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Discrete sequential boundaries for clinical trials

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SUMMARY

Pocock (1977), O'Brien & Fleming (1979) and Slud & Wei (1982) have proposed different methods to construct discrete sequential boundaries for clinical trials. These methods require that the total number of decision times be specified in advance. In the present paper, we propose a more flexible way to construct discrete sequential boundaries. The method is based on the choice of a function, $\alpha^*(t)$, which characterizes the rate at which the error level α is spent. The boundary at a decision time is determined by $\alpha^*(t)$, and by past and current decision times, but does not depend on the future decision times or the total number of decision times.

Some key words: Brownian motion; Decision time; Group sequential design.

1. INTRODUCTION

It is common practice that accumulating data are reviewed periodically during the course of a clinical trial. In contrast to a single stage, fixed sample size or fixed duration, test, it is widely recognized that when statistical data analyses are performed repeatedly, some adjustment has to be made to maintain the probability of type I error at a specified level (Armitage, McPherson & Rowe, 1969). Pocock (1977) proposed use of an adjusted critical value, so that when standard significance tests are planned to be performed repeatedly for a fixed number of times, an overall significance level α will be achieved. O'Brien & Fleming (1979) also proposed to use an adjusted constant to achieve a fixed level α, but their consecutive test statistics are defined to have variances proportional to the accumulated sample sizes. Recently, Slud & Wei (1982) derived the asymptotic distribution of sequentially computed modified Wilcoxon, i.e. Gehan, scores, and pointed out that for staggered patient entry and random loss to follow-up, the process is asymptotically Gaussian, but generally has dependent increments. They proposed a procedure to construct discrete sequential boundaries for this situation, as outlined in the next section. All the methods mentioned so far require specifying the total number of decision times K in advance. In practice, this could cause some problems since the decision making group of a trial may change the frequency of data review at some point during the course of the trial. Another possibility is that slower recruitment than anticipated could force extension of the trial, and hence increase the number of decision times.

The purpose of this paper is to propose a procedure to compute a flexible discrete boundary $(b_1, \ldots, b_K)$ for a discrete stochastic process $(S_1, \ldots, S_K)$. The procedure requires only the specification in advance of an increasing function $\alpha^*(t)$, which characterizes the rate at which the error level α is spent.

Although we describe our method in terms of a one-sided test, the generalization to a symmetric two-sided test is immediate. That is, we simply replace α by $\frac{1}{2}\alpha$ to construct a one-sided boundary as proposed, and then apply it symmetrically.

2. DESCRIPTION OF THE PROCEDURE

Let $\{B(t): 0 \leqslant t \leqslant 1\}$ be a standard Brownian motion process and consider the horizontal boundary $b(t) = z_{\frac{1}{2}\alpha}$ for $0 \leqslant t \leqslant 1$, to be the boundary of interest. Let τ be the first exit time across the boundary. If $\alpha^*(t) = \text{pr}(\tau \leqslant t)$ $(0 \leqslant t \leqslant 1)$ it is well known that

$$\alpha^*(t) = \begin{cases} 0 & (t = 0), \\ 2 - 2\Phi(z_{\frac{1}{2}\alpha}/\sqrt{t}) & (0 < t \leqslant 1), \end{cases} \tag{1}$$

where Φ is the standard normal distribution function. The function $\alpha^*(t)$ is strictly increasing in t and $\alpha^*(1) = \alpha$, the predetermined significance level.

Assume that $B(t)$ be observed only at time t_i $(i = 1, \ldots, K)$ with $0 < t_1 < \ldots < t_K = 1$. Since $B(t)$ is not observed between 0 and t_1, we can assign an accumulated boundary crossing probability $\alpha^*(t_1)$ to the point t_1, by defining b_1 to satisfy

$$\text{pr}\{B(t_1) > b_1\} = \text{pr}\{\tau \in [0, t_1]\} = \alpha^*(t_1).$$

Similarly, we can find constants $b_2, \ldots, b_K$ such that for $i = 2, \ldots, K$

$$\text{pr}\{B(t_j) < b_j,\ j = 1, \ldots, i-1;\ B(t_i) > b_i\} = \text{pr}\{\tau \in (t_{i-1}, t_i]\} = \alpha^*(t_i) - \alpha^*(t_{i-1}).$$

It can be shown that $b_1 = \sqrt{t_1}\,\Phi^{-1}\{2\Phi(z_{\frac{1}{2}\alpha}/\sqrt{t_1}) - 1\}$, but the evaluation of $b_2, \ldots, b_K$ requires numerical integration (Armitage *et al.*, 1969). A program in FORTRAN is available from the authors. Note that the evaluation of b_i depends only on $\alpha^*(t)$ and $t_1, \ldots, t_i$, but, in contrast to the procedures of Pocock and O'Brien & Fleming, we do not need to know the values of K or $t_{i+1}, \ldots, t_K$.

Theoretically, we can generalize the idea of discretizing a continuous boundary to more general settings. Suppose we have a continuous stochastic process $\{S(t);\ 0 \leqslant t \leqslant 1\}$, which is not necessarily Brownian motion, and a continuous boundary $b(t)$ $(0 \leqslant t \leqslant 1)$ with probability α of being crossed in $0 \leqslant t \leqslant 1$. Then $\alpha^*(t)$, the probability of crossing before t, is an increasing function with $\alpha^*(1) = \alpha$. Applying the idea just described for Brownian motion, one can again compute the boundary points b_i consecutively by using up the accumulated probabilities. In particular, if $b(t)$ is the optimal continuous boundary for a certain one-sided alternative, the corresponding discretized boundary $(b_1, \ldots, b_K)$ should enjoy, approximately, the same optimal properties. One could, of course, choose any increasing function α^* with $\alpha^*(1) = \alpha$, and construct a boundary $(b_1, \ldots, b_K)$ in the above manner. The α^* chosen need not be associated with a well-defined continuous sequential boundary, so long as the choice of α^* can be otherwise justified. Recently, Slud & Wei (1982) suggested the construction of a discrete sequential boundary $(b_1, \ldots, b_K)$ by choosing positive constants $\alpha_1, \ldots, \alpha_K$, so that $\Sigma\alpha_i = \alpha$, $\text{pr}\{S(t_1) \geqslant b_1\} = \alpha_1$ and, for $i = 2, \ldots, K$,

$$\text{pr}\{S(t_i) \geqslant b_i,\ S(t_j) < b_j,\ j = 1, \ldots, i-1\} = \alpha_i.$$

Their choice of $\{\alpha_i\}$ is independent of the decision times $\{t_i\}$.

3. Choice of $\alpha^*(t)$

In the previous section, we constructed an increasing function $\{\alpha^*(t), 0 \leqslant t \leqslant 1\}$, for a boundary $\{b(t), 0 \leqslant t \leqslant 1\}$, so that $\alpha^*(t)$ is the cumulative boundary crossing probability of a process $\{S(t), 0 \leqslant t \leqslant 1\}$. In continuous sequential analysis, we can either introduce a boundary $b(t)$, so that the total boundary crossing probability is α, or, we can introduce an increasing function $\alpha^*(t)$ with $\alpha^*(1) = \alpha$. These two concepts are essentially equivalent. A single stage test can be viewed as a special case of a sequential test, with

$$\alpha^*(t) = \begin{cases} 0 & (0 \leqslant t < 1), \\ \alpha & (t = 1), \end{cases} \tag{2}$$

or equivalently, $b(t) = \infty$ $(0 \leqslant t < 1)$ and $b(1) = c$, where c is chosen so that $\text{pr}\{S(1) > c\} = \alpha$. Clearly, choice of $\alpha^*(t)$ should be made before the data are monitored. We discuss three possible choices of $\alpha^*(t)$ for the Brownian motion process.

In case (i), $\alpha_1^*(t) = \alpha^*(t)$ as defined in (1). This $\alpha_1^*(t)$ corresponds to the horizontal boundary for the Brownian motion discussed in §2. For the continuous case, this boundary has been discussed by Davis (1978) and Koziol & Petkau (1978). O'Brien & Fleming's (1979) method can be viewed as one way to discretize this horizontal boundary. When $t_i = i/K$ $(i = 1, \ldots, K)$ our procedure will result in a discrete boundary close to the O'Brien & Fleming boundary; see Table 1. Since $\alpha_1^*(\frac{1}{2}) < 0{\cdot}006$ for $\alpha = 0{\cdot}05$, if $\alpha_1^*(t)$ is employed a clinical trial is unlikely to stop very early. Therefore, $\alpha_1^*(t)$ may be a suitable choice when long-term treatment effect is a major concern of a trial. Note, for this choice of $\alpha^*(t)$, although we essentially obtain O'Brien & Fleming's boundary, we have no need to specify either K or spacing between decision times in advance.

In case (ii), $\alpha_2^*(t) = \alpha \log\{1 + (e-1)t\}$. Since $\alpha_2^*(0{\cdot}5) \doteq 0{\cdot}62\alpha$, we spend 62% of the error probability α by $t = \frac{1}{2}$. Thus, this $\alpha_2^*(t)$ will generally result in earlier termination, but we will suffer a reduction in power. Note that when $t_i = i/K$ $(i = 1, \ldots, K)$, this choice of $\alpha_2^*(t)$ gives us a discrete boundary somewhat similar to Pocock's boundary; see Table 1. The function $\alpha_2^*(t)$ just defined is not exactly the cumulative boundary crossing

Table 1. *One sided boundaries for* $\{B(t_i)/\sqrt{t_i}, t_i = i/5, i = 1, 2, 3, 4, 5\}$

	(a) $\alpha = 0{\cdot}025$					(b) $\alpha = 0{\cdot}05$				
	c_1	c_2	c_3	c_4	c_5	c_1	c_2	c_3	c_4	c_5
O'Brien & Fleming	4·56	3·23	2·63	2·28	2·04	3·92	2·77	2·26	1·96	1·75
$\alpha_1^*(t)$	4·90	3·35	2·68	2·29	2·03	4·23	2·89	2·30	1·96	1·74
Pocock	2·41	2·41	2·41	2·41	2·41	2·12	2·12	2·12	2·12	2·12
$\alpha_2^*(t)$	2·44	2·43	2·41	2·40	2·39	2·18	2·14	2·11	2·09	2·07
$\alpha_3^*(t)$	2·58	2·49	2·41	2·34	2·28	2·33	2·22	2·12	2·03	1·96

probability function for a continuous version of the Pocock boundary. A natural continuous version of the Pocock boundary seems to be of the form $b(t) = c\sqrt{t}$, $0 \leqslant t \leqslant 1$. However, according to the law of the iterated logarithm, $\text{pr}\{B(t) \geqslant c\sqrt{t}$ for some t, $0 \leqslant t \leqslant 1\} = 1$, no matter how large c is. One can by-pass this difficulty by introducing a small positive number ε, which represents a delay before the first examination of the data (Majumdar & Sen, 1977). Then there exists a constant $c(\alpha, \varepsilon)$ such that $\text{pr}\{B(t) \geqslant c(\alpha, \varepsilon)\sqrt{t}$ for some $t, \varepsilon \leqslant t \leqslant 1\} = \alpha$, but the distribution for the corresponding first exit time is complicated (DeLong, 1981). We chose $\alpha_2^*(t)$ here both because of its simplicity and the similarity of its derived boundary with the Pocock boundary.

For case (iii), $\alpha_3^*(t) = \alpha t$. This $\alpha_3^*(t)$ represents a way of spending the error probability uniformly over time, and which is intermediate between the previous two functions $\alpha_1^*(t)$ and $\alpha_2^*(t)$.

In Table 1, we compare the boundaries computed from $\alpha_1^*(t)$, $\alpha_2^*(t)$, $\alpha_3^*(t)$, and those proposed by Pocock (1977) and O'Brien & Fleming (1979). The comparison is made for a one-sided test with $\alpha = 0{\cdot}025$ and $0{\cdot}05$, $K = 5$, and $t_i = i/K$ $(i = 1, \ldots, 5)$. The stochastic process $\{B(t), 0 \leqslant t \leqslant 1\}$ is assumed to be the standard Brownian motion. Since both Pocock and O'Brien & Fleming discussed their boundaries for the $N(0, 1)$ process $\{S_i = B(t_i)/\sqrt{t_i}, i = 1, \ldots, K\}$, the boundary given in Table 1, is $\{c_i = b_i/\sqrt{t_i}, i = 1, \ldots, K\}$. As noted earlier, the correspondence between results for $\alpha_1^*(t)$ and the O'Brien & Fleming boundary is close as also is the correspondence between $\alpha_2^*(t)$ and Pocock's boundary. We have also compared boundaries for values of K up to 12, with a similar conclusion.

In our experience, $\alpha_1^*(t)$ tends to introduce a boundary that can be very conservative at the beginning, especially for large K. A quick and easy remedy to this conservatism is to impose an extra constraint that c_i be bounded by some constant, say 3·5. With this constraint, for example, the boundary (4·23, 2·89, 2·30, 1·96, 1·74) for $\alpha_1^*(t)$ in Table 1b becomes (3·50, 2·91, 2·30, 1·96, 1·74).

4. DISCUSSION

In the previous sections, we introduced the idea of constructing a discrete sequential boundary according to an increasing function α^*, which characterizes the rate at which we wish to spend α. We did not define or consider the optimality of α^* in differing situations. However, if response is immediate, we could adapt the approach of Pocock (1982) to find α^* approximately optimal in Pocock's sense. That is, we would divide the unit interval into N equally spaced subintervals and then apply Pocock's numerical iterative minimization to evaluate α^* at the values i/N for $i = 1, \ldots, N$. The value of N would govern the quality of the approximation. It would, of course, be of interest to define optimal α^* and consider its determination in a variety of other contexts. We hope to pursue this issue.

As noted earlier, our procedure is easily altered to consider two-sided symmetric tests. But for a treatment–placebo comparative trial, in order to protect patients from toxicity, we should introduce also a lower boundary. Since we would not be interested in proving a new treatment to be harmful, we should be interested in asymmetric boundaries. Recently, Lan, Simon & Halperin (1982) used a stochastic curtailing argument to propose a lower boundary for this situation. They proposed that when the conditional power of getting a positive conclusion drops below a certain level, consideration should be given to early termination of the trial. This type of lower boundary appears appropriate in the treatment–placebo case but the level of conditional power should be allowed to vary with time.

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