), the interest measure may be area under curve and peak concentration. But ABE ignores the variability of the measure for T and R. PBE emphasizes total variability of the measure in population. IBE takes into account the within-subject variability and subject-by-formulation interaction for T and R. The mixed-effects model usually be used to evaluate BE.

The original bootstrap method is used to study BE (FDA [2]). FDA [3] proposed a parametric method to evaluate BE. Shao et al. [4] improved the assessing procedure of FDA [1]. Pigeot [5] continued to investigate IBE by bootstrap percentile method. Wan et al. [6] investigated IBE by bootstrap and Bayesian bootstrap methods, but they did not consider the type I error for hypothesis testing. In this paper we shall give the type I error and compare the modified large-sample method with bootstrap methods. Efron [7] proposed a new method named bootstrap which can simulate confidence interval for interest parameter such as mean and variance. Now there are many different styles about the bootstrap. The asymptotic theory of bootstrap can be seen in the literatures (e.g., Singh [8]; Bickel and Freedman [9]).

The hybrid bootstrap percentile method is to approximate the distribution of $\hat{\theta}-\theta$ by $\hat{\theta}^*-\hat{\theta}$. On the basis of bootstrap percentile method, the approximated upper confidence bound is $2\hat{\theta}-\hat{\theta}^*(\mathrm{B}\alpha)$. Hall [10] pointed out the coverage error was also $O(n^{-\frac{1}{2}})$. Rubin [11] proposed the Bayesian bootstrap method to construct confidence interval.

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Ting et al. [12] extended the idea of modified large-sample(MLS) method to obtain an upper confidence bound for $\eta=c_1\sigma_1^2+\cdots+c_p\sigma_p^2$ in which $c_i(i=1,2,\ldots,p)$ has different sign. The 1-α upper confidence bound is

$$c_1\hat{\sigma}_1^2+\cdots+c_p\hat{\sigma}_p^2+\sqrt{c_1^2\hat{\sigma}_1^4(\frac{n_1}{u_1}-1)^2+\cdots+c_p^2\hat{\sigma}_p^4(\frac{n_p}{u_p}-1)^2}, \quad (1)$$

where

$$u_i=\begin{cases}\chi^2_{\alpha,n_i}, & c_i>0,\\ \chi^2_{\alpha,n_i}, & c_i<0,\end{cases} \quad (2)$$

n_i denotes the number of samples in each sequence and $\hat{\sigma}_1^2,\hat{\sigma}_2^2,\cdots,\hat{\sigma}_p^2$ are independent. Lee et al. [13] considered the case that $\hat{\sigma}_1^2,\hat{\sigma}_2^2,\cdots,\hat{\sigma}_p^2$ are dependent and used the new method to evaluate PBE.

The rest of this article is organized as follows. In Section 2, we provide a description of the statistical model and criteria for evaluating IBE in Appendix G of FDA's Guidance [3]. In Section 3, the power of different bootstrap methods and MLS method for test procedures is simulated, and the type I error of several tests is investigated. We present some conclusions in Section 4.

II. Statistical model and criteria

To assess IBE s-sequence and four-period experiment usually be considered. FDA [3] recommended the mixed-effect model

$$Y_{ijkl}=\mu_k+\gamma_{ikl}+\delta_{ijk}+\varepsilon_{ijkl} \quad (3)$$

where $i=1,2,\ldots,s$ indicates sequence, $j=1,2,\ldots,n_i$ indicates subject within sequence i, k=R,T denotes treatment, l=1,2 denotes replicate on treatment k for subjects within sequence i. Y_{ijkl} is the response of replicate l on treatment k for subject j in sequence i, γ_{ikl} represents the fixed effect of replicate l on treatment k in sequence i, δ_{ijk} is the random subject effect for subject j in sequence i on treatment k, and ε_{ijkl} is the random error for subject j within sequence i on replicate l of treatment k.

The linearized criteria are as follows in FDA [3]

(a) reference-scaled($\sigma_{WR}^2\geq\sigma_{W0}^2$):

$$\eta_1=(\mu_T-\mu_R)^2+\sigma_D^2+\sigma_{WT}^2-\sigma_{WR}^2-\theta_I\cdot\sigma_{WR}^2, \quad (4)$$

(b) constant-scaled($\sigma_{WR}^2<\sigma_{W0}^2$):

$$\eta_2=(\mu_T-\mu_R)^2+\sigma_D^2+\sigma_{WT}^2-\sigma_{WR}^2-\theta_I\cdot\sigma_{W0}^2, \quad (5)$$

where μ_T and μ_R indicate population average responses of the log-transformed measure for the T and R formulation, respectively. $\sigma_D^2=\sigma_{BT}^2+\sigma_{BR}^2-2\rho\sigma_{BT}\sigma_{BR}$ indicates subject-by-formulation interaction variance component, σ_{WT}^2 and σ_{WR}^2

represent the within-subject variance of the T formulation and R formulation, respectively. σ^2_{W0} represents specified constant within-subject variance and θ_I BE limit. Consider the testing hypothesis

$$H_0 : \eta \geq 0 \quad \text{versus} \quad H_1 : \eta < 0 \tag{6}$$

where $\eta = \eta_1$ if $\sigma^2_{WR} \geq \sigma^2_{W0}$ and $\eta = \eta_2$ if $\sigma^2_{WR} < \sigma^2_{W0}$.

Some statistics are defined as follows:

$I_{ij} = Y_{ijT\cdot} - Y_{ijR\cdot}$, $T_{ij} = Y_{ijT1} - Y_{ijT2}$,

$R_{ij} = Y_{ijR1} - Y_{ijR2}$, i=1,2,...,s, j=1,2,...,n_i,

$Y_{ijT\cdot} = \frac{1}{2}(Y_{ijT1} + Y_{ijT2})$, $Y_{ijR\cdot} = \frac{1}{2}(Y_{ijR1} + Y_{ijR2})$,

$\hat{\mu}_k = \frac{1}{s}\sum_{i=1}^{s} \overline{Y_{i\cdot k\cdot}}$, k=R,T.

$\overline{Y_{i\cdot k\cdot}} = \frac{1}{n_i}\sum_{j=1}^{n_i} \frac{1}{2}\sum_{l=1}^{2} Y_{ijkl}$, $\hat{\Delta} = \hat{\mu}_T - \hat{\mu}_R$,

$M_I = \hat{\sigma}^2_I = \frac{1}{n_I}\sum_{i=1}^{s}\sum_{j=1}^{n_i}(I_{ij} - \overline{I_{i\cdot}})^2$,

$M_T = \hat{\sigma}^2_{WT} = \frac{1}{2n_T}\sum_{i=1}^{s}\sum_{j=1}^{n_i}(T_{ij} - \overline{T_{i\cdot}})^2$,

$M_R = \hat{\sigma}^2_{WR} = \frac{1}{2n_R}\sum_{i=1}^{s}\sum_{j=1}^{n_i}(R_{ij} - \overline{R_{i\cdot}})^2$,

$n_I = n_T = n_R = \sum_{i=1}^{s} n_i - s$.

$\overline{I_{i\cdot}} = \frac{1}{n_i}\sum_{j=1}^{n_i} I_{ij}$, $\overline{T_{i\cdot}} = \frac{1}{n_i}\sum_{j=1}^{n_i} T_{ij}$,

$\overline{R_{i\cdot}} = \frac{1}{n_i}\sum_{j=1}^{n_i} R_{ij}$.

Then the above linearized criteria are estimated by

(c) reference-scaled($M_R \geq \sigma^2_{W0}$):

$$\tilde{\eta}_1 = \hat{\Delta}^2 + M_I + 0.5M_T - (1.5 + \theta_I)M_R, \tag{7}$$

(d) constant-scaled($M_R < \sigma^2_{W0}$):

$$\tilde{\eta}_2 = \hat{\Delta}^2 + M_I + 0.5M_T - 1.5M_R - \theta_I\sigma^2_{W0}. \tag{8}$$

Compute the 95% upper bound of the parameter η . If the upper bound is negative or zero, we can draw a conclusion that the IBE is equivalent for T and R. To calculate the upper bound there are parametric methods such as FDA [3] and nonparametric method(e.g., FDA [2]; Shao et al. [4]). On the basis of the mixed-model(FDA [3]), we study IBE by using bootstrap and Bayesian bootstrap methods.

Note that

$\sigma^2_I = \text{var}(\frac{Y_{ijT1}+Y_{ijT2}}{2} - \frac{Y_{ijR1}+Y_{ijR2}}{2})$,

$\sigma^2_{WT} = \text{var}(\frac{Y_{ijT1}-Y_{ijT2}}{2\sqrt{2}})$, $\sigma^2_{WR} = \text{var}(\frac{Y_{ijR1}-Y_{ijR2}}{2\sqrt{2}})$,

and $\text{cov}(\frac{Y_{ijT1}-Y_{ijT2}}{2\sqrt{2}}, \frac{Y_{ijR1}-Y_{ijR2}}{2\sqrt{2}}) = 0$,

$$\text{cov}(\frac{Y_{ijT1}+Y_{ijT2}}{2} - \frac{Y_{ijR1}+Y_{ijR2}}{2}, \frac{Y_{ijT1}-Y_{ijT2}}{2\sqrt{2}}) = 0,$$

$$\text{cov}(\frac{Y_{ijT1}+Y_{ijT2}}{2} - \frac{Y_{ijR1}+Y_{ijR2}}{2}, \frac{Y_{ijR1}-Y_{ijR2}}{2\sqrt{2}}) = 0,$$

since $\text{cov}(T_1, T_2) = \sigma^2_{BT}$, $\text{cov}(R_1, R_2) = \sigma^2_{BR}$,
$\text{cov}(T_1, R_1) = \text{cov}(T_1, R_2) = \text{cov}(T_2, R_1) = \text{cov}(T_2, R_2) = \rho\sigma_{BT}\sigma_{BR}$. Hence M_I, M_T, M_R are independent.

III. Simulation Results

Given s=2 and $n_1 = n_2 = n$, let

$$y_{1j} = (Y_{1jT1}, Y_{1jT2}, Y_{1jR1}, Y_{1jR2}),$$

$$y_{2j} = (Y_{2jT1}, Y_{2jT2}, Y_{2jR1}, Y_{2jR2}),$$

($j = 1, 2, \ldots, n$), the bootstrap sample $(y^*_{11}, y^*_{12}, \ldots, y^*_{1n})$ and $(y^*_{21}, y^*_{22}, \ldots, y^*_{2n})$ are drawn from $(y_{11}, y_{12}, \ldots, y_{1n})$ and $(y_{21}, y_{22}, \ldots, y_{2n})$ with replacement, respectively.

We choose appropriate criterion to calculate $\hat{\eta}^*_1$ or $\hat{\eta}^*_2$, either $\hat{\eta}^*_1$ or $\hat{\eta}^*_2$ denoted by $\hat{\eta}^{*1}$.

The following methods (M1-M4) can be found in [6].

(M1) bootstrap percentile method(BP): For each bootstrap sample, we calculate the bootstrap estimator M^*_R of σ^2_{WR} to compare with $\sigma^2_{W0} = 0.04$ so as to choose the approximate the criterion. Repeat the above step B times (choose B=500), we can calculate the bootstrap estimator $\hat{\eta}^{*b}(b = 1, 2, \ldots, B)$ of η, let $\hat{\eta}^*(i)$ represent the i-th largest number of $\hat{\eta}^{*b}(b = 1, 2, \ldots, B)$. The approximate $100(1-\alpha)$ confidence upper bound is $\hat{\eta}^*(\text{B} - \text{B}\alpha)$ for η . IBE is equivalent to T and R if $\hat{\eta}^*(\text{B} - \text{B}\alpha) \leq 0$.

(M2) hybrid bootstrap percentile method(HBP): We analogously compute the approximate $100(1-\alpha)$ confidence upper bound for η is $2\hat{\eta} - \hat{\eta}^*(\text{B}\alpha)$. IBE is equivalent to T and R if $2\hat{\eta} - \hat{\eta}^*(\text{B}\alpha) \leq 0$.

(M3) Bayesian bootstrap percentile method(BBP): To estimate the interest parameters Δ, σ^2_I, σ^2_{WT} and σ^2_{WR}, we generate s random vectors V_i=$D(n_i; 1, 1, ..., 1)$ (i=1,2,...,s). Then the Bayesian bootstrap estimator of Δ is

$$\hat{\Delta}^* = \frac{1}{s}\sum_{i=1}^{s}\sum_{j=1}^{n_i} V_{ij}I_{ij}. \tag{9}$$

The Bayesian bootstrap estimators of σ^2_I, σ^2_{WT} and σ^2_{WR} are

$$M^*_I = \frac{1}{n_I}\sum_{i=1}^{s} n_i \sum_{j=1}^{n_i} V_{ij}(I_{ij} - \sum_{j=1}^{n_i} V_{ij}I_{ij})^2, \tag{10}$$

$$M^*_T = \frac{1}{2n_T}\sum_{i=1}^{s} n_i \sum_{j=1}^{n_i} V_{ij}(T_{ij} - \sum_{j=1}^{n_i} V_{ij}T_{ij})^2, \tag{11}$$

and

$$M^*_R = \frac{1}{2n_R}\sum_{i=1}^{s} n_i \sum_{j=1}^{n_i} V_{ij}(R_{ij} - \sum_{j=1}^{n_i} V_{ij}R_{ij})^2, \tag{12}$$

respectively. Denoted Bayesian bootstrap estimator of η by $\hat{\eta}^{*b}_{\text{BB}}(b = 1, 2, \ldots, \text{B})$. IBE is equivalent to T and R if $\hat{\eta}^*_{\text{BB}}(\text{B} - \text{B}\alpha) \leq 0$.

(M4) hybrid Bayesian bootstrap percentile method (HBBP): The process for assessing IBE is similar to Bayesian bootstrap percentile method. IBE can be claimed for T and R if $2\hat{\eta} - \hat{\eta}^*_{\text{BB}}(\text{B}\alpha) \leq 0$.

(M5) by the work of Section 2 we use formulas (1) and (2) to calculate the upper confidence bound for the parameter η.

The following parameter setting to enable H_0 hold is considered (ps represents parameter setting).

ps	$\mu_T-\mu_R$	σ^2_{WT}	σ^2_{WR}	σ^2_{BT}	σ^2_{BR}	ρ	η
1	0.30	0.06	0.01	0.03	0.01	0.9	0.0490
2	0.30	0.03	0.01	0.06	0.03	0.9	0.0238
3	0.40	0.10	0.03	0.09	0.01	0.9	0.1762
4	0.10	0.02	0.01	0.03	0.02	0.9	0.0262

The above six methods are used to evaluate IBE for the dataset in [1]. Let $\alpha = 0.05$, the $1-\alpha$ upper confidence bound are -0.0305, -0.0425, -0.0506, -0.0505, -0.0471 and -0.0316, respectively, the smallest number is -0.0505 which is associated with Bayesian bootstrap percentile method.

TABLE I
TYPE I ERROR SIMULATION

ps	method	β (n=12)	β (n=24)	β (n=36)	β (n=48)
1	FDA's	0	0	0	0
	BP	0.05	0.01	0	0
	HBP	0.01	0	0	0
	BBP	0	0	0	0
	HBBP	0	0	0	0
	MLS	0	0	0	0
2	FDA's	0.01	0.03	0.04	0.04
	BP	0.10	0.20	0.16	0.18
	HBP	0.15	0.13	0.13	0.15
	BBP	0.09	0.08	0.07	0.09
	HBBP	0.12	0.09	0.09	0.07
	MLS	0.01	0.03	0.04	0.04
3	FDA's	0	0	0	0
	BP	0	0	0	0
	HBP	0	0	0	0
	BBP	0	0	0	0
	HBBP	0	0	0	0
	MLS	0	0	0	0
4	FDA's	0	0.01	0	0
	BP	0.04	0.04	0.03	0.02
	HBP	0.07	0.05	0	0.03
	BBP	0.05	0.02	0.01	0
	HBBP	0.07	0.01	0.01	0
	MLS	0	0.01	0	0

The following parameter setting is considered:

ps	$\mu_T-\mu_R$	σ^2_{WT}	σ^2_{WR}	σ^2_{BT}	σ^2_{BR}	ρ	η
1	0.10	0.06	0.05	0.03	0.02	0.9	-0.0988
2	0.10	0.03	0.01	0.03	0.02	0.9	-0.0639
3	0.20	0.03	0.03	0.03	0.02	0.9	-0.0539
4	0.20	0.02	0.01	0.03	0.02	0.9	-0.0439

All these above 4 parameters setting satisfy $\eta < 0$. For each parameter setting we generate 100 groups random nubers under the model in FDA [3] and B=500 bootstrap samples for each group. Denote β the number that the upper confidence bound of η is less than or equal to 0, then $\beta/100$ means the power simulated for the test procedure. We evaluate IBE by parametric method (FDA [3]), BP mehtod, HBP method, BBP method, HBBP method and MLS mtehod (see, Ting et al. [12]; Lee et al. [13]) at significance level $\alpha = 0.05$.

IV. Conclusion

As shown in the above tables, we see that modified large-sample method achieves the same type I error and power of FDA [3].

TABLE II
POWER SIMULATION

ps	method	β (n=12)	β (n=24)	β (n=36)	β (n=48)
1	FDA's	0.75	0.92	1	1
	BP	0.73	0.92	0.98	1
	HBP	0.59	0.83	0.90	0.98
	BBP	0.96	1	1	1
	HBBP	0.81	0.90	0.99	0.99
	MLS	0.81	0.90	0.99	0.99
2	FDA's	0.95	1	1	1
	BP	0.97	1	1	1
	HBP	0.85	0.94	0.98	1
	BBP	1	1	1	1
	HBBP	0.98	1	1	1
	MLS	0.81	0.90	0.99	0.99
3	FDA's	0.67	0.90	0.97	0.99
	BP	0.81	0.88	0.99	1
	HBP	0.65	0.78	0.75	0.86
	BBP	1	1	1	1
	HBBP	0.53	0.58	0.68	0.76
	MLS	0.81	0.90	0.99	0.99
4	FDA's	0.87	0.99	1	1
	BP	0.91	0.97	1	1
	HBP	0.71	0.88	0.95	0.98
	BBP	1	1	1	1
	HBBP	0.50	0.51	0.79	0.81
	MLS	0.81	0.90	0.99	0.99

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