AN UNBIASED TEST FOR THE BIOEQUIVALENCE PROBLEM

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ABSTRACT. 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 α–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 α–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% or less relative to the cost of developing a new one.

The statistical formulation of the problem is by 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, $C_{\max}$ or $T_{\max}$) of the concentration–time curves.

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

$$H_0 : \rho > \Delta_2 \text{ or } \rho < \Delta_1 \quad \text{versus} \quad H_1 : \Delta_1 \leq \rho \leq \Delta_2.$$

If one can reject H_0, then one can declare bioequivalence. In the American FDA (1992) guidance, $\Delta_1 = .8$ and $\Delta_2 = 1.25$.

It is also recommended in the same guidance that a logarithmic transformation be applied and hence the ratio problem is turned into a difference problem, i.e.,

$$\theta = \ln(\rho) = \mu_1 - \mu_2$$

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where $\mu_i = \log m_i$. The hypotheses become

$$H_0 : |\theta| > \Delta \quad \text{versus} \quad H_1 : |\theta| < \Delta, \tag{1.1}$$

where $\Delta = \log 1.25$ in the FDA's guidance. Note in this special case, the transformation leads to a symmetric interval of θ. 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 as required in the FDA guidance (1992) is the two one–sided tests procedure. To describe this test, let D be an estimate of θ with

$$D \sim N(\theta, \sigma^2) \tag{1.2}$$

and S^2 be an independent observation such that

$$S^2/\sigma^2 \sim \text{ chi squared distribution with } v \text{ degrees of freedom.} \tag{1.3}$$

The simplest special case involves a two sample problem with observations

$$X_1 \cdots X_m \overset{i.i.d.}{\sim} N(\mu_1, \sigma_0^2) \quad \text{and} \quad Y_1 \cdots Y_n \overset{i.i.d.}{\sim} N(\mu_2, \sigma_0^2)$$

where for example these are the independent observations corresponding to two different treatments. Let $D = \overline{X} - \overline{Y}$ and $S^2 = \left(\frac{1}{m} + \frac{1}{n}\right)\left(\sum(X_i - \overline{X})^2 + \sum(Y_i - \overline{Y})^2\right)$ reducing to the above setting with $\sigma^2 = \left(\frac{1}{m} + \frac{1}{n}\right)\sigma_0^2$ and $v = m + n - 2$. The general linear model, including the cross over design or more generally ANOVA, can be reduced to (1.2) and (1.3) as well.

The α 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

$$\Delta \geq |D| + t_\alpha \frac{S}{\sqrt{v}}, \tag{1.4}$$

where t_α is the upper α 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 and 1985). These alternative tests, however, are only approximately α–level. Existence of a better test with exact level α was established in Hwang and Liu (1992). Munk (1993) constructed a test which is shown numerically to be α–level ($\alpha = .1$) for degrees of freedom larger than 10 and which is uniformly more powerful than the two one–sided test procedure.

In this paper we construct an unbiased α–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 α–level two one–sided tests procedure. See Theorem 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, i.e., 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 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 θ. This is also true for any level α.

Anderson and Hauck (1983, 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 paper indicate that the level of their nominally $\alpha = .05$ test may actually be in the range .057 to .061, which is of course close, but not equal, to the nominal value. Their test is not unbiased (unlike ours) but the qualitative similarity does reinforce the value of their proposal.

——————— Figure 1 should be placed around here ———————

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 remarks 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, p. 673–676) for a careful presentation of these arguments.

We tried to find a fundamental argument for the assertion that a reasonable rejection region should not be unbounded by using a likelihood approach, Bayesian approach, etc. However we did not succeed. Therefore we are not convinced it has to be so. It can even be shown (Munk, 1992) that every test with a bounded critical region has a vanishing power at any given θ 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 acceptance 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. The practical argument for this modification is that often a bioequivalence decision is followed by a point estimate of θ (and/or an associated confidence interval). The usual point estimate (and/or center of a confidence interval) is $\widehat{\theta} = D$. If S is quite large the procedure given by C_U can thus leave the statistician in the embarrassing position of rejecting the alternative hypothesis that $|\theta| > \Delta$ while at the same time estimating a value $\widehat{\theta}$ for which $|\widehat{\theta}| > \Delta$. For this reason the modification C_M may be appealing, since the rejection region is cut off at $D = \pm\Delta$. (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. Since the transformation $(D, S) \to (D/\Delta, S/\Delta)$ 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 $|\theta| \geqq 1$, then for a general Δ, rejecting H_0 if and only if $(D/\Delta, S/\Delta) \in C_U$ is the α–level unbiased test.)

As shown in Figure 1 as well as in Theorem 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 2–9. Note that for a given v and $\Delta = 1$, the only unspecified parameters are σ and θ. For $v = 19$, $\alpha = 0.05$, the powers are plotted against θ while σ 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 pictures for $\sigma \geq .7$) 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 computer software Gauss which runs on an IBM personal computer. The power of C_M lies between that of C_U and C_T.

————————Figures 2–9 should be placed around here ————————

The powers of the two tests C_U and C_2 are quite similar in some cases. However, in some figures such as 3–6, 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 σ 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 σ is not unusual in bioequivalence tests. For example in Westlake's data (1976, 1974), after the logarithmic transformation (with a base 10) the estimated variance is $\frac{1}{6}(0.012) = 0.002$. In our context, however, every quantity is scaled with respect to Δ. If Δ is taken to be $\log_{10} 1.25 = 0.0969$ as recommended in FDA (1992), the estimate of σ (scaled with respect to Δ) is $\sqrt{(0.002)}/0.0969 = .46$. If $\Delta = \log 1.20$ corresponding to the earlier recommendation of FDA, then the corresponding quantity is 0.56.

We also plotted pictures corresponding to $v = 39$. The resultant pictures are similar and are not reported.

The power of C_T is also plotted in Figures 2–9, 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. Ther 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 strong motivation for use of any one of the improved tests C_U, C_M or C_T rather than C_2.

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

$$e^{-(D-\theta)^2/2\sigma^2} S^p e^{-S^2/2\sigma^2}, \tag{4.1}$$

where $p = v - 1$.

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

Unbiasedness of φ_U implies that it is similar, i.e.,

$$E_{\theta,\sigma}\varphi_U(D, S) = \alpha \tag{4.2}$$

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

$$R^2 = (D - \Delta)^2 + S^2 \tag{4.3}$$

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

$$E_{\theta,\sigma}(\varphi_U(D, S) \mid R = r) = \alpha \quad \text{for} \quad \theta = \Delta, \tag{4.4}$$

and for every value of σ and r.

Similar statements as in the last paragraph can be concluded when Δ is replaced by $-\Delta$. However, the critical function φ_U to be constructed is symmetric in D, i.e.,

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

Therefore condition (4.4) remains unchanged when Δ 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, β), where the origin of the polar coordinate is $(\Delta, 0)$. Hence R is defined in (4.3) and

(4.5) β is the angle between the D axis and the line segment joining (D, S) and $(\Delta, 0)$.

(See Figure 10.) It can be calculated easily that the probability density function of (R, β) is proportional to

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

————Figure 10 should be placed around here ————————-

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

$$\begin{aligned}(k_p)^{-1} &= \int_0^\pi (\sin\beta)^p d\beta \\ &= \begin{cases} \dfrac{(p-1)(p-3)\cdots 1}{p(p-2)\cdots 2}\,\pi & \text{if } p \text{ is even} \\ \dfrac{(p-1)(p-3)\cdots 2}{p(p-2)\cdots 3}\,2 & \text{if } p \text{ is odd.} \end{cases}\end{aligned}$$

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, β) is the polar coordinate of (D, S) defined in (4.3) and (4.5).

Lemma 1. *Suppose the critical function $\varphi(D, S)$ is symmetric with respect to D. Then φ is similar if and only if*

$$k_p \int_0^\pi \varphi^*(r, \beta) \sin^p \beta d\beta = \alpha \tag{4.6}$$

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 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 $\{(\pm D'(r), S'(r)) : 0 \le r \le \Delta/\cos(\pi - \xi)\}$ where ξ satisfies

$$\begin{aligned} k_p \int_\xi^\pi (\sin\beta)^p d\beta &= \alpha \\ D'(r) &= \Delta + r\cos\xi \\ S'(r) &= r\sin\xi. \end{aligned} \tag{4.7}$$

(See the triangle in Figure 11.)

————Figure 11 should be placed around here ————————-

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

$$\alpha_* < \alpha < 1/2 \tag{4.8}$$

where

$$\alpha_* = k_p \int_{3\pi/4}^{\pi} (\sin\beta)^p \, d\beta.$$

Table 1 shows the values of α_* for $0 \le p \le 19$. Since α_* is decreasing in p, $\alpha_* < .0001$ for $v = p + 1 \ge 21$. For the FDA recommended choice $\alpha = 0.05$, the condition is met if and only if $v \ge 4$. The restriction is therefore quite minor. (See also Section 7.)

$p+1=v$:	1	2	3	4	5	6	7
α_*:	.25	.1464	.0581	.0378	.0249	.0166	.0111
$p+1=v$:	8	9	10	11	12	13	14
α_*:	.0075	.0051	.0034	.0023	.0016	.0011	.0008
$p+1=v$:	15	16	17	18	19	20	≥ 21
α_*:	.0005	.0004	.0002	.0002	.0001	.0001	$< .0001$

Table 1: Values of α_* in (4.8).

As noted, $r_0 = 0$. Then let

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

Condition (4.8) guarantees that $3\pi/4 > \xi > \pi/2$, so that $\sqrt{2}\Delta < r_1 < 2\Delta$. On this region, namely $0 < r \le r_1$, the boundary curve is the same as that for the two one sided tests region. See Figure 11, which also shows r_2 as defined below.

Suppose now that the curve has been defined for $r \le r_i$. See Figure 12. Let

$$r_{i+1} = [(\Delta + D(r_i))^2 + S^2(r_i)]^{1/2} \tag{4.9}$$

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.

————–Figure 12 should be placed around here ————————–-

Note that for $r_i < r < r_{i+1}$, the arc centered at $(\Delta, 0)$ with radius r intersects the curve $\{(-D(r), S(r)) : 0 < r < r_i\}$. 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 already 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 11.

Let

$$\eta(r) = \begin{matrix} 3\pi/2 - \xi + \cos^{-1}(r_1/r) & \text{if } \ r < 2\Delta \\ \pi & \text{otherwise.} \end{matrix} \tag{4.10}$$

(For $r < 2\Delta$, η is the angle between 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 11.)

Now define $D(r)$ by

$$\left\{ \int_\eta^\pi + \int_{\cos^{-1}(\frac{D(r)-\Delta}{r})}^{\cos^{-1}(\frac{p_1(r)-\Delta}{r})} \right\} k_p \sin^p \beta d\beta = \alpha. \tag{4.11}$$

This definition guarantees that (4.6) is satisfied.

We summarize the above construction in the following theorem.

The theorem below 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. 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 5 of Munk (1992), which is closest to violation but still satisfies the interval assumption.

Theorem 1. *Assume that $\alpha_* < \alpha < 1/2$. 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 α–level two one–sided tests procedure. The test is similar. Moreover if C_U satisfies the interval assumption, C_U is an α–level unbiased test.*

Proof: It is shown in Section 6 that when $\alpha_* < \alpha < 1/2$ 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 ξ' between the D axis and the line segment joining $(D(r), S(r))$ and $(\Delta, 0)$ is smaller than ξ. (In terms of the earlier notation, $\xi' = \cos^{-1}\left(\frac{D(r)-\Delta}{r}\right)$.) This is true, since

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

and by (4.7)

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

Now we argue for the second statement. By construction, C_U is similar which implies that the power function $P_{\theta,\sigma}((D,S) \in C_U)$ is α for $\theta = \pm\Delta$ and for every σ. The power function depends on θ 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 σ, $P_\theta((D,S) \in C_U \mid S)$ is decreasing in $|\theta|$, implying the same for the unconditional power. This implies that C_U has α–level and is unbiased.

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

$$S(r) = D(r)/\tan\lambda \tag{4.12}$$

where λ is the angle such that

$$\int_{\frac{\pi}{2}-\lambda}^{\frac{\pi}{2}+\lambda} k_p \sin^p \beta d\beta = \alpha. \tag{4.13}$$

The rationale for this is that when r is large then Δ/r is small and the region approaches that for $\Delta = 0$, 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 ξ 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 has to happen if and only if $p \geq 4$. See Table 1.

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

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

Step 3. Now proceed inductively as illustrated in Figure 12 where r_i and r correspond, respectively, to ρ_k and ρ_{k+1} to be described below. Let $\rho_1 = r_1$. Suppose $D(r)$ and $S(r)$ have already been defined for $0 \leq r \leq \rho_k$. Choose $\varepsilon > 0$ so that $\varepsilon \leq D(\rho_k)$. (The smaller ε is, the more precise the approximation will be; but the total computation will be longer.) Generally a value of ε can be fixed throughout the computation, but one must check at each stage that $\varepsilon \le D(\rho_k)$.) Then let

$$\rho_{k+1}^2 = \rho_k^2 + 4\varepsilon\Delta$$

and let ρ_{k+1}^* solve

$$(-\Delta - D(\rho_{k+1}^*))^2 + S^2(\rho_{k+1}^*) = \rho_{k+1}^2. \tag{5.1}$$

(If ε is fixed throughout the computation, to this stage, then $\rho_{k+1}^2 = \rho_1^2 + 4\varepsilon\Delta k$.)

Note, from the above construction,

$$\rho_{k+1}^* < \rho_k$$

and hence the point $P_{k+1} = (D(\rho_{k+1}^*), S(\rho_{k+1}^*))$ is well defined and can be solved. To see this, by definition the distance between P_{k+1} and $(\Delta, 0)$ is ρ_{k+1}^*, i.e.,

$$(D(\rho_{k+1}^*) - \Delta)^2 + S^2(\rho_{k+1}^*) = (\rho_{k+1}^*)^2.$$

This and (5.1) then imply

$$\begin{aligned}(\rho_{k+1}^*)^2 &= (D(\rho_{k+1}^* - \Delta)^2 + \rho_{k+1}^2 - (-\Delta - D(\rho_{k+1}^*))^2 \\ &= \rho_{k+1}^2 - 4\Delta D(\rho_{k+1}^*) < \rho_k^2,\end{aligned}$$

assuming $D(\rho_{k+1}^*) > \varepsilon$ as well.

Then define $(D(\rho_{k+1}), S(\rho_{k+1}))$ to be the solution to

$$\left\{ \int_\eta^\pi + \int_{\cos^{-1}\left(\frac{D(\rho_{k+1})-\Delta}{\rho_{k+1}}\right)}^{\cos^{-1}\left(\frac{-D(\rho_{k+1}^*)-\Delta}{\rho_{k+1}}\right)} \right\} k_p(\sin\beta)^p\, d\beta = \alpha$$

and

$$(D(\rho_{k+1}) - \Delta)^2 + S^2(\rho_{k+1}) = \rho_{k+1}^2,$$

where η is defined in (4.11).

Connect the points by line segments. Hence for $\rho_k < r \le \rho_{k+1}$ 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 $\rho_k < r \le \rho_{k+1}$.

Step 4. Terminate the calculation at some (large) ρ_{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 lemma is crucial to the proof of this validity.

Let $O = (a, 0)$ with $a > 0$ be a point on the horizontal axis. See Figure 13. 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

$$\overline{OB} = \overline{OA},$$

where, for example, $\overline{OB}$ denotes the distance between O and B. It is assumed that

$$\overline{OA} > a \tag{6.1}$$

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 13 are $E = (0, y)$, $\alpha = \angle BOC$, $\beta = \angle DOB$ and $\gamma = \angle AOD$.

——————Figure 13 should be placed around here ——————————-

Figure 13 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 the following lemma.

Lemma 1. *The condition*

$$x^2 + y^2 > a^2 \tag{6.2}$$

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 assumpiton (6.2) is equivalent to $(\overline{O'C})^2 + (\overline{CO})^2 > (\overline{O'O})^2$, 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 $\gamma > 0$. □

The other important geometric fact is contained in the following lemma.

Lemma 2. *In the above construction $\angle DOC < \angle AOB$.*

Proof: Examination of the construction displayed in Figure 13 and some algebraic calculation show that $\overline{ED} = \overline{EB}$ if and only if $\angle EOO' = \pi/4$ and $x < a$.

If $\overline{ED} \leq \overline{EB}$ then $\angle EOO' \leq \pi/4$ and B falls below the segment CO so that $DOC \subset AOB$ by Lemma 1. It follows trivially that $\angle DOC < \angle AOB$.

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

These two geometric lemmas combine to yield the following analytic result. Here, let $\eta_1 \doteq \angle O''OA$, $\eta_2 \doteq \angle O''OB$, $\eta_3 \doteq \angle O''OD$, $\eta_4 = \angle O''OC$.

Lemma 3. *Assume (6.1) and (6.2). Then*

$$\int_{\eta_1}^{\eta_2} \sin^p \beta d\beta > \int_{\eta_3}^{\eta_4} \sin^p \beta d\beta.$$

Proof: $\eta_2 - \eta_1 > \eta_4 - \eta_3$ by Lemma 2, and $\eta_1 < \eta_3$ by Lemma 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

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

which establishes the lemma. □

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

Theorem 2. *When $\alpha_* < \alpha < 1/2$, 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 and the corresponding test is unbiased.*

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

$$r^* = \inf\{r : D(r) = 0\} < \infty \tag{6.3}$$

or

$$r^* = \lim_{i\to\infty} r_i < \infty. \tag{6.4}$$

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 convenient 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

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

(Expressed in terms of the construction in Section 4, $p(r^*) = (-D(r^{**}), S(r^{**}))$.) See Figure 13 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 the last equation 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 3 is applicable.

By continuity from (4.11)

$$\alpha = \left\{ \int_{\eta(r^*)}^{\pi} + \int_{\eta_3}^{\eta_4} \right\} \sin^p \beta d\beta \tag{6.6}$$

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

$$\int_{\eta(r^{**})}^{\pi} k_p \sin^p \beta d\beta. \tag{6.7}$$

By Lemma 3 the second integral is strictly less than

$$\int_{\eta_1}^{\eta_2} k_p \sin^p \beta d\beta, \tag{6.8}$$

where $\eta_1 = \cos^{-1}(\frac{D(r^{**})-\Delta}{r^{**}})$ and $\eta_2 = \cos^{-1}(\frac{-\Delta}{r^{**}})$. Therefore (6.6) is strictly less than (6.7) plus (6.8), which equals α. 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 $D'VD$ of the α level two one–sided tests procedure to the corresponding region $D'V'D$ of α^*.

——————Figure 14 should be placed around here ————————-

See Figure 14. Since $\angle V'DD' = \pi/4$, the vertex V' has the cordinate $(0, a)$. It is then obvious that $S(r_1) > a$ and $\overline{JO} > a$. Therefore point A should be in region T, which is a subset of the first quadrant outside the 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 15 for $\alpha = .25$ 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 approximately unbiased tests which dominate the two one–sided tests procedure. One can also use a different argument to show that there exists a dominating test which is approximately unbiased.

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Figure 1: Rejection regions with $\alpha = 0.05$, $v = 14$, and $\Delta = 1$.
$C_2 =$ the triangle ABC and its inside; $C_U =$ 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.

Figure 2: Power functions $\sigma = 0.4$. The power functions of C_U, C_2, and C_T are plotted against θ using a solid line, a dashed line, and a dash and dot line, respectively. In this figure and Figures 3–5 the dash and dot line is invisible since it coincides with the solid line.

Figure 3: Power function as described in the title of Figure 2, except $\sigma = 0.5$.

Figure 4: Power function as described in the title of Figure 2, except $\sigma = 0.55$.

Figure 5: Power function as described in the title of Figure 2, except $\sigma = 0.6$.

Figure 6: Power function as described in the title of Figure 2, except $\sigma = 0.7$.

Figure 7: Power function as described in the title of Figure 2, except $\sigma = 0.8$.

Figure 8: Power function as described in the title of Figure 2, except $\sigma = 0.9$.

Figure 9: Power function as described in the title of Figure 2, except $\sigma = 1.0$.

Figure 10: With respect to $(\Delta, 0)$, (R, β) is the polar coordinate of (D, S).

Figure 11: 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.

Figure 12: Inductive construction of the boundary of C_U.

Figure 13: Illustration of the construction in Lemmas 1–3.

Figure 14: This and Figure 13 are used to establish that the intersection of the boundary with the vertical axis leads to a contradiction.

Figure 15: Rejection region of an unbiased test when $\nu = 1$ and $\alpha = \alpha^* = .25$. The arcs with radii r_1^*, r_2^*, r_3^* and r_4^* all lie within the rejection region.