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CONTENTS

1. Introduction

In pharmacology, comparison of bioavailability is an important problem. A new formulation of a drug is compared with a standard formulation in human subjects. When the extent of absorption is studied the areas under the concentration/time curves (AUC) are the statistics used for analysis. These statistics are determined by some parametric or nonparamatric methods from the basic concentration measurements e.g. every half hour during a day.

Data are often collected for both new and standard formulations according to a two-period cross-over design with totally n subjects. For the subjects the bioavailability ratios

$$R_i = AUC_i \text{ (new)}/AUC_i \text{ (standard)}$$
$$i = 1, 2, \ldots, n$$

are formed. These seem to be preferable to differences

$$D_i = AUC_i \text{ (new)} - AUC_i \text{ (standard)}$$
$$i = 1, 2, \ldots, n$$

which usually can not be supposed to be independent of the variable AUC_i (standard) or AUC_i (new). The distribution of the ratios R_i $i = 1, 2, \ldots, n$ can however be suspected to be right skewed and in most contexts it is more suitable to consider the log ratios

$$Z_i = \ln R_i = \ln AUC_i \text{ (new)} - \ln AUC_i \text{ (standard)}$$
$$i = 1, 2, \ldots, n.$$

The log ratios Z_i $i = 1, 2, \ldots, n$ (as well as the ratios R_i, $i = 1, 2, \ldots, n$) are supposed to be independent, identically distributed.

The most interesting parameter is the expectation $\mu = E[Z_i]$ or the median m determined by $P(Z_i > m) = P(Z_i < m)$. For symmetric distributions μ and m both coincide with the symmetry point. Bioeqvivalence means that μ (or m) is close enough to 0. A typical

definition in some applications is that the new drug and the standard drug are considered bioequivalent if $-0.233 < \mu < 0.223$ which corresponds to $e^{-0.223} = 0,8 \leq e^{\mu} \leq e^{+0.223} = 1,25$ in the "ratio scale". There are several parametric and non-parametric methods proposed for this type of problem.

Methods can be given in confidence interval formulations or hypothesis test formulations. See e.g. Westlake (1972, 1976, 1979, 1981), Hauck and Andersson (1984), Steinijans and Diletti (1985) and Kirkwood (1981).

Our methods are formulated in terms of tests of hypotheses. They are somewhat related to methods proposed by Westlake (1972, 1976, 1979), but his methods are formulated in terms of confidence intervals. Furthermore his intervals do not have a predetermined confidence coefficient which is the same for all parameter values. Our methods are also somewhat related to the test method by Hauck and Andersson (1984) but their method has only an approximative level of significance, which can be considerably higher than the nominal level in some cases.

2. Proposed tests

When the aim of a bioequivalence trial is to show that a new drug is bioequivalent to a standard drug, the natural hypothesis to test is

$$H_0 : \mu \notin (a, b)$$

for some a and b, when we consider the parameter $\mu = E [Z_i]$. Suppose we can reject the hypothesis H_0 in a test with small level of significance α. Then the rejective statement $\mu \in (a, b)$ (meaning that there is bioequivalence) is defensible in the sence that the event of falsely making this statement, when the hypothesis $\mu \notin (a, b)$ is true, has at most the small probability α. A good test of the hypothesis

$$H_0 : \mu \notin (a, b)$$

with level of significance α will have a power function (probablility of rejection), which is smaller than α for $\mu \notin (a, b)$ and which has big values for μ in the central parts of the interval (a, b).

For the case, when Z_i i = 1, 2, ..., n are independent N (μ,σ) distributed with known σ there exists a uniformly most powerful (UMP) test of $H_0 : \mu \notin (a, b)$ with level of significance α. In this test H_0 is rejected when

$$\bar{Z} = \frac{1}{n} \sum_{k=1}^{n} Z_k \in (a + \lambda, b - \lambda)$$

where λ is determined by

$$P_a (\bar{Z} \in (a + \lambda, b - \lambda)) = P_b (\bar{Z} \in (a + \lambda, b - \lambda)) = \alpha$$

and P_μ means probability calculated when Z_i, i = 1, 2, ..., n, are N (μ, σ) distributed. See Lehmann (1959) p 89. Observe that λ is not only smaller than the half length $u_{1-\frac{\alpha}{2}} \frac{\sigma}{\sqrt{n}}$ of a two sided confidence coefficient 1 - α, but also smaller than $u_{1-\alpha} \frac{\sigma}{\sqrt{n}}$, which is used to determine a one-sided confidence

interval with confidence coefficient $1 - \alpha$. Here u_q means the q fractile in the N (0,1) distribution. For instance for $a = -0{,}223$ $b = 0{,}223$ $\sigma = 0{,}35$ and $n = 12$ we get $\lambda = 0{,}164$ while $\mu_1 - \frac{\alpha}{2} \frac{\sigma}{\sqrt{n}} = 0{,}198$ and $\mu_1 - \alpha \frac{\sigma}{\sqrt{n}} = 0{,}167$.

In practice the standard deviation σ can not be supposed to be known, but must be considered to be a nuisance parameter. For problems with nuisance parameters a standard technique is to construct a UMP unbiased test. But the common technique does not apply to our problem. See Lehmann (1959) chapter 5. In this paper we will propose a test which is not (exactly) unbiased but has a power function which is a little smaller than the level of significance at the boundaries $\mu = a$, $0 < \sigma < \infty$ and $\mu = b$, $0 < \sigma < \infty$ of the hypothesis H_0.

The parametric normal method we propose is based on the following simple theorem.

Theorem 1. Let $Z_1, Z_2, \ldots, Z_n$ be independent N (μ, σ) random variables with mean

$$\bar{Z} = \frac{1}{n} \sum_{k=1}^{n} Z_k \quad \text{and}$$

standard deviation $S = \left(\frac{1}{n-1} \sum_{k=1}^{n} (Z_k - \bar{Z})^2\right)^{1/2}$

and let $t_{1-\alpha}$ be the $1 - \alpha$ fractile in the t distribution with $n - 1$ degrees of freedom. Then

$$\sup P_{\mu, \sigma} \left(a + t_{1-\alpha} \frac{S}{\sqrt{n}} \leq \bar{X} \leq b - t_{1-\alpha} \frac{S}{\sqrt{n}}\right) \leq \alpha \text{ for } \mu \notin (a, b)$$

where $P_{\mu,\sigma}$ denotes probability for the parameters μ and σ.

Proof Let A and B be the events

$$A = \left\{a + t_{1-\alpha} \frac{S}{\sqrt{n}} \leq \bar{X}\right\}$$

$$B = \left\{\bar{X} \leq b - t_{1-\alpha} \frac{S}{\sqrt{n}}\right\}$$

Then for $\mu \leq a$

$$P_{\mu,\alpha}\left(a + t_{1-\alpha}\frac{S}{\sqrt{n}} \leq \bar{X} \leq b - t_{1-\alpha}\frac{S}{\sqrt{n}}\right) =$$

$$= P_{\mu,\alpha}(A \cap B) \leq P_{\mu,\alpha}(A) \leq \alpha$$

In the same way for $\mu \geq b$

$$P_{\mu,\alpha}\left(a + t_{1-\alpha}\frac{S}{\sqrt{n}} \leq \bar{X} \leq b - t_{1-\alpha}\frac{S}{\sqrt{n}}\right) =$$

$$= P_{\mu,\alpha}(A \cap B) \leq P_{\mu,\alpha}(B) \leq \alpha$$

Q.E.D.

The theorem shows that a test of the hypothesis

$H_0 : \mu \notin (a, b)$

rejecting when

$$a + t_{1-\alpha}\frac{S}{\sqrt{n}} \leq \bar{X} \leq b - t_{1-\alpha}\frac{S}{\sqrt{n}}$$

has a level of significance $\leq \alpha$. It is to be noted that the distance $t_{1-\alpha}\frac{S}{\sqrt{n}}$ between $\bar{X}$ and the limits a and b corresponds to a one-sided confidence interval for μ with confidence coefficient $1 - \alpha$ although the test problem has a two-sided hypothesis. We will discuss further properties of the test later.

The type of test construction, used for the normal case above, is possible to apply to other parametric or nonparametric families of distributions. We will consider next a nonparametric test related to the (one-sample) Wilcoxon test.

Suppose that $Z_1, Z_2, \ldots, Z_n$ are independent and that they have a probability density $f(x - \theta)$, where f is any (unknown) symmetric density. The Wilcoxon test of the hypothesis $H_{\theta_0} : \theta = \theta_0$ can be based on the sum of ranks of $\left|Z_i - \theta_0\right|$ for the Z_i:s

satisfying $Z_i > \Theta_0$ in the series of all $|Z_i - \Theta_0|$. Equivalently it can be based on the number of Z_i:s satisfying $Z_i > \Theta_0$ and the number of pairs i, j; $i \leq j$ satisfying $\frac{1}{2}(Z_i + Z_j) > \Theta_0$ See e.g. Lehmann (1975) section 3.2. Let us denote

V_{Θ_0} = number of averages $\frac{Z_i + Z_j}{2} > \Theta_0$

with $i \leq j$.

Then $H_{\Theta_0} : \Theta = \Theta_0$ is rejected

if $V_{\Theta_0} \leq k$ or $V_{\Theta_0} \geq \frac{n(n+1)}{2} - k$

for some suitable k, determined by the level of significance.

For one-sided hypotheses $H_{\Theta_0} : \Theta \leq \Theta_0$ or $H_{\Theta_0} : \Theta \geq \Theta_0$ a Wilcoxon one-sample test analogously rejects for $V_{\Theta_0} \geq k_1$ or $V_{\Theta_0} \leq k_2$ for suitably chosen k_1 and k_2. A Wilcoxon type test for our problem is given by the following theorem.

Theorem 2 Let $Z_1, Z_2, \ldots, Z_n$ be independent random variables with density $f(x - \Theta)$, where $f(x)$ is a symmetric function. Further let k be a number such that

$$P_0(V_0 \leq k) = P_0\left(V_0 \geq \frac{n(n+1)}{2} - k\right) \leq \alpha$$

Then

$$\sup_{\Theta \notin (a,b)} P_\Theta\left(V_a \geq \frac{n(n+1)}{2} - k \text{ and } V_b \leq k\right) \leq \alpha$$

Proof Let A and B be the events

$$A = \left\{ V_a \geq \frac{n(n+1)}{2} - k \right\}$$

and

$$B = \left\{ V_b \leq k \right\}$$

Then for $\theta \leq a$

$$P_\theta \left(V_a \geq \frac{n\,(n+1)}{2} - k \text{ and } V_b \leq k\right)$$

$$= P_\theta\,(A \cap B) \leq P_\theta\,(A) \leq \alpha$$

and in the same way for $\theta \geq b$

$$P_\theta \left(V_a \geq \frac{n\,(n+1)}{2} - k \text{ and } V_b \leq k\right) =$$

$$= P_\theta\,(A \cap B) \leq P_\theta\,(B) \leq \alpha$$

Q.E.D

The theorem 2 means that we get a test of

$H_0 : \theta \notin (a, b)$

with level of significance at most α if we reject when both

$$V_a \geq \frac{n\,(n+1)}{2} - k$$

and

$$V_b \leq k.$$

This means that $H_0 : \theta \notin (a, b)$ is rejected if there are at most k means $\frac{Z_i + Z_j}{2}$, $i \leq j$, on each side of the interval (a, b).

Observe that the test constructions in theorems 1 and 2 are quite analogous, but there is one essential difference. In theorem 1 the test is based on the <u>position</u> of an estimate ($\bar{Z}$) in relation to the interval (a, b), while in theorem 2 the test is based on the <u>number</u> of values (means $(Z_i + Z_j)/2$, outside (a, b) on the different sides.

Another example of a (non-parametric) test of the second type is obtained by using sign test statistics. Suppose that $Z_1, Z_2, \ldots, Z_n$ are n independent random variables with some continous density f (x) having median m. Let S_{m_0} be the number of Z_i:s such that $Z_i > m_0$, and let k satisfy

$$P_0\,(S_0 \leq k) = P_0\,(S_0 \geq n - k) = \alpha$$

Then it easily follows that

$$\sup_{m \notin (a,b)} P_m (S_a \geq n - k \text{ and } S_b \leq k) \leq \alpha$$

Thus we get a test of $H_0 : m \notin (a, b)$ with level of significance at most α by rejecting H_0 when the numbers of Z_i:s on the two sides of (a, b) are at most k each.

3. Power properties

First let us consider some properties of the test obtained in theorem 1 for normally distributed observations. Our test is not (exactly) unbiased and there is no uniformly most powerful (UMP) unbiased test available when σ is unknown. It might however be reasonable to compare its power with the power of the UMP unbiased test of $H_1 : \mu \leq a$ against $\mu > a$ and the power of the UMP unbiased test of $H_2 : \mu \geq b$ against $\mu < b$. The two latter power functions act as upper bounds for the obtainable power function of unbiased tests of the greater hypothesis $H_0 : \mu \notin (a, b)$. The following table 1 gives some power function values obtained by non-central t distribution for the test of H_1 and H_2, by simulations with 100.000 replicates for our test of H_0 with unknown σ and by the normal distribution for the test of H_0 with known σ.

Table 1. Power functions for the tests of $H_1 : \mu \leq a$, $H_2 : \mu \geq b$ and $H_0 : \mu \notin (a, b)$ with known and unknown σ based on 12 independent $N(\mu, \sigma)$ observations, $a = -0.2$ and $b = 0.2$, nominal level of significance 0.05.

σ	x	H_1	H_2	H_0 σ= known	H_0 σ= unknown
	-0.2	0.05	1.00	0.05	0.05
	-0.1	0.94	1.00	0.97	0.94
0.1	0.0	1.00	1.00	1.00	1.00
	0.1	1.00	0.94	0.97	0.94
	0.2	1.00	0.05	0.05	0.05
	-0.2	0.05	1.00	0.05	0.05
	-0.1	0.49	1.00	0.53	0.49
0.2	0.0	0.94	0.94	0.93	0.89
	0.1	1.00	0.49	0.53	0.49
	0.2	1.00	0.05	0.05	0.05
	-0.2	0.05	1.00	0.05	0.05
	-0.1	0.29	0.94	0.28	0.23
0.3	0.0	0.70	0.70	0.50	0.40
	0.1	0.94	0.29	0.28	0.23
	0.2	1.00	0.05	0.05	0.05
	-0.2	0.05	0.94	0.05	0.03
	-0.1	0.20	0.78	0.15	0.07
0.4	0.0	0.49	0.49	0.21	0.11
	0.1	0.78	0.20	0.15	0.08
	0.2	0.94	0.05	0.05	0.03

It is seen from table 1 that for small σ:s our test has a level of significance (size) close to the prescribed value and that the test is nearly optimal. For big σ:s the level of significance is not so close to the prescribed value and the power is not so close to the upper bound. This is however a case where also the upper bound describes bad power. The sample size n=12 is not big enough to give a good test of any kind for big σ:s.

Hodges and Lehmann (1954) have given a method to test the converse hypothesis $\mu \notin (a, b)$ against the alternative $\mu \in (a, b)$. Their modified Student t test has test limits between ordinary one-sided and two-sided test limits. In our problem however the limits of ordinary one-sided tests serve as upper bounds, which we also use in our test.

4. A bootstrap method

As an alternative to the test for the case with normally distributed observations we have in section 2 described the test of Wilcoxon type requiring only symmetric distribution and the test of sign type valid for any continuous distribution.
A possibility to get a test with approximate level of significance α and without distributional assumptions is to use bootstrap technique. The basis of this technique is given in Efron (1982).

Let $f(u)$ be any probability density with corresponding expectation 0 and variance 1. Then if the observations $Z_1, Z_2, \ldots, Z_n$ are independent and have the density

$$\frac{1}{\sigma} f\left(\frac{z - \mu}{\sigma}\right)$$

we have a translation-scale family of distributions with the translation parameter $\mu = E[Z_1]$ and scale parameter $\sigma = (\text{Var } Z_1)^{\frac{1}{2}}$.

The distribution of the statistic

$$T = \frac{\bar{Z} - \mu}{S/\sqrt{n}}$$

depends on the density f but not on μ and σ. If we knew the α and $1 - \alpha$ fractiles t_α and $t_{1-\alpha}$ of this distribution we could test

$$H_0 : \mu \notin (a, b)$$

on level of significane at most α by rejecting when

$$a + t_{1-\alpha} \frac{S}{\sqrt{n}} \leq \bar{Z} \leq b - t_\alpha \frac{S}{\sqrt{n}}$$

Observe that t_α is not equal to $- t_{1-\alpha}$ in general when f is not symmetric.

The bootstrap method means that properties of statistical methods are determined for the empirical distribution obtained in the experiment. This is done in practice by a simulation where

observations are drawn at random from the series of results with replacement.

Let $Z_1^*, Z_2^*, \ldots, Z_n^*$ be n elements drawn at random from $Z_1, Z_2, \ldots, Z_n$ with replacement and let

$$\bar{Z}^* = \frac{1}{n} \sum_{k=1}^{n} Z_k^*$$

$$(S^*)^2 = \frac{1}{n-1} \sum_{k=1}^{n} (Z_k^* - \bar{Z}^*)^2$$

$$T^* = \frac{\bar{Z}^* - \bar{Z}}{S^*/\sqrt{n}}$$

Then T^* is a bootstrap variable with approximately the same distribution as T. The fractiles t_α and $t_{1-\alpha}$ can be estimated from the empirical distribution of a big number of independent copies of T^*.

Observe however that the bootstrap method is an approximate one. The really obtained level of significance is only approximately equal to α.

5. An example

As an illustration of the methods described earlier we will use a real life example with 12 persons having got both a standard and a new drug. The datas are given in the following table 2.

Table 2.

Subject no	AUC (standard)	AUC (new)	Ratio	Logratio Z
1	4776	4295	0.899	-0.106
2	8765	7880	0.898	-0.108
3	1551	788	0.508	-0.677
4	1964	1778	0.905	-0.099
5	6728	7010	1.042	0.041
6	5290	6428	1.026	0.026
7	1864	1883	1.010	0.010
8	3686	2525	0.685	-0.378
9	4214	3564	0.846	-0.168
10	11730	9700	0.827	-0.190
11	2936	2813	0.958	-0.043
12	1399	2423	1.732	0.549

From the data can be seen that there is a big variation of AUC values between the individuals, while the ratios and logratios are quite stable. We will use these logratio data to illustrate the different test methods discussed earlier with the hypothesis limits a = ln 0.8 = -0.223 and b = ln 1.25 = 0.223.

The mean of these data is $\bar{Z} = -0.095$ and the standard deviation is S = 0.285. In the normal method obtained from theorem 1 for level of significance $\alpha = 0.05$ the hypothesis $H_0 : \mu \notin (a, b)$ is rejected if the distance from both points a and b to $\bar{Z}$ is at least

$$t_{1-\alpha} \frac{S}{\sqrt{n}} = 0.148$$

i.e between -0.075 and 0.075. Since $\bar{Z} = -0.095$ the hypothesis H_0 can not be rejected.

Using the method obtained from theorem 2 we first calculate the 78 means $\frac{1}{2}(Z_i + Z_j), i \leq j$. There are 17 means below -0.223 and 6 means above 0.223. According to the table of the Wilcoxon one sample test the one-sided test limit gives level of significance 0.046, and thus the hypothesis can be rejected.

A third possibility is to make a test of sign type. There are 2 values below -0.223 and 1 value above 0.223. From a table of sign test we get the probability 1.93% for 2 positive values or less when the median is 0. Thus in our modified sign test $H_0 : m \in (a, b$ can be rejected in a test at level of significance $\alpha = 0.0193$.

If the observations are supposed to be normally distributed an ordinary two-sided 95% confidence interval for μ becomes (-0.276, 0.086). From this it does not follow that $-0.223 < \mu < 0.223$. Under the nonparametric assumptions of symmetric distribution a two-sided 94.8% Wilcoxon interval for the symmetric point μ becomes (-0.486, 0.051). Again this does not imply that $-0.223 < \mu < 0.223$. A two-sided sign interval for the median m with confidence coefficient 96.1% becomes (-0.190, 0.026). In this case the confidence interval is included in (-0.223, 0.223).

The example shows the advantage of the proposed methods over the simple methods based on ordinary symmetric confidence intervals. Because the data have a "heavy tail tendency" there also appear a slight advantage of the nonparametric methods over the normal parametric method in this case.

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