AN UNBIASED TEST FOR THE BIOEQUIVALENCE PROBLEM

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It is shown that the standard two one-sided tests procedure for bioequivalence is a biased test. Better tests exist. In this paper, an unbiased \( \alpha \)-level test and other tests which are uniformly more powerful than the two one-sided tests procedure are constructed. Its power can be noticeably larger than that of the \( \alpha \)-level two one-sided tests procedure.

1. Introduction. Recently there has been great interest in the problem of demonstrating bioequivalence of treatments, especially in the pharmaceutical industry. One of the reasons is that developing a marketable drug which is bioequivalent (i.e., equivalent in efficacy) to a well-established drug typically costs 1 percent or less relative to the cost of developing a new one.

The statistical formulation of the problem is now agreed upon to be the following hypothesis testing problem. Let \( m_1 \) and \( m_2 \) be the parameters corresponding to the two treatments. For example, the parameter of interest may be one of the pharmacokinetic parameters (AUC, \( C_{\text{max}} \) or \( T_{\text{max}} \)) of the concentration–time curves. Here AUC, \( C_{\text{max}} \) and \( T_{\text{max}} \) stand for the area under the curve, the maximum concentration level and the time until the maximum concentration level is achieved.

Bioequivalence of the two treatments is defined as \( \Delta_1 \leq \rho \leq \Delta_2 \), where \( \rho = m_1/m_2 \) and \( \Delta_i, i = 1, 2 \), is the tolerance limit prespecified by a regulatory agency. The statistical problem is then to test

\[ H_0: \rho \geq \Delta_2 \text{ or } \rho \leq \Delta_1 \text{ versus } H_1: \Delta_1 < \rho < \Delta_2. \]

If one can reject \( H_0 \), then one can declare bioequivalence. The regulatory agencies in both the United States and the European community use \( \Delta_1 = 0.8 \) and \( \Delta_2 = 1.25 \).

It is also recommended that a logarithmic transformation be applied and hence the ratio problem is turned into a difference problem, that is,

\[ \theta = \ln(\rho) = \mu_1 - \mu_2 \]

where \( \mu_i = \ln m_i \). For the aforementioned recommended choice of \( \Delta_1 \) and \( \Delta_2 \) of the regulatory agencies, the hypotheses become

\[ H_0: |\theta| \geq \Delta \text{ versus } H_1: |\theta| < \Delta, \]

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where $\Delta = \ln 1.25$. Note that in this special case the transformation leads to a symmetric interval of $\theta$. In general, even if an asymmetric interval is obtained, one can make a simple location transformation to turn it into a symmetric interval. Therefore symmetry in (1.1) can be assumed without loss of generality.

The standard test recommended in the United States [FDA (1992)] and the European Communities [EC-GCP (1993)] is the two one-sided tests procedure. To describe this test, let $D$ be an estimate of $\theta$ with

(1.2) \[ D \sim N(\theta, \sigma^2) \]
and $S^2$ be an independent observation such that

(1.3) \[ S^2/\sigma^2 \sim \text{chi squared distribution with } v \text{ degrees of freedom.} \]

The above canonical form applies to many different models such as the general linear model, ANOVA and crossover designs. One of the simplest special cases involves a $2 \times 2$ crossover design. Let $X_i$, $1 \leq i \leq n$, i.i.d. observations, be the response of the $i$th subject after receiving the treatment. Similarly let $Y_i$, $1 \leq i \leq n$, i.i.d., be the response of the $i$th subject after receiving the reference treatment.

More specifically, for a $2 \times 2$ crossover design with subject effects (and without period effect), we may define

\[ D_i = X_i - Y_i, \quad 1 \leq i \leq n, \]
which are i.i.d. Under the customary assumption that $D_i$ is normally distributed, letting

\[ D = \Sigma D_i/n \]
and

\[ S^2 = \Sigma (D_i - D)^2/n \]
implies (1.2) and (1.3) with $v = n - 1$. In the simple case where $X_i$ and $Y_i$ have the common standard deviation $\sigma_0$, then $\sigma$ in (1.2) and (1.3) equals

\[ \sigma = (n/2)^{1/2}\sigma_0. \]

The $\alpha$-level two one-sided tests procedure proposed in Schuirmann (1987) corresponds to the rejection region $C_2$, which consists of $D$ and $S$ such that

(1.4) \[ \Delta \geq |D| + t_{\alpha} \frac{S}{\sqrt{v}}, \]
where $t_{\alpha}$ is the upper $\alpha$ quantile of a $t$ distribution with $v$ degrees of freedom. [A related but more general type of test has been proposed in Berger (1982).] The two one-sided tests procedure is, however, biased. In fact even for $\theta = 0$, it can be seen that the power function satisfies

\[ \lim_{\sigma \to \infty} P(C_2) = 0. \]
Several attempts have been made to improve upon the two one-sided tests procedure. See, for example, Anderson and Hauck (1983) and Rocke (1984, 1985). These alternative tests, however, are only approximately \( \alpha \)-level. Existence of a better test with exact level \( \alpha \) was established in Hwang and Liu (1992). Munk (1993) constructed a test which is shown numerically to be \( \alpha \)-level (\( \alpha = 0.1 \)) for degrees of freedom larger than 10 and which is uniformly more powerful than the two one-sided tests procedure. For a recent related confidence interval approach, see Hsu, Hwang, Liu and Ruberg (1994).

In this paper we construct an unbiased \( \alpha \)-level test. In the construction, it is seen that the rejection region of the unbiased test always contains properly the rejection region (1.4). Therefore the unbiased test is uniformly more powerful than the \( \alpha \)-level two one-sided tests procedure. See Theorem 4.1. The improvement in power may be quite noticeable.

2. Description of the test. A precise construction of the unbiased test is given in Section 4. As described in Section 5, it is feasible to numerically implement this construction and picture the critical region, that is, the rejection region, \( C_U \), of the unbiased test. This is the region on which one can declare bioequivalence.

Figure 1 shows a typical picture of \( C_U \) and some other regions, as described below. The coordinates of this plot are \((D, S)\), as defined previously. The triangle \( ABC \) and its inside is the rejection region \( C_2 \) of the two one-sided tests.

![Fig. 1](image_url)  

*Fig. 1. Rejection regions with \( \alpha = 0.05 \), \( v = 14 \) and \( \Delta = 1 \). \( C_2 \) is the triangle \( ABC \) and its inside; \( C_U \) is the union of \( C_2 \) and the region on top of \( C_2 \) bounded by the two solid curves; \( C_M = C_U \) after removing the two regions outside the vertical lines \( L_1 \) and \( L_2 \); \( C_T = C_U \) after removing the region above \( L_3 \).*
procedure. The region bounded by the solid curves forms $C_U$. Note that the boundaries $C_2$ and $C_U$ coincide for small $S$, and $C_U$ strictly contains $C_2$. Therefore $C_U$ is uniformly more powerful than $C_2$ for any $\theta$. This is also true for any level $\alpha$.

Anderson and Hauck (1983) and Hauck and Anderson (1984) have proposed a test whose boundaries are qualitatively rather similar to those we display in Figure 1. Their test is motivated by a partly ad hoc argument. Numerical results for the few examples which are reported in their papers indicate that the level of their nominally $\alpha = 0.05$ test may actually be in the range 0.057 to 0.061, which is of course close, but not equal, to the nominal value. See Frick (1987) for some numerical studies about their levels. Their test is not unbiased (unlike ours), but the qualitative similarity does reinforce the value of their proposal.

When one of the authors, Hwang, presented a preliminary version of this paper in an invited session about bioequivalence in the August 1993 ASA Annual Meeting in San Francisco, two criticisms were raised about the unbiased test. It was argued that the rejection region of $C_U$ is unbounded, and also that for any $D$ it is possible to establish bioequivalence when $S$ is large enough. Similar criticisms have been made about the test proposed by Anderson and Hauck (1983) which, as we have noted, has boundaries with the same qualitative features as ours. See Schuirmann (1987), pages 673–676 for a careful presentation of these arguments. See also Schuirmann (1996), point 1 and Berger and Hsu’s counterargument (1996), page 317 in the Rejoinder, by comparing $C_{L_1}$ to the usual $t$-interval.

We tried to find a fundamental argument for the assertion that a reasonable rejection region should not be unbounded by using a likelihood approach, a Bayesian approach, and so on. However, we did not succeed. Therefore we are not convinced it should not be unbounded. It can even be shown [Munk (1992)] that every test with a bounded critical region has a vanishing power at any given $\theta$ when the variance is large. Nevertheless, for those who find an unbounded region unappealing, we recommend using the truncated procedure $C_T$ illustrated in Figure 1. The rejection region of $C_T$ is $C_U$ after removing points above $L_3$, which is drawn in Figure 1. Formally, $L_3$ passes through the two points on the boundaries of $C_U$ with smallest $|D|$. This region has the added monotonicity property (which some may find appealing) that if $(D, S_1)$ is in the rejection region and $S_2 < S_1$ then $(D, S_2)$ will also be in that region.

An alternate modification for which we do see a practical argument is also shown in Figure 1, as $C_M$, which is $C_U$ except that points with $|D| > \Delta$ are removed. That is, the points outside $L_1$ and $L_2$ are removed. The practical argument for this modification is that often a bioequivalence decision is followed by a point estimate of $\theta$ (and/or an associated confidence interval). The usual point estimate (and/or center of a confidence interval) is $\hat{\theta} = D$. If $S$ is quite large, the procedure given by $C_U$ can thus leave the statistician in the embarrassing position of rejecting the null hypothesis that $|\theta| \geq \Delta$ while at
the same time estimating a value \( \hat{\theta} \) for which \(|\hat{\theta}| > \Delta \). For this reason, the modification \( C_M \) may be appealing, since the rejection region is cut off at \( L_1 \) and \( L_2 \). (Formally, \( C_M \) is formed by truncating \( C_U \) at \( D = \pm \Delta \).)

3. Numerical results. By using the approach in Section 5, we construct the rejection region \( C_U \) (see also Figure 7). Since the transformation \((D, S) \rightarrow (D/\Delta, S/\Delta)\) can be used to reduce the problem of testing \( H_0: |\theta| \geq \Delta \) down to the case where \( \Delta = 1 \) as in Section 3, we shall focus on \( \Delta = 1 \). (Therefore if \( C_U \) is the critical region for testing \(|\theta| \geq 1\), then for a general \( \Delta \), the test that rejects \( H_0 \) if and only if \((D/\Delta, S/\Delta) \in C_U \) is the \( \alpha \)-level unbiased test.)

As shown in Figure 1 as well as in Theorem 4.1, the rejection region of the unbiased test contains that of the two one-sided tests procedure. Therefore the unbiased test is uniformly more powerful than the two one-sided test.

The power functions are plotted in Figures 2–5. Note that for a given \( v \) and \( \Delta = 1 \), the only unspecified parameters are \( \sigma \) and \( \theta \). For \( v = 19 \), \( \alpha = 0.05 \), the powers are plotted against \( \theta \) while \( \sigma \) varies from picture to picture. The dashed line corresponds to the two one-sided tests whereas the solid line corresponds to the unbiased test. As expected, the power of the unbiased test is always higher. The dash and dot lines (more visible in the figures for \( \sigma \geq 0.7 \)) corresponds to the power of the truncated test \( C_T \). These powers are calculated by numerically integrating the normal cumulative distribution functions with respect to \( S \), using the 20-point quadrature integration routine in the com-

![Fig. 2. Power functions \( \sigma = 0.4 \). The power functions of \( C_U \), \( C_2 \) and \( C_T \) are plotted against \( \theta \) using a solid line, a dashed line, and a dash-and-dot line, respectively. In this figure and Figure 3, the dash and dot line is invisible since it coincides with the solid line.](image-url)
Fig. 3. Power function as described in the title of Figure 2, except $\sigma = 0.5$.

Fig. 4. Power function as described in the title of Figure 2, except $\sigma = 0.8$. 
Fig. 5. Power function as described in the title of Figure 2, except $\sigma = 1.0$.

Computer software Gauss which runs on an IBM personal computer. The power of $C_M$ lies between that of $C_U$ and $C_T$.

The powers of the two tests $C_U$ and $C_2$ are quite similar in some cases, especially when $\sigma$ is small. This is the reason why no figures are reported for $\sigma < 0.4$: the powers of $C_U$ and $C_2$ are almost identical. However, in many other cases, we see a noticeable improvement in power of the unbiased test over the two one-sided tests procedure. (The two one-sided tests procedure can have very poor power when $\sigma$ becomes large.) In particular, for $\sigma = 0.55$, the power at $\theta = 0$ of the unbiased test is almost twice as big as that of the two one-sided tests procedure. This range of $\sigma$ may happen in bioequivalence data. For example in Westlake’s data (1974, 1976), after the logarithmic transformation the estimated variance is $\frac{1}{3}(0.012) = 0.002$. In our context, however, every quantity is scaled with respect to $\Delta$. Taking this into consideration, the estimate of $\sigma$ after scaling with respect to $\Delta = \log 1.25$ is

$$\sqrt{0.002}/\log 1.25 = 0.46.$$

However for the FDA’s earlier recommendation, $\Delta = \log 1.2$. The corresponding estimate is

$$\sqrt{0.002}/\log 1.2 = 0.56.$$

(In this discussion, we have used the logarithmic transformation log with the base 10, since Westlake did so. Obviously these estimates of $\sigma$ would remain the same if we and Westlake had used ln all the way through.)

We also plotted figures corresponding to $v = 39$. The resultant pictures are similar to Figures 2–5 and are not reported.
The power of $C_T$ is also plotted in Figures 2–5, using a dot-and-dash line. In all cases, $C_T$ obviously has a power less than that of $C_U$. In many cases ($\sigma \leq 0.6$), however, the power functions of these two tests are indistinguishable. (Therefore the dot-and-dash lines disappear into the solid lines.) It so happens that these are the cases where the noticeable improvement of $C_U$ over the two one-sided tests procedure occurs. Therefore $C_T$ also has a noticeable improvement upon the two one-sided tests procedure in these cases. Although $C_T$ is biased, it is bounded and it improves upon the two one-sided tests procedures in all cases, since the former contains the rejection region of the latter. The power of $C_M$ hence is not plotted, since it is strictly between that of $C_U$ and $C_T$. Therefore $C_M$ also has noticeable improvement over $C_2$. These numerical results, together with the fact that $C_U$ is unbiased, provide motivation for use of any one of the improved tests $C_U$, $C_M$ or $C_T$ rather than $C_2$.

Finally, even though all the alternative tests improve upon $C_2$, the improvement is negligible when $\sigma$ is less than 0.4 or when the maximum power is high (higher than 80 percent). In well-designed studies, $\sigma$ often falls in this range. However, in situations when the variability of the observations has been underestimated, these alternative tests are valuable. See Hauck and Anderson (1996).

4. Construction of $C_U$: theory. We consider the canonical model based on $D$ and $S$ which are independent and satisfy (1.2) and (1.3). The joint probability density function of $(D, S)$ is proportional to

$$\exp\left(-\frac{(D - \theta)^2}{2\sigma^2}\right)S^p \exp\left(-\frac{S^2}{2\sigma^2}\right),$$

where $p = v - 1$.

An unbiased test denoted by a critical function $\varphi_v$ will be constructed by an approach similar to that of Hodges and Lehmann (1954). They considered testing the null hypothesis $H_1$ versus the alternative $H_0$. Somewhat surprisingly, their solution is quite different from ours.

Unbiasedness of $\varphi_v$ implies that it is similar, that is,

$$E_{\theta, \sigma} \varphi_v(D, S) = \alpha$$

for $\theta = \pm \Delta$ and every $\sigma > 0$. [See, e.g., Chapter 4 of Lehmann (1986).] From (4.1), when $\theta = \Delta$, the statistic

$$R^2 = (D - \Delta)^2 + S^2$$

is sufficient and complete for $\sigma > 0$. This and (4.2) imply that

$$E_{\theta, \sigma}(\varphi_v(D, S) | R = r) = \alpha \quad \text{for } \theta = \Delta$$

and for every value of $\sigma$ and $r$. 
Statements similar to those in the last paragraph can be concluded when $\Delta$ is replaced by $-\Delta$. However, the critical function $\varphi_v$ to be constructed is symmetric in $D$, that is,

$$\varphi_v(D, S) = \varphi_v(-D, S).$$

Therefore condition (4.4) remains unchanged when $\Delta$ is replaced by $-\Delta$. Hence, it is sufficient to focus on $\theta = \Delta$, which is assumed throughout this section unless mentioned otherwise.

It is convenient to express $(D, S)$ in terms of the polar coordinate $(R, \beta)$, where the origin of the polar coordinate is $(\Delta, 0)$. Here $R$ is defined in (4.3) and $\beta$ is the angle between the $D$ axis and the line segment joining $(D, S)$ and $(\Delta, 0)$. (See Figure 6.) It can be calculated easily that the probability density function of $(R, \beta)$ is proportional to

$$\left(\frac{r}{\sigma}\right)^{p+1} \exp\left(-\frac{r^2}{2\sigma^2}\right)(\sin \beta)^p, \quad 0 < \beta < \pi \text{ and } r > 0.$$

This obviously implies independence of $R$ and $\beta$. Therefore in calculating the conditional expectation (4.4), only the marginal distribution of $\beta$ is involved. The probability density function of $\beta$ is

$$k_\beta(\sin \beta)^p.$$
where

$$(k_p)^{-1} = \int_{0}^{\pi} (\sin \beta)^p \, d\beta$$

$$= \begin{cases} 
(p - 1)(p - 3) \cdots 1 \frac{\pi}{p(p - 2) \cdots 2}, & \text{if } p \text{ is even}, \\
(p - 1)(p - 3) \cdots 2 \frac{1}{p(p - 2) \cdots 3}, & \text{if } p \text{ is odd}.
\end{cases}$$

We shall summarize the above discussion in the following lemma. For any critical function $\varphi(D, S)$, $\varphi^*(R, \beta)$ denotes the same function value as $\varphi(D, S)$ where $(R, \beta)$ is the polar coordinate of $(D, S)$ defined above and in Figure 6.

**LEMMA 4.1.** Suppose the critical function $\varphi(D, S)$ is symmetric with respect to $D$. Then $\varphi$ is similar if and only if

$$k_p \int_{0}^{\pi} \varphi^*(r, \beta) \sin^p \beta \, d\beta = \alpha$$

for every value of $r$.

We shall now construct the unbiased test. In fact, we shall describe the boundary $(D(r), S(r))$ of the critical region $C_U$. We shall focus on the boundary points in the first quadrant. By symmetry, the boundary point in the second quadrant is $(-D(r), S(r))$ where $r$ is the distance from $(-D(r), S(r))$ to $(-\Delta, 0)$. This relationship is mathematically described by (4.3) as well. The critical region $C_U$ to be constructed below using Lemma 4.1 is the region between the curves $\{(D(r), S(r)): r > 0\}$ and $\{(D(r), S(r)): r > 0\}$.

In the above terms, the two one-sided tests boundary is $\{(\pm D'(r), S'(r)): 0 \leq r \leq \Delta/\cos(\pi - \xi)\}$ where $\xi$ satisfies

$$k_p \int_{\xi}^{\pi} (\sin \beta)^p \, d\beta = \alpha,$$

$$D'(r) = \Delta + r \cos \xi,$$

$$S'(r) = r \sin \xi.$$

(See the triangle in Figure 7.)

The boundary of $C_U$ is constructed inductively on regions $(r_i, r_{i+1})$, $i = 0, 1, \ldots$, with $r_0 = 0$ and $\lim_{i \to \infty} r_i = \infty$. It will later be shown that the construction is valid for

$$\alpha_0 < \alpha < 1/2,$$

where

$$\alpha_0 = k_p \int_{3\pi/4}^{\pi} (\sin \beta)^p \, d\beta.$$
Fig. 7. Construction of $r_1$, $r_2$ and $\eta(r)$. The dashed lines represent the boundary of the two one-sided tests corresponding to $v = 19$ and $\alpha = 0.05$. Below the points ($\pm D(r_1)$, $S(r_1)$), this coincides with the boundary of $C_U$, which is represented by the solid line.

As noted, $r_0 = 0$. Then let

$$r_1 = 2\Delta \sin(\pi - \xi);$$

that is, $r_1$ is the distance between $(\Delta, 0)$ and the opposite side of the triangle. Condition (4.8) guarantees that $3\pi/4 > \xi > \pi/2$, so that $\sqrt{2}\Delta < r_1 < 2\Delta$.

On this region, namely $0 < r \leq r_1$, the boundary curve is the same as that for the two one-sided tests region. To explain why they agree, note first that the one-sided $t$ test with a critical region to the left of line $L$ (in Figure 7) has type one error $\alpha$. By sufficiency and completeness of $R$ under $\theta = \Delta$, the conditional rejection probability of the one-sided $t$ test, given $R$, is $\alpha$. Hence integrating the density (4.5), while $\beta$ varies from $\xi$ to the horizontal axis pointing to the negative infinity, is $\alpha$. Therefore when $r < r_1$, we cannot add

<table>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<th>6</th>
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<td>0.0378</td>
<td>0.0249</td>
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<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
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<td>0.0075</td>
<td>0.0051</td>
<td>0.0034</td>
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<td>0.0016</td>
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</tr>
<tr>
<td>$p + 1 = v$:</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>20</td>
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</tr>
<tr>
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<td>0.0005</td>
<td>0.0004</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0001</td>
<td>$&lt; 0.0001$</td>
</tr>
</tbody>
</table>
more region than the set defined by $L$ and the horizontal axis and still hope that (4.6) is satisfied. Consequently, $C_U$ and $C_2$ have the same boundary.

However, when $r > r_1$, the situation is different. The arc from $L$ to the horizontal axis is not entirely included in the rejection region. See Figure 7, which also shows $r_2$ as defined in the next paragraph.

Suppose now that the curve has been defined for $r \leq r_i$. See Figure 7. Let

\[(4.9)\]

\[r_{i+1} = [\Delta + D(r_i)]^2 + S^2(r_i)]^{1/2},\]

which is greater than

\[r_i = [\Delta - D(r_i)]^2 + S^2(r_i)]^{1/2}\]

as long as $D(r_i)$ is never zero, which, among other things, shall be proved in Section 6.

Note that for $r_i < r < r_{i+1}$, the arc centered at $(\Delta, 0)$ with radius $r$ intersects the left boundary of $C_U$. For a fixed $r$, let $P(r) = (-p_1(r), p_2(r))$ be the intersection point with the largest second coordinate.

Note that $P(r)$ is defined, being symmetric to $P_*(r) = (p_1(r), p_2(r))$ (in the first quadrant), which is already defined, since the distance between $P_*(r)$ and $(\Delta, 0)$ is smaller than $r_i$. See Figure 8.

Let

\[(4.10)\]

\[\eta = \eta(r) = \begin{cases} \frac{3\pi}{2} - \xi + \cos^{-1}(r_1/r), & \text{if } r < 2\Delta, \\ \pi, & \text{otherwise}. \end{cases}\]

\[\text{Fig. 8. Inductive construction of the boundary of } C_U.\]
[For \( r < 2\Delta \), \( \eta \) is the angle between the \( D \) axis and the vector joining \((\Delta, 0)\) and \( Q(r) \) where \( Q(r) \) is the lower intersection point of the left portion of the boundary and the arc with length \( r \). See Figure 7.]

Now define \( D(r) \) by

\[
(4.11) \quad \left( \int_{\eta}^{\pi} + \int_{\cos^{-1}(-(r/D(r)) - \Delta)}^{\cos^{-1}(D(r) - \Delta)/r} \right) k_p \sin^p \beta d\beta = \alpha.
\]

This definition guarantees that (4.6) is satisfied. Further, \( S(r) \) can be found by solving \((D(r) - \Delta)^2 + S^2(r) = r^2\).

We summarize the above construction in the following theorem. Theorem 4.1 is based on an assumption, called the interval assumption: the subset that consists of points in \( C_U \) with a given \( S, S > 0 \), forms an interval. Namely, the intersection of \( C_U \) and a horizontal line is a line segment or an empty set. This assumption has been observed to be satisfied in all our numerical studies. We believe that the violation of the interval assumption must be quite rare, if at all possible. The assumption is satisfied by other unbiased tests which are not constructed in a way described above. An example can be found in Figure 4 of Munk (1992), which is closest to violation but still satisfies the interval assumption.

**Theorem 4.1.** Assume that \( \alpha_s < \alpha < 1/2 \). The test with the rejection region \( C_U \), whose boundary points \((\pm D(r), S(r))\) are constructed above, is uniformly more powerful than the \( \alpha \)-level two one-sided tests procedure. The test is similar. Moreover if \( C_U \) satisfies the interval assumption, \( C_U \) is an \( \alpha \)-level unbiased test.

**Proof.** It is shown in Section 6 that when \( \alpha_s < \alpha < 1/2 \) then \( r_{i+1} > r_i \), \( i = 0, 1, \ldots \), and \( \lim_{i \to \infty} r_i = \infty \). Hence \( C_U \) is well defined.

The first statement of the theorem follows from the fact that \( C_U \) contains the triangle, which is the rejection region of the two one-sided tests procedure. To see this, we need focus only on the first quadrant by symmetry. Here all we need to argue is that for every \( r \) the angle \( \xi' \) between the \( D \) axis and the line segment joining \((D(r), S(r))\) and \((\Delta, 0)\) is smaller than \( \xi \). [In terms of the earlier notation, \( \xi' = \cos^{-1}((D(r) - \Delta)/r) \).] This is true, since

\[
\alpha = k_p \int \varphi(r, \beta)(\sin \beta)^p d\beta \leq \int_{\xi'}^{\pi} k_p (\sin \beta)^p d\beta
\]

and by (4.7),

\[
\int_{\xi'}^{\pi} k_p (\sin \beta)^p d\beta = \alpha.
\]

Now we argue for the second statement. By construction, \( C_U \) is similar, that is, which implies that the power function \( P_{\theta, \alpha}((D, S) \in C_U) \) is \( \alpha \) for \( \theta = \pm \Delta \) and for every \( \sigma \). The power function depends on \( \theta \) only through \( |\theta| \). By construction, \( C_U \) is symmetric about zero with respect to \( D \), and given an \( S \), \( C_U \) is an interval by the interval assumption. It follows that, for each \( \sigma \), \( P_{\theta}((D, S) \in C_U) \) is \( \alpha \) for \( \theta = \pm \Delta \) and for every \( \sigma \).
$C_{U | S}$ is decreasing in $|\theta|$, implying the same for the unconditional power. This implies that $C_U$ has $\alpha$-level and is unbiased. \(\square\)

Finally, we discuss an asymptotic formula in the first quadrant. When $r$ is large, the boundary approaches the line determined by

\[(4.12)\quad S(r) = D(r)/\tan \lambda,\]

where $\lambda$ is the angle such that

\[(4.13)\quad \int_{\pi/2-\lambda}^{\pi/2+\lambda} k_p \sin^p \beta \, d\beta = \alpha.\]

The rationale for this is that when $r$ is large, then $1/r$ is small and the region approaches that for $1 = 0$, leading to the above line.

5. Numerical computation. The following steps indicate how to construct a numerical approximation to $C_U$. The approximate boundary points will still be denoted in this section as $(D(r), S(r))$.

**Step 1.** Find $\xi$ that satisfies (4.7),

\[\int_{\xi}^{\pi} k_p (\sin \theta)^p \, d\theta = \alpha\]

and verify $\xi < 3\pi/4$. If $\alpha = 0.05$, this inequality holds if and only if $p \geq 4$. See Table 1.

**Step 2.** For $0 < r \leq 2\Delta \sin(\pi - \xi) = r_1$, define

\[D(r) = \Delta + r \cos \xi \quad \text{and} \quad S(r) = r \sin \xi.\]

For Steps 1 and 2, see Figure 7.

**Step 3.** Let $\rho_1 = r_1$. Suppose $D(r)$ and $S(r)$ have already been defined for $0 \leq r \leq \rho_k$. We now describe how to define the next point $P(\rho_{k+1}) = (D(\rho_{k+1}), S(\rho_{k+1}))$. Choose $\varepsilon > 0$ so that $\varepsilon \leq D(\rho_k)$. (The smaller $\varepsilon$ is, the more precise the approximation will be, but the total computation will be longer.) Generally a value of $\varepsilon$ can be fixed throughout the computation, but one must check at each stage that $\varepsilon \leq D(\rho_k)$.) Then let

\[\rho^2_{k+1} = \rho^2_k + 4\varepsilon \Delta.\]

Let $P$ denote the intersection point of the left boundary of $C_U$ and the arc $A$ centered at $(\Delta, 0)$ with radius $\rho_{k+1}$. See Figure 9. Note that $P$ is well defined since the point $P^*_s$, symmetric to $P$ with respect to the $S$ axis, is well defined. To see this, let $\rho^*_k$ denote the distance between $P^*_s$ and $(\Delta, 0)$, that is,

\[(D(\rho^*_k) - \Delta)^2 + S^2(\rho^*_k) = (\rho^*_k)^2\]
where \( P_* = (D(p_{k+1}^*), S(p_{k+1}^*)) \). We now show that \( p_{k+1}^* < p_k \), which implies that \( P_* \) is defined and hence that \( P \) is also. Note that \( P = (-D(c_{k+1}^*), S(c_{k+1}^*)) \) and the distance between \( P \) and \( (\Delta, 0) \) is \( p_{k+1} \). Hence

\[
(-D(p_{k+1}^*) - \Delta)^2 + (S(p_{k+1}^*))^2 = p_{k+1}^2.
\]

Putting the last two displayed equations together, we have

\[
(p_{k+1}^*)^2 = (D(p_{k+1}^*) - \Delta)^2 + S^2(p_{k+1}^*) = (D(p_{k+1}^*) - \Delta)^2 + p_{k+1}^* - (-D(p_{k+1}^*) - \Delta)^2 = p_{k+1}^2 - 4\Delta D(p_{k+1}^*) < p_k^2,
\]

assuming \( D(p_{k+1}^*) > \varepsilon \) as well. If \( D(p_{k+1}^*) \) is not larger than \( \varepsilon \), we have to start with a smaller \( \varepsilon \).

Now we define the point \( (D(p_{k+1}), S(p_{k+1})) \) to be on the arc \( A \) such that (4.11) is satisfied; that is,

\[
\left( \int_{\eta}^{\pi} + \int_{\cos^{-1}((-D(p_{k+1}^*) - \Delta)/p_{k+1})}^{\cos^{-1}((D(p_{k+1}^*) - \Delta)/p_{k+1})} \right) k_p (\sin \beta)^p \, d\beta = \alpha
\]

and

\[
(D(p_{k+1}) - \Delta)^2 + S^2(p_{k+1}) = p_{k+1}^2,
\]

where \( \eta = \eta(p_{k+1}) \) is defined in (4.10).

---

**Fig. 9. Inductive construction of the boundary of \( C_U \).**
Equation (5.1) can be used to solve for \( D(\rho_{k+1}) \), since \( D(\rho^*_{k+1}) \) is known. Due to the monotonicity of the left-hand side of (5.1) in \( D(\rho_{k+1}) \), this can be done without much effort. Using \( D(\rho_{k+1}) \) and (5.2), one can then solve for \( S(\rho_{k+1}) \) easily.

Connect the points by line segments. Hence for \( \rho_k < r < \rho_{k+1} \) define

\[
D(r) = D(\rho_k) + \frac{r - \rho_k}{\rho_{k+1} - \rho_k} (D(\rho_{k+1}) - D(\rho_k))
\]

and

\[
S(r) = S(\rho_k) + \frac{r - \rho_k}{\rho_{k+1} - \rho_k} (S(\rho_{k+1}) - S(\rho_k)).
\]

This completes the definition of \( (D(r), S(r)) \) for \( \rho_k < r < \rho_{k+1} \).

**STEP 4.** Terminate the calculation at some (large) \( \rho_{k+1} \) when the points are close to the asymptote described by (4.12) and (4.13). For a larger \( r \), the boundary in the first quadrant is then the asymptote.

**6. Existence of \( C_U \).** The construction in Section 4 relies on the facts that \( r_{i+1} > r_i \), \( i = 0, 1, \ldots \), and \( \lim_{i \to \infty} r_i = \infty \). The following geometric lemmas are crucial to the proof of these facts.

Let \( O = (a, 0) \) with \( a > 0 \) be a point on the horizontal axis. See Figure 10. For a fixed point \( A = (x, y) \) in the first quadrant, let \( B = (0, h_1) \), \( h_1 > 0 \) be the point on the vertical axis such that \( OB = OA \),

where, for example, \( OB \) denotes the distance between \( O \) and \( B \). It is assumed that

\[
\overline{OA} > a
\]

so that point \( B \) exists. Let \( C = (-x, y) \) denote the symmetric point of \( A \) with respect to the vertical axis and let \( D = (0, h_2) \), \( h_2 > 0 \), denote the point on the vertical axis such that \( \overline{OD} = \overline{OC} \). Also shown in Figure 10 are \( E = (0, y) \), \( \alpha = \angle BOC \), \( \beta = \angle DOB \) and \( \gamma = \angle AOD \).

Figure 10 illustrates only the most interesting of the possible geometric configurations for this construction, where \( x \leq a \) and \( \alpha > 0 \). All configurations have \( \gamma > 0 \), as verified in Lemma 6.1.

**Lemma 6.1.** The condition

\[
x^2 + y^2 > a^2
\]
implies, in the above construction, \( \gamma > 0 \). (That is, the segment \( DO \) is located counterclockwise from \( AO \).)

**Proof.** If \( x \geq a \), the lemma is trivial. Assume \( x < a \) below. Extend the line \( OA \) to meet the vertical axis at \( F \). Algebraic manipulation shows that the assumption (6.2) is equivalent to \( (O'C)^2 + (CO)^2 > (O'O)^2 \), where \( O' \) is the symmetric point of \( O \) with respect to the vertical line. This implies \( \angle O'CO < \pi/2 \). It follows that the point \( F' \) on the \( y \)-axis, such that \( \angle OCF' = \pi/2 \), lies below \( F \). Since \( OCD \) is an equilateral triangle, \( F' \) is above \( D \). Hence \( F \) is above \( D \) and \( \gamma > 0 \). \( \square \)

The other important geometric fact is contained in Lemma 6.2.

**Lemma 6.2.** In the above construction \( \angle DOC < \angle AOB \).

**Proof.** Examination of the construction displayed in Figure 10 and some algebraic calculation show that \( ED = EB \) if and only if \( \angle EOO' = \pi/4 \) and \( x < a \).
If $ED < EB$ then $\angle EOO' < \pi/4$ and $B$ falls below the segment $CO$ so that $DOC \subset AOB$ by Lemma 6.1. It follows trivially that $\angle DOC < \angle AOB$.

If $EB < ED$ then $CB < CD = AD$. Consider the triangles $COB$ and $DOA$. They then have $CO = DO$, $OB = OA$ and $CB < DA$. Hence $\alpha < \gamma$. It follows that $\angle DOC = \alpha + \beta < \gamma + \beta = \angle AOB$. $\Box$

These two geometric lemmas combine to yield the following analytic result.

Here, let $\eta_1 = \angle O'OA$, $\eta_2 = \angle O'OB$, $\eta_3 = \angle O'OD$, $\eta_4 = \angle O'OC$.

**Lemma 6.3.** Assume (6.1) and (6.2). Then

$$\int_{\eta_1}^{\eta_2} \sin p \beta \, d\beta > \int_{\eta_3}^{\eta_4} \sin p \beta \, d\beta.$$  \hspace{1cm} (6.3)

**Proof.** $\eta_2 - \eta_1 > \eta_4 - \eta_3$ by Lemma 6.2, and $\eta_1 < \eta_3$ by Lemma 6.1. If $\alpha \leq 0$, then $\eta_1 < \eta_3 < \eta_4 \leq \eta_2$ so the conclusion of this lemma follows trivially. If $\alpha > 0$, make use of the fact that $\sin \beta$ is unimodal and symmetric about $\pi/2$ and $\eta_4 - \alpha = \eta_2 > \pi/2$ and $\eta_3 > \pi/2$ to write

$$\int_{\eta_3}^{\eta_4} (\sin \beta)^p \beta d\beta < \int_{\eta_3 - \alpha}^{\eta_4 - \alpha} (\sin \beta)^p \beta d\beta = \int_{\eta_3 - \alpha}^{\eta_2} (\sin \beta)^p \beta d\beta < \int_{\eta_1}^{\eta_2} (\sin \beta)^p \beta d\beta,$$

which establishes the lemma. $\Box$

We can now establish the validity of the construction of $C_U$, as follows.

**Theorem 6.1.** When $\alpha_\circ < \alpha < 1/2$, the quantities $r_i$ defined in the construction of $C_U$ satisfy $r_i < r_{i+1}$, $i = 0, 1, \ldots$, and $\lim_{i \to \infty} r_i = \infty$. Hence $C_U$ exists. The corresponding test is unbiased if the interval assumption is satisfied.

**Proof.** We will suppose the theorem is false and obtain a contradiction. Hence, suppose

$$r^* = \lim_{i \to \infty} r_i < \infty.$$  \hspace{1cm} (6.4)

Since $D$ is continuous, in the case of (6.3) $D(r^*) = 0$. In the case of (6.4) there must be a sequence $\{r_i\}$ increasing to $r^*$ so that $\lim_{i \to \infty} D(r_i)$ and $\lim S(r_i)$ exist. So, for notational convenience in this case, let $D(r^*) = \lim_{i \to \infty} D(r_i)$, $S(r^*) = \lim_{i \to \infty} S(r_i)$.

In either case, there is an $r^{**} < r^*$ such that

$$(-D(r^{**}) - \Delta)^2 + S(r^{**})^2 = (r^*)^2.$$  \hspace{1cm} (6.5)

(Expressed in terms of the construction in Section 4, $p(r^*) = (-D(r^{**}), S(r^{**}))$.) See Figure 10 with $O = (\Delta, 0) = (a, 0)$, $A = (D(r^{**}), S(r^{**})) = (x, y)$, $C = (-D(r^{**}), S(r^{**}))$, $\overline{DO} = r^*$ and $\overline{BO} = r^{**}$. Here we assume that there
exists $B$ on the vertical axis so that (6.5) holds. To argue that this is the case, it suffices to establish (6.1), which together with (6.2) shall be established at the end of the proof. Consequently, Lemma 6.3 is applicable.

By continuity from (4.11),

$$\alpha = \left( \int_{\eta(r')}^{\pi} + \int_{\eta_2}^{\eta_4} \right) \sin^p \beta \, d\beta,$$

where $\eta(r')$ is as defined in (2.9), $\eta_3 = \cos^{-1}(-\Delta/r^*)$ and $\eta_4 = \cos^{-1}([\Delta - D(r^{**})]/r^*)$.

Since $r^{**} > r^*$, the first integral on the right-hand side of (6.6) is bounded above by

$$\int_{\eta(r')}^{\pi} k_p \sin^p \beta \, d\beta.$$  

By Lemma 6.3, the second integral is strictly less than

$$\int_{\eta_1}^{\eta_2} k_p \sin^p \beta \, d\beta,$$

where $\eta_1 = \cos^{-1}((D(r^{**}) - \Delta)/r^{**})$ and $\eta_2 = \cos^{-1}(-\Delta/r^{**}).$ Therefore (6.6) is strictly less than (6.7) plus (6.8), which equals $\alpha$. This shows $\alpha < \alpha$, a contradiction. Hence $r^* = \infty$.

Finally we shall prove (6.1) and (6.2), using $\alpha > \alpha^*$. We compare the rejection region $O'VO$ of the $\alpha$-level two one-sided tests procedure to the corresponding region $O'V'O$ of $\alpha^*$. See Figure 11. Since $\angle V'OO' = \pi/4$, the vertex $V'$ has the coordinate $(0, a)$. It is then obvious that $S(r_1) > a$ and $J_O > a$, where $J = (D(r_1), D(r_1))$ is on $VO$. Therefore point $A$ should be in region $T$, which is a subset of the first quadrant outside the bigger triangle and the circle passing $J$ centered at $O$. The reason is that point $A$ is on the upper boundary beyond the point $J$ and the boundary can only be in $T$. [The intersecting point on the lower boundary corresponds not to $A$ but to $\eta'(r^*)$, which results in the first integral on the right-hand side of (6.6).] Now all the points in $T$ satisfy (6.1) and (6.2) and so does $A$. □

**7. An approximately unbiased test for $\alpha < \alpha^*$**. Up to this point, it has been assumed that $\alpha > \alpha^*$. Although most practical problems satisfy the condition, it may be of interest to discuss briefly what results are available when the condition fails.

For some cases, it is possible to construct tests which are exactly unbiased. See Figure 12 for $\alpha = 0.25$ and $\nu = 1$. (Here $\alpha^* = \alpha$.) In general, for $\alpha \leq \alpha^*$ we do not have existence results. However, Munk (1992) has an algorithm to construct numerically unbiased tests which dominate the two one-sided tests procedure. Note that there is a simple proof that a dominating test exists, as in Hwang and Liu (1992).
8. Comparing our numerical results with those of Diletti, Hauschke and Steinijans. A referee pointed out that there seems to be inconsistency between our numerical results and that of Diletti, Hauschke and Steinijans (1991). We therefore explain briefly here by an example which serves to connect our results with theirs and also serves to illustrate our notation.

As in Diletti, Hauschke and Steinijans (1991), let $\bar{X}_T$ and $\bar{X}_R$ represent the sample averages corresponding to the logarithmically transformed characteristics of the test treatment and the reference treatment. The typical unbiased estimate of $\theta$, the difference of the characteristics corresponding to the test treatment and the reference treatment, is then $\bar{X}_T - \bar{X}_R$, which is assumed to be normally distributed with variance $2\sigma_0^2/n$ where $n$ is the total number of subjects and $\sigma_0^2$ is the within subject variance of the logarithmically transformed characteristic. Note that $\sigma_0$ is roughly equal to the coefficient of variation (CV) of the untransformed characteristic as specified in all the figures of Diletti, Hauschke and Steinijans (1991). Define

$$D = \frac{\bar{X}_T - \bar{X}_R}{\ln 1.25}.$$
Fig. 12. Rejection region of an unbiased test when \( v = 1 \) and \( \alpha = \alpha^* = 0.25 \). The arcs with radii \( r_1^*, r_2^*, r_3^* \) and \( r_4^* \) all lie within the rejection region.

Then \( D \sim N(\theta, \sigma^2) \), where

\[
(8.1) \quad \sigma^2 = \frac{2\sigma_0^2}{n(\ln 1.25)^2},
\]

which gives the canonical form (1.2) and (1.3). The corresponding hypothesis tested is then (1.1) with \( \Delta = 1 \).

As an example, let \( n = 21 \) and under the \( 2 \times 2 \) crossover design model with subject and period effects, the degrees of freedom are \( v = 19 \). Also consider

\[ \sigma_0 = 0.2892, \]

which interests us since it leads, by (8.1), to

\[ \sigma = \sqrt{\frac{2(0.2892)^2}{21(\ln(1.25))^2}} = 0.4. \]

With this \( \sigma \) and \( v \), the maximum power according to Figure 4, is about 0.57. Using Figure 2d of Dilletti, Hauschke and Steinijans (1991), for \( n = 21 \) and
CV = 0.25, the maximum power is about 0.69. The discrepancy is due to the fact that our CV is 0.2892 whereas theirs is 0.25. By considering their Figure 2a for the case with CV = 20% and the approximate maximum power 0.89, we may linearly extrapolate to give an approximate maximum power for CV = 0.2892 to be 0.53, which is close to our answer 0.57.

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