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NUMERICAL SOLUTIONS FOR A SEQUENTIAL APPROACH TO BIOEQUIVALENCE

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Abstract: Bioequivalence is an important area of pharmaceutical research containing many questions which are not yet resolved. Various statistical approaches have been discussed in the literature. We address stopping rules for testing bioequivalence from a decision-theoretic point of view. Numerical techniques for Bayes sequential decision problems are employed to obtain solutions of the continuous time optimal stopping problem on bioequivalence.

Key words and phrases: Bioequivalence, backward induction, Bayes risk, decision theory, optimal stopping, sequential analysis.

1. Statement of the Problem

Two or more formulations of a drug are often compared in a bioequivalence trial. The purpose of such a trial is to determine whether alternative formulations which contain equal amount of the same active ingredient give rise to comparable concentrations in the blood or produce, in some sense, equivalent therapeutic effects.

Let μ, measured on some scale, represent the true difference between the two population treatment means. The regulatory agency demands that the proposer claiming bioequivalence demonstrates that it is reasonably certain that $|\mu| \leq \Delta$, where Δ is a prespecified tolerance limit. One major statistical assessment of bioequivalence is the interval hypothesis proposed by Schuirmann (1987) and Anderson and Hauck (1983). It is different from usual hypothesis testing because of the hypothesis expressed as an interval, $H_a : |\mu| \leq \Delta$. The other version is based on confidence intervals associated with tests for bioequivalence developed by Hsu, Hwang, Liu and Ruberg (1994). For other important issues regarding bioequivalence studies, readers are referred to Chow and Liu (1992).

We consider a clinical trial with an associated design for comparing two formulations, a new formulation and the standard. To formalize the bioequivalence problem for the trial, we present a Bayesian decision theoretic approach instead of a traditional hypothesis testing approach. The design allows the manager to terminate the program early if the two formulations are almost equivalent or far from equivalent and to continue the trial otherwise.

The Bayesian approach allows, in fact requires, explicit consideration of the information available about the drug prior to the current trial. The prior information is quantified in terms of a (prior) probability distribution on μ. To be specific we assume $\mu \sim N(\mu_0, \sigma_0^2)$. If μ_0 and σ_0 are close to zero then the manager's prior assessment is that the two formulations are likely to be bioequivalent; and large σ_0 corresponds to a high degree of uncertainty regarding μ.

Let X_i denote the observed difference in responses for the ith pair of patients, $i = 1, \ldots, n$. Assume that $X_1, \ldots, X_n$ are independent $N(\mu, \sigma^2)$, where σ^2 is known. The posterior distribution of μ given $X_1, \ldots, X_n$ is $N(Y_n, s_n)$, where

$$Y_n = \frac{\mu_0\sigma_0^{-2} + (X_1 + \cdots + X_n)\sigma^{-2}}{\sigma_0^{-2} + n\sigma^{-2}} \quad \text{and} \quad s_n^{-1} = \sigma_0^{-2} + n\sigma^{-2}.$$

So, after each observation, we need to know n, the current Bayes estimate Y_n of μ, and its precision s_n; (Y_n, s_n) is the "state of information" after the nth observation. Then we may decide to continue sampling or to stop. In the latter case we must decide on whether or not we have bioequivalence. While it will be only approximately true in practice, we assume that the cost of the trial is linear in the number of pairs of patients in the experiment. That is, we assume that the marginal sampling cost per pair is c. When the trial is stopped, one must decide to reject or claim bioequivalence. The cost of rejecting bioequivalence is k, the expected cost of having to start over. The cost of claiming bioequivalence may be an increasing function of the absolute difference between the two population treatment means. We consider the quadratic cost μ^2 in the following illustrations and refer to the related problem as problem 1.

At stage n, we have the risk associated with stopping and deciding for or against bioequivalence plus the cost of sampling cn yielding $d_1(Y_n, s_n)$, where

$$\begin{aligned} d_1(y, s) &= cn + \min\{k, E[\mu^2 | Y_n = y, s_n = s]\} \\ &= \frac{c\sigma^2}{s} + \min\{k, y^2 + s\} - \frac{c\sigma^2}{\sigma_0^2}. \end{aligned} \tag{1}$$

The problem of finding the Bayes procedure for testing bioequivalence has been reduced to a standard stopping problem of the type described in Chernoff (1972). That is, to find a stopping rule (a random variable N) so as to minimize $E[d_1(Y_N, s_N)]$.

For the continuous time version of the bioequivalence problem, μ is regarded as a random variable, and the limiting form of the (Y_n, s_n) process is a Gaussian process of independent increments $Y(s)$ in the $-s$ scale for $s_0 \geq s \geq 0$, where $E[dY(s)] = 0$, $\mathrm{Var}\,[dY(s)] = -ds$, with $Y(s_0) = \mu_0$ at $s_0 = \sigma_0^2$ and $s^{-1} = \sigma_0^{-2} + t\sigma^{-2}$. Note that as time t increases from 0 to ∞, s decreases from σ_0^2 to 0. Thus $(-ds)$ may be thought of as positive.

The continuous time version of the bioequivalence problem is essentially determined by finding a stopping time S to minimize the *risk*, $E[d_1(Y(S), S)]$, where the cost function $d_1(y, s) = c\sigma^2/s + \min\{k, y^2 + s\}$, after dropping the constant $c\sigma^2/\sigma_0^2$ which does not affect the choice of the optimal procedure.

From the point of view of solving the bioequivalence problem, certain simplifying transformations can be made. With the transformation $y^* = k^{-1/2}y$, $s^* = k^{-1}s$, our problem may be normalized to that of dealing with a stopping cost $d_1^*(y^*, s^*) = c^*/s^* + \min\{0, y^{*^2} + s^* - 1\}$ and sampling cost parameter $c^* = c\sigma^2 k^{-2}$. We can now drop the stars and express the optimal stopping problem in a standard form with

$$d_1(y, s) = \frac{c}{s} + \min\{0, y^2 + s - 1\}. \tag{2}$$

This form involves only the single parameter c.

2. Numerical Techniques and Implementation

Chernoff and Petkau (1986) have described a number of techniques employed in obtaining numerical descriptions of the solutions of the general optimal stopping problem for a zero drift Wiener process in the (y, s) scale. These procedures are useful tools for solving general optimal stopping problems. But for the bioequivalence problem, we need additional techniques to overcome a difficulty in the implementation.

The symmetry of $d_1(y, s)$ about $y = 0$ implies that the computations involved in the backward induction can be confined to $y \geq 0$, that is, computing on the grid

$$\{(y, s) : s = s^1 + i\delta,\ y = j\sqrt{\delta};\ i = 0, 1, \ldots, m_s,\ j = 0, 1, \ldots, m_y\}, \tag{3}$$

which yields the optimal solution to the stopping problem as

$$\begin{aligned} \hat{d}_1(y, s) &= d_1(y, s) \quad \text{for} \quad s = s^1, \\ &= \min\Big\{d_1(y, s), \frac{1}{2}[\hat{d}_1(y + \sqrt{\delta}, s - \delta) + \hat{d}_1(y - \sqrt{\delta}, s - \delta)]\Big\} \text{ for } s > s^1. \end{aligned} \tag{4}$$

In the course of this computation which yields the optimal risk for the random walk problem, each individual grid point is classified as either a stopping point or a continuation point for the random walk. Thus, the continuation regions and their boundaries are determined and continuity correction methods can be employed to obtain approximations to the continuous time boundaries. For accuracy, the computation is carried out in stages or *phases* where grid spacings are changed from one phase to the next.

The first phase consists of starting at $s^1 = 0$ and applying m_s steps of size δ for a suitably small value of δ. Then m_y, the number of grid points along the y-axis, must be chosen large enough to contain all the continuation points for this first phase. In the next phase we increase the size of δ by a factor of 4 which automatically doubles the grid distance along the y-axis. Instead of starting phase 2 at the end of phase 1 where $s = m_s\delta$, we prefer to overlap these two phases, to give the new coarser calculation an opportunity to adjust, thereby avoiding some possible discontinuities due to the transition. Thus we have a new δ, four times the original, and a new s^1 between the original s^1 and $s^1 + m_s\delta$, and new values of m_s and m_y. Where we have overlapping phases, we use the finer grid to determine the values of the Bayes risk and optimal stopping boundaries. This procedure can be repeated through successive phases of coarsening the grid.

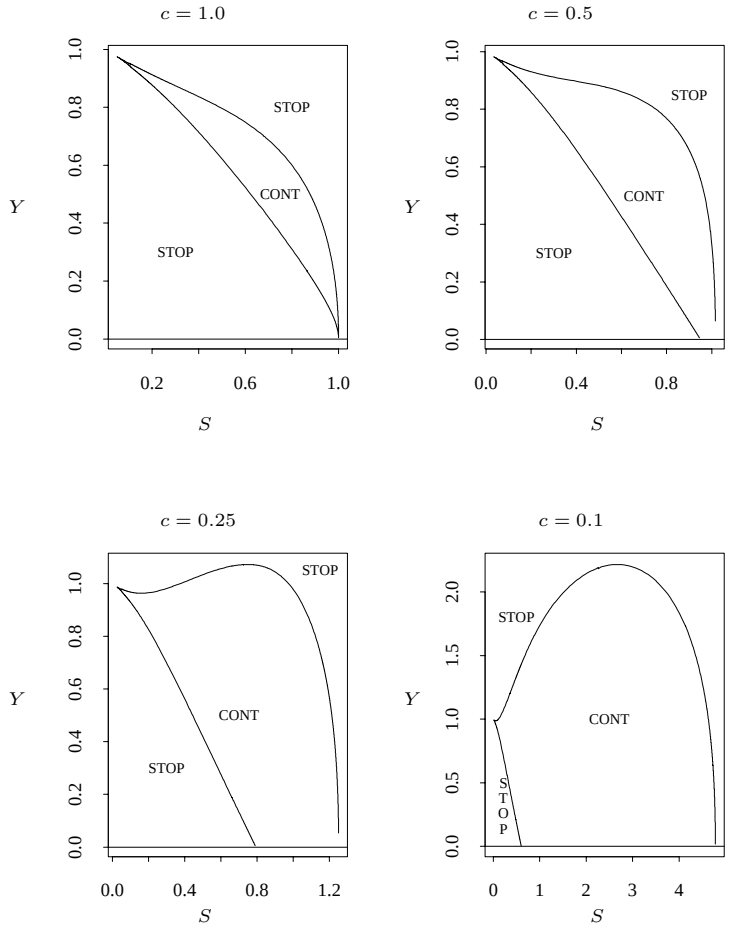

Figure 1. Stopping boundaries of problem 1.

Referring to Figure 1, we see that there are two boundaries above the y-

axis. For sufficiently large values of the constant c, the outer boundary turns back toward the s-axis. It may be desirable to change δ again so that the grid spacings become more refined as the boundary gets closer to the s-axis. In this case we refine the grids by *reducing* δ by a factor 4 when moving to the next phase. Then the new s^1 will be the last value of s, i.e., $s^1 + m_s\delta = s^*$. Now we face a technical difficulty. If we label the old and new values of δ, δ_0 and $\delta_n = \delta_0/4$, then the new values of y are $i\sqrt{\delta_n} = i\sqrt{\delta_0}/2$ and we can not proceed because we have not evaluated $\hat{d}_1$ at $i\sqrt{\delta_n} = i\sqrt{\delta_0}/2$ for the odd values of i when $s = s^*$.

To overcome this difficulty we evaluate $\hat{d}_1(y, s^*)$ for $y = i\sqrt{\delta_0}/2$ with odd values of i, by replacing the last dichotomous step of $\pm\sqrt{\delta_0}$ by a four valued step with the same mean 0 and variance δ_0. In other words, if we let y go to $y \pm \frac{1}{2}\sqrt{\delta_0}$ with probability p_1 and $y \pm \frac{3}{2}\sqrt{\delta_0}$ with probability p_2, then the mean change $E[dY] = 0$ and the variance $E[dY]^2 = \delta_0$ if $p_1 + p_2 = \frac{1}{2}$ and $p_1 + 9p_2 = 2$.

Thus, for the intermediate values of $y = i\sqrt{\delta_0}/2$ with odd i, the Bayes risk at (y, s^*) will be the minimum of $d_1(y, s^*)$ and

$$\begin{aligned}\hat{d}_1(y, s^*) \;=\; & \frac{5}{16}\hat{d}_1\Big(y - \frac{1}{2}\sqrt{\delta_0}, s^* - \delta_0\Big) + \frac{5}{16}\hat{d}_1\Big(y + \frac{1}{2}\sqrt{\delta_0}, s^* - \delta_0\Big) \\ & + \frac{3}{16}\hat{d}_1\Big(y - \frac{3}{2}\sqrt{\delta_0}, s^* - \delta_0\Big) + \frac{3}{16}\hat{d}_1\Big(y + \frac{3}{2}\sqrt{\delta_0}, s^* - \delta_0\Big). \quad (5)\end{aligned}$$

Having calculated these values we can now proceed with the numerical calculations using the reduced value δ_n of δ. We expected this technique to reveal slight discontinuities in the estimates of both the Bayes risk and the stopping boundary on moving from one phase to the next. But experience shows that the jumps are so small that we can ignore them.

3. Solutions

Bather and Chernoff (1993) have characterized the general picture of the solutions by studying the effect of changing the standardized sampling cost parameter c. First, the optimal continuation region $\mathcal{C}$ will cover the curve $y = \pm\sqrt{1 - s}$ for $0 < s < 1$. This is because the discontinuity in first derivatives of the stopping cost $\min\{0, y^2 + s - 1\}$ implies a local advantage in sampling. The advantage is of order $\sqrt{|\delta s|}$, whereas the sampling cost is of order $|\delta s|$, for any small increments δs. Secondly $\mathcal{C}$ is monotone in the sampling cost c, that is, $c_1 \geq c_2$ implies $\mathcal{C}_1 \subset \mathcal{C}_2$. As we already noted, every point on the parabola $y^2 + s - 1 = 0$ belongs to $\mathcal{C}$, with the possible exception of $(y, s) = (0, 1)$. In fact, there is a definite advantage in sampling if $c < \sqrt{2/\pi e} \doteq 0.484$, i.e., $(0, 1) \in \mathcal{C}$ if $c < \sqrt{2/\pi e}$. Fourth, for $c \geq 1$, all points $(0, s)$ lie in the optimal stopping set $\mathcal{S}$ and for $0 < c \leq 1$, all

points $(0, s)$ with $0 \le s \le \sqrt{c}$ also lie in $\mathcal{S}$. Furthermore,

$$(y, s) \in \mathcal{S}, \quad \text{if} \quad c > \frac{1}{4} \quad \text{and} \quad s \ge \frac{c}{2\sqrt{c} - 1}.$$

From the above results, they have drawn the stopping boundaries roughly for $c \ge 1$, $\frac{1}{4} < c < \sqrt{2/\pi e}$, and sufficiently small c.

We have learned how the solutions would be related to c, but there is no closed-form solution so far. While the above results do provide valuable insight, they do not provide an adequate approximation to the solution. Applying the previously discussed numerical techniques, we explored the optimal boundaries for a large set of sampling cost parameter values. The numerical descriptions of the solutions are summarized in Figure 1, presenting plots for the continuous time version for $c = 1.0$, 0.5, 0.25, and 0.1.

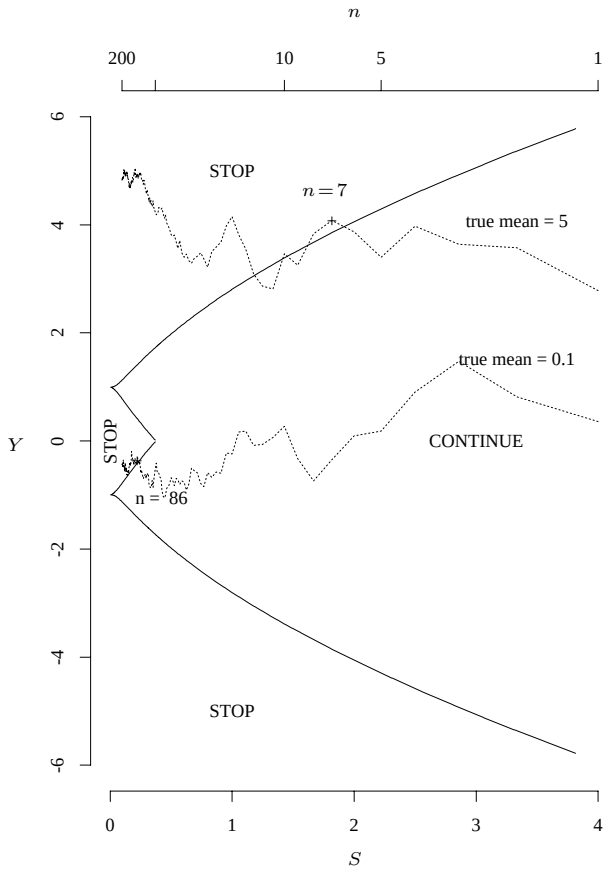

Figure 2. Two hypothetical series with $\mu = 5, 0.1$ and $\sigma^2 = 20$, $\sigma_0^2 = 5$, $k = 1$, $c = 0.001$; and the optimal boundaries.

Given any fixed σ_0^2, σ^2, k, and c, we can calculate the optimal boundaries for the original discrete time problem in which people are interested in practice. First we implement the computer program with the standardized sampling cost $c^* = c\sigma^2 k^{-2}$, then apply a method in Chernoff (1965) to adjust the optimal boundaries of the continuous time version problem. As an example, suppose $\sigma_0^2 = 5$, $\sigma^2 = 20$, $k = 1$, and $c = 0.001$, then c^* equals 0.02, and the initial value s_0^* in the normalized scale is given by $s_0^* = k^{-1}s_0 = k^{-1}\sigma_0^2 = 5$. The optimal outer and inner boundaries are given in Figure 2. For demonstration of how the boundaries can be used in the decision making, we simulated two series of paired difference measurements of size 200 with means 5 and 0.1 respectively. The two series of posterior means Y_n plotted with the boundaries show that the first simulated series cross the outer boundary at $n = 7$ and the second series cross the inner boundary at $n = 86$. That is, the manager may stop the trial at stage 7 and reject to claim bioequivalence quickly for the first simulated data. For the second hypothetical data, the manager has to wait a little longer until stage 86 to claim bioequivalence for the two treatments.

An alternative model is to consider that the cost of claiming bioequivalence is not μ^2, but $|\mu|$. This leads to a different stopping cost.

$$E[|\mu| \mid Y(s) = y] = s^{\frac{1}{2}}[G_1(\alpha) + G_1(-\alpha)], \tag{6}$$

where

$$\alpha = y\, s^{-\frac{1}{2}}, \quad G_1(\alpha) = \varphi(\alpha) + \alpha\Phi(\alpha),$$

and φ and Φ are the density and cumulative distribution functions for the standard normal distribution.

Note that

$$G_1(\alpha) + G_1(-\alpha) = 2\Big\{\varphi(\alpha) + \alpha[\Phi(\alpha) - \frac{1}{2}]\Big\} = H_1(\alpha).$$

Instead of (2), we now have a standardized stopping cost

$$d_2(y, s) = \frac{c}{s} + \min(0, s^{\frac{1}{2}}H_1(\alpha) - 1), \tag{7}$$

and we will call the optimization problem related to d_2 problem 2. It seems that the continuation regions of this problem should have shapes similar to those of problem 1. In particular when s is small both $d_1(y, s)$ and $d_2(y, s)$ are approximated by the same term c/s, representing the sampling cost, and so we expect similar behavior near $s = 0$.

The implementation of this second version is the same as the previous one except for replacing the cost function $d_1(y, s)$ by $d_2(y, s)$. Figure 3 shows that the shapes of the stopping boundaries are very similar for the two versions for the chosen values of c.

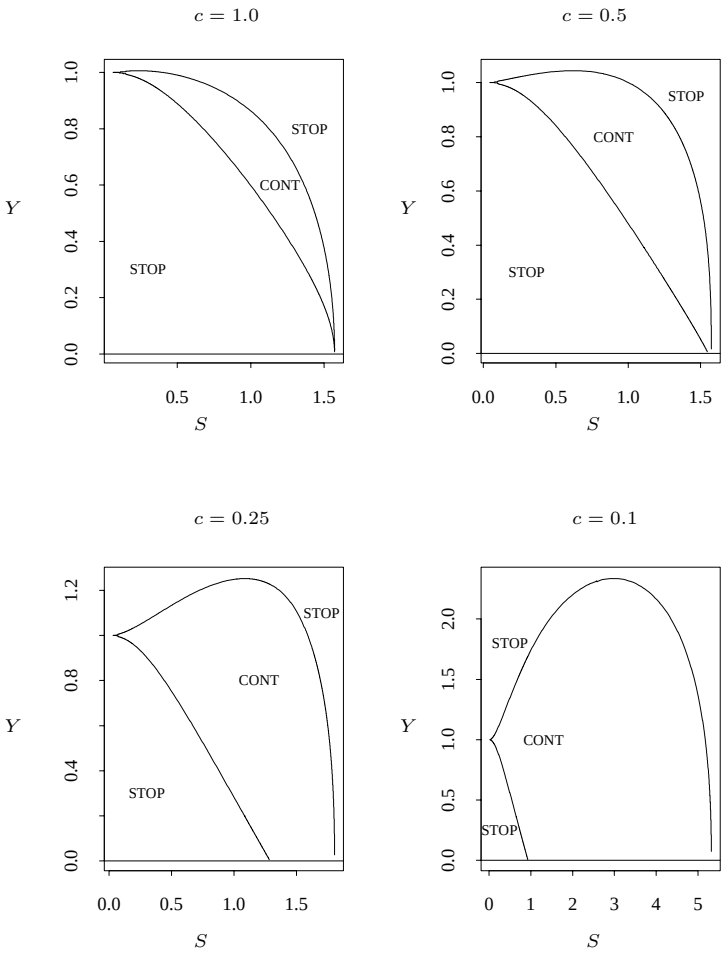

Figure 3. Stopping boundaries of problem 2.

4. Asymptotic Results

The cost functions $d_1(y, s)$ and $d_2(y, s)$ defined in (2) and (7) show that the risk becomes infinite as $s \to 0$. To avoid this and to simplify the calculations for s close to zero, Bather and Chernoff (1993) modified the cost functions and derived the asymptotic expansions of the optimal boundaries

$$\begin{aligned} \tilde{y}^i &= 1 - \frac{s}{2} - \frac{s^2}{8} + a^i s^2, \\ \tilde{y}^o &= 1 - \frac{s}{2} - \frac{s^2}{8} + a^o s^2, \end{aligned} \tag{8}$$

where $\tilde{y}^i$ gives the inner boundary for accepting bioequivalence, $\tilde{y}^o$ applies to rejection and there are symmetric curves near $y = -1$. The values of a^i and

a^0 are $a^i = -\frac{1}{2c}$ and $a^0 = \frac{1}{2c}$ respectively. Note that $1 - \frac{s}{2} - \frac{s^2}{8}$ describes the approximate behavior of the curve $y^2 + s = 1$ near $(y, s) = (1, 0)$.

For problem 2, similar arguments suggest that there are almost symmetrical boundary curves near each critical point $(y, s) = (\pm 1,\ 0)$, at $y = 1 \pm O(s^2)$ and $y = -1 \pm O(s^2)$.

From the asymptotic result (8), we would expect to see the two boundaries close to each other for small values of s when c is large. In order to demonstrate the numerical results for small values of s, we chose sufficiently small c values and computed the numerical approximations for $s < 1$. Figure 4 shows clear pictures of the behavior of the boundaries near the critical points $(y, s) = (1, 0)$. We see, for problem 2, the estimated stopping boundaries are symmetrical about $y = 1$. The angles of the curves get larger and the curves move forward as c becomes smaller. The continuous curves were calculated using a small initial step size $\delta = 2^{-18}$ and considerably more computer time. Even these refined calculations can stand some improvement for s very close to zero, where asymptotic expansions tend to be quite accurate.

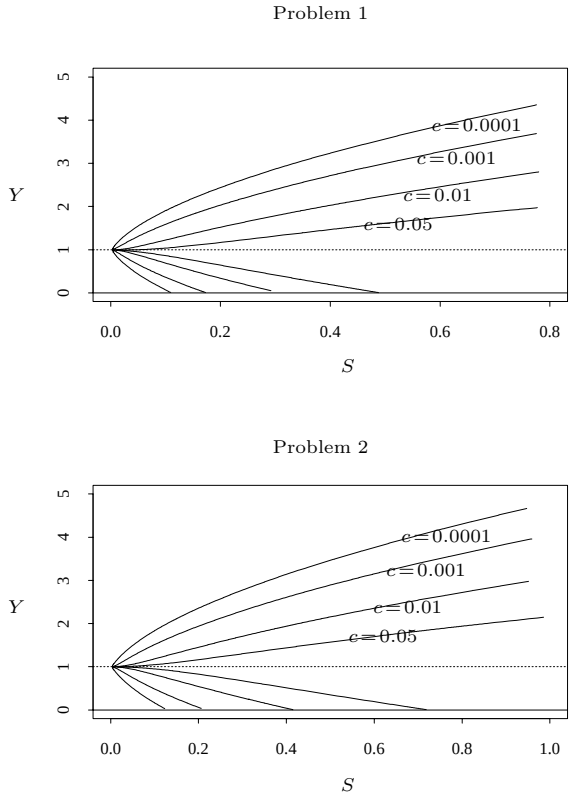

Figure 4. Stopping boundaries of problems 1 and 2 – small c.

We are also interested in how small c must be for the outer boundary curve to never return to $y = 0$. In general, we would like to see how the inner and outer curves behave as the sampling cost changes. We have already noted that the inner curve and outer curve will meet at $(y, s) = (0, 1)$ for $c \geq 1$ in problem 1. The numerical results show that when $c \geq 1$ the inner and outer curves meet at $(y, s) = (0, 1.57)$ for problem 2. From the numerical results, we also found that as c decreases to 0, the inner critical s value, the s value where the inner curve reaches the s-axis, decreases to 0 and the outer critical s value increases to ∞ . In fact, when c is smaller than 0.05, we see the outer curves never returns to $y = 0$ for problems 1 and 2.

5. Remarks

We have addressed stopping rules for testing bioequivalence from a Bayes sequential decision-theoretic point of view. It has the advantages of facing squarely the decision problem that the U. S. FDA should state. It has the disadvantage of ignoring most of the issues raised in the literature, for example, Anderson and Hauck (1990), Locke (1990), Schuirmann (1990) and Hsuan (1993). It does not face the sequence and period-effects at all. It implicitly assumes that the individual drug interaction is negligible. In addition to normality, homoscedasticity and known variance are assumed, and it has been applied only to the two drug case. Given the shortcomings of this formulation, it still has the advantage of providing a solution which gives insight into how to handle the general problem. There is no confusion about what constitutes a suitable null hypothesis that accompanies the attempt to pose the problem in terms of some standard significance level testing problem.

The Bather-Chernoff-Petkau formulation and the numerical results presented in this paper provide some guidance on what constitutes a reasonable formulation and a reasonable solution in the simplest cases. For realistic problems, these can only be rough guides. On the other hand the elaborate solutions proposed by Hsuan and others suffer from a certain amount of vagueness and sloppiness about what are the fundamental decision problem costs. The most serious problems, concerning the model structure, remain unresolved unless FDA studies have provided more information than is hinted at in the papers presented.

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