Adaptive Designs
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CERTAIN SEQUENTIAL ADAPTIVE DESIGN PROBLEMS

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Abstract

Here we discuss three problems, namely (i) Robbins - Monro procedure, (ii) sequential estimation of the common mean of a set of normal populations and (iii) sequential estimation of the mean of response function using Spearman-Karber estimator, the common thread among them being that they use adaptive sequential designs.

1. Introduction. In sequential analysis, especially in sequential estimation, it is natural to resort to adaptive designs. In the following we will discuss three such problems. An early adaptive sequential design was proposed by Robbins and Monro (1951). Since the problems are somewhat disjoint, in each problem, we briefly survey the literature and provide a summary as well.

2. The Robbins-Monro procedure. Given a random response $Y(x)$ at x having $EY(x) = M(x)$, we wish to estimate θ such that for specified α
(2.1)

$$M(\theta) = \alpha\,,$$

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where $M(\theta)$ is unknown. Two examples for which the Robbins-Monro (1951) procedure applies follow.

EXAMPLE 1. Let $F(x)$ be the probability that a metallic specimen will fracture when subjected to x cycles in a fatigue trial. A specimen tested in this manner will produce an observation that takes values either 0 or 1. The problem of interest is to estimate the number of cycles x such that, for specified α,

$$F(x) = \alpha .$$

Here $M(x) = F(x)$, the functional form of which may be unknown.

EXAMPLE 2. For real x, let $Y(x)$ denote the response to an experiment carried out at a controlled level x with unknown distribution function $H(y|x)$ and regression function
(2.2)

$$M(x) = E\{Y(x)|x\} = \int_{-\infty}^{\infty} y dH(y|x) .$$

We need to assume only that $M(x)$ is nondecreasing in order to estimate x for a specified value of $M(x)$.

2.1. The Robbins-Monro procedure. Let $\{a_n\}$ be a decreasing sequence of positive constants with $a_n \to 0$ as $n \to \infty$. Guess an initial value x_1 and let $y_n(x_n)$ denote the response at x_n. Then choose x_{n+1} by the formula
(2.3)

$$x_{n+1} = x_n - a_n \{y_n(x_n) - \alpha\} .$$

Without loss of generality, we can set $\alpha = 0$. Then notice that

$$x_{n+1} < x_n \text{ if } y_n(x_n) > 0$$

and

$$x_{n+1} > x_n \text{ if } y_n(x_n) < 0 .$$

An appropriate choice for a_n is c/n where c is chosen in an "optimal way" that is described below. Robbins and Monro (1951) provided sufficient conditions for x_n to converge to θ in probability as $n \to \infty$. Later

researchers obtained results pertaining to the rate of convergence, convergence with probability one, convergence in mean square and asymptotic normality of the sequence x_n. (See Loginov (1966) for a review of these results).

When $a_n = c/n$, Sacks (1958) has shown that $(x_{n+1} - \theta)\sqrt{n}$ is asymptotically normal with mean 0 and variance $\sigma^2 c^2/(2c\beta - 1)$, where $\beta = M'(\theta)$ and σ^2 =var $(Y(x)|x)$. Lehmann and Hodges (1956) suggest taking $c = 1/\beta$ since it minimizes the asymptotic variance $\sigma^2 c^2/(2\beta c - 1)$ at the minimum value of σ^2/β^2. However β is unknown and we have to guess its value. Since $\beta > 0$ (because we have assumed that $M(x)$ is nondecreasing), it suffices to require that $c > 1/2\beta$ and this ensures the positivity of the asymptotic variance.

In quantal response situations, $H(y|x)$ is Bernoulli with success probability a function of a real parameter γ that is to be estimated. Let

$$E(Y(x)|x) = M_\gamma(x)\,.$$

Then $\text{var}(Y(x)|x) = M_\gamma(x)[1 - M_\gamma(x)]$. Since γ determines the model, θ, the solution of (2.1), is a function of α and γ. Assume that there is a $1-1$ correspondence between θ and γ so that there exists a function $h(x)$ such that $\gamma = h_\alpha(\theta)$. We use x_n as the Robbins-Monro estimate of θ and estimate γ by $h_\alpha(x_n)$.

2.2. Stopping rules. Farrell (1962) and Sielken (1973) considered stopping times of bounded length confidence intervals for θ. However, their two approaches are different. We present only Sielken's (1973) rule which is adaptive. For given D and α, we want

$$1 - \alpha = P(|x_{n+1} - \theta| \le D) \approx 2\Phi\left(\frac{D\sqrt{(2c\beta - 1)n}}{c\sigma}\right) - 1$$

because of the asymptotic normality of x_{n+1} when suitably standardized. If z denotes the $(1 - \alpha/2)100$th percentile of a standard normal distribution, the optimal choice for n is given by

(2.4)

$$n^* = z^2 c^2 \sigma^2/(2c\beta - 1)D^2\,.$$

However, since β and σ are unknown, Sielken (1973) resorts to the adaptive rule:

(2.5)

$$N_{D,\alpha} = \inf\{n : n \ge z^2 c^2 \hat{\sigma}_n^2/(2c\hat{\beta}_n - 1)D^2\}$$

where $\hat{\sigma}_n^2$ and $\hat{\beta}_n$ are Burkholder's (1956) estimators of σ^2 and β, respectively. Burkholder (1956) proposed estimators of β and σ^2 and gave sufficient conditions for these estimators to converge to β and σ^2, respectively, with probability one. Burkholder's estimates of β require at the nth step in Robbins - Monro procedure that an observation is taken not only on $Y(x_n)$, but also on $Y(x_n + d_n)$, where $\{d_n\}$ is a sequence of positive constants such that $n^{\lambda} d_n \to d$ as $n \to \infty$, $d > 0$ and $0 < \lambda < 1/2$.

Let $\{y_n'\}$ be a sequence of random variables such that the conditional distribution of y_n'' for specified x_n is equal to the distribution of $Y(x_n + c_n)$ and is independent of $x_1, x_n, \ldots, x_{n-1}, y_1, y_2, \ldots, y_n, y_1'', y_2'', \ldots, y_{n-1}''$. Then, under certain regularity assumptions (see Sielken (1973, assumptions C1 -C12), Burkholder's (1956) results imply

(2.6)

$$\hat{\beta}_n = \max\left[1/2c, \sum_{j=1}^{n}(y_1'' - y_j)/nd_j\right] \to \beta \quad w.p.1$$

and

(2.7)

$$\hat{\sigma}_n^2 = \left(\frac{1}{2}\right)\left\{\left[\sum_{j=1}^{n}(y_j'' - \alpha)^2/n\right] + \left[\sum_{j=1}^{n}(y_j - \alpha)^2/n\right]\right\} \to \sigma^2 \quad w.p.1$$

as $n \to \infty$. Furthermore, under these regularity conditions, Sielken (1973, Theorems 1 and 2) established the first order asymptotic properties of rule (2.5). These are

$$\text{(i)} \lim_{D \to 0} N_{d,\alpha} / \left[z^2 c^2 \sigma^2 / 2(c\beta - 1)D^2\right] = 1 \quad a.s.$$

and

$$\text{(ii)} \lim_{D \to 0} P\left[|X_{N_{D,\alpha}+1} - \theta| \leq D\right] = 1 - \alpha\,.$$

Note that, (i) implies that $N_{D,\alpha}$ is asymptotically optimal.

REMARK 2.1. It should be noted that although two observations are taken at each step in order to obtain useful information on β, only one of these two observations is used to generate the next estimate of θ. To remedy this shortcoming, the following modified Robbins - Monroe procedure has been proposed in the literature: let x_1 be any constant, and let

$$x_{n+1} = x_n - a_n\left[\frac{1}{2}(y_n' + y_n'') - \alpha\right]$$

where $y'_n = Y_n(x_n - d_n)$ and $y''_n = Y_n(x_n + d_n)$ which are independent of $x_1, \ldots, x_{n-1}, y'_1, \ldots, y'_{n-1}, y''_1, y''_2, \ldots, y''_{n-1}$.

Recognizing that the asymptotic variance of $(x_{n+1} - \theta)\sqrt{n}$ is minimized when $a_n = c/n$ and $c = 1/\beta$, Ventner (1967) proposed that the sequence $\{x_n\}$ be generated according to the recurrence formula
(2.8)

$$x_{n+1} = x_n - \left(1/n\hat{\beta}_n\right)\left[\frac{1}{2}(y''_n + y'_n) - \alpha\right].$$

Then the stopping time is given by
(2.9)

$$\tilde{N}_{D,\alpha} = \inf\left\{n : n > \left(z\hat{\sigma}_n/d\hat{\beta}_n\right)^2\right\}.$$

Sielken (1973) pointed out that properties that are analogous to (i) and (ii) also hold for the sequential rule (2.9).

2.3. A risk efficient rule. Let the loss incurred in estimating θ by x_n be given by
(2.10)

$$l(\theta, x_n) = (x_n - \theta)^2 + An,$$

where A denotes the cost per one iteration. Then the risk for given n is given by

$$E(l(\theta, x_n)|n] \doteq \frac{\sigma^2 c^2}{n(2c\beta - 1)} + An$$

and

$$\min_c \{\text{Risk } + \text{ cost}\} = R = \frac{\sigma^2}{n\beta^2} + An.$$

Then $\partial R/\partial n = 0$ implies that the optimal n is given by $n_A = \sigma/\beta\sqrt{A}$. Since σ and β are unknown, we use the adaptive rule
(2.11)

$$N_A = \inf\{n : n \geq \hat{\sigma}_n/\hat{\beta}_n\sqrt{A}\},$$

where $\hat{\sigma}_n^2$ and $\hat{\beta}_n$ are Burkholder's (1956) estimators of β and σ^2 and the sequence $\{x_n\}$ is generated according to (2.8). It is desirable to investigate the properties of N_A.

3. Sequential estimation of a set of normal variables.

3.1. Introduction and summary. Let $\pi_1, \pi_2, \ldots, \pi_k$ be normal populations with common mean, that is, let π_i be Normal (μ, θ_i), $i =$

$1, \ldots, k$, where μ and θ_i are unknown. The problem is to construct a confidence interval of length at most $2d$ for μ. In the case of $k = 2$, Mallik (1971) considered risk-efficient estimation of the common mean when one of the variances is known. His solution is a combination of the solutions of two related problems, namely, the sequential estimation of the mean of a normal population when the variance is unknown (considered by Robbins (1959) and Starr (1966)) and the one-armed bandit problem (considered by Robbins (1952) and Chernoff (1968)). Chernoff (1971), using the solution of the two-armed bandit problem, solved the risk-efficient estimation problem when both the variances are unknown. For any k, Alam and Saxena (1984) gave two-stage procedures for obtaining bounded length confidence intervals for μ. These two-stage procedures take an equal number of observations from each population in the first stage. On the basis of these observations, which population to sample in the second stage and the (random) size of that sample is determined.

3.2. The quasi-sequential fixed-width procedure. If $x_{ij}, j = 1, \ldots, n_i$, is a random sample of size n_i from π_i, let $\bar{x}_i(n_i) \equiv n_i^{-1} \sum_{j=1}^{n_i} x_{ij}$ and $S_i(n_i) \equiv n_i^{-1} \sum_{j=1}^{n_i} (x_{ij} - \bar{x}_i(n_i))^2$, $i = 1, \ldots, k$. If the variances were known, one would sample from the population with the smallest variance only. However, when the variances are unknown, one can apply a selection procedure (for instance, the one by Bechhofer and Sobel (1954)) for first selecting the population with the smallest variance, where an initial sample of predetermined size r is drawn from each population, and then select the population with the smallest sample variance. Let $\theta_\lambda = \min(\theta_1, \ldots, \theta_k), \Delta^* > 1$ and l be the index of the selected population. Condition (3.1) determines the value of r for specified Δ^* and P^*:
(3.1)

$$P(l = \lambda) \geq P^* \text{ whenever } \theta_i/\theta_\lambda \geq \Delta^* \text{ for all } i \neq \lambda, i = 1, \ldots, k .$$

Parnes and Srinivasan (1986) point out that the same value of r assures the stronger result:
(3.2)

$$P(\theta_l/\theta_\lambda < \Delta^*) \geq P^* .$$

Note that (3.1) holds true only if there is a unique smallest population variance, whereas (3.2) implies no restriction on the configuration

of population variances. It assures that the selected population has variance close to the minimum of the population variances.

Let $2d$ be the specified width of the confidence interval with confidence $1-\beta$.The quasi-sequential procedure of Govindarajulu and Geertsema (1989) follows:

1. First take r observations from each population and choose population π_l where l indicates the population with the smallest sample variance. $S_l(r) = \min(S_1(r), \ldots, S_k(r))$.

2. Let $N = \inf\{n \geq r \text{ and } n \geq z^2 S_l(n)/d^2\}$, where

$$\hat{\mu}(N) = \sum_{i=1}^{k} n_i \bar{X}_i(n_i) S_i(n_i)^{-1} / \left\{ \sum_{i=1}^{k} n_i S_i(n_i)^{-1} \right\};$$

$$n_i = \begin{cases} r \text{ for } i \neq l \\ N \text{ for } i = l, \end{cases}$$

and z is such that $\Phi(z) = 1 - \beta/2$. Let the confidence interval for μ be $\hat{\mu}(N) \pm d$.

Govindarajulu and Geertsema (1989) derive several first order asymptotic properties of this procedure. They also present a more general procedure based on the maximum likelihood estimate of μ (which can be solved only iteratively) and its first order asymptotic properties. They also show that the sequential procedure is infinitely more efficient than the two-stage procedures of Alam and Saxena (1986). Govindarajulu and Geertsema (1991) carry out some Monte Carlo studies which indicate agreement between the asymptotic results and the actual behavior of the procedure.

We note that the normality assumption is not necessary for the proof of the asymptotic properties except for the form and existence of fourth moments. An analogous procedure can be obtained for the risk-efficient estimation problem. Is it possible to obtain completely sequential procedures for the problem of risk-efficient or fixed-width estimation of μ?

4. Sequential estimation of the mean of logistic response function using the Spearman-Karber estimator.

4.1. Introduction and summary. Spearman (1908), Karber (1931), Finney (1952), Berkson (1955), Brown (1961), Miller (1973), and Church

and Kobb (1973) have studied the theoretical merits of the Spearman-Karber estimator. Epstein and Churchman (1944), Cornfield and Mantel (1950) and Chmiel (1976) have investigated the theoretical merits of a Spearman-type variance estimator. For a discussion of the preceding references the reader is referred to Govindarajulu (1988).

Nanthakumar and Govindarajulu (1994a, 1994b) derive the fixed-width and risk-efficient sequential rules for estimating the mean of the logistic response function based on quantal responses observed at equally spaced dose levels. These rules are reviewed in Sections 4.3 and 4.4. The Spearman-Karber (S-K) and Spearman-type variance (S-T-V) estimators are employed for the mean and variance, respectively, in the sequential estimation. Let d denote the difference between two successive dose levels. Some asymptotic properties of the sequential estimates are studied as d becomes small.

4.2. The Spearman-Karber estimator. Let x_{-k}, x_{-k+1}, ..., x_0, x_1, ..., x_{k-1}, x_k denote the $2k+1$ dose levels with $x_i = x_0 + id$, $i = -k, \ldots, 0, \ldots, k$, where x_0 is chosen at random (uniformly) between 0 and d. We subject n experimental units at each dose level and record the responses as 1 or 0 according as the experimental unit responds to the dose or not.

In the following we provide a motivation for the form of the Spearman-Karber estimator. Let $P_j = P(x_j)$ denote the probability of a positive response at dose $x_j = x_0 + jd$. By definition, μ, the mean of the tolerance distribution is given by

$$\mu = \int_{-\infty}^{\infty} x dP = \sum_{i=\infty}^{\infty} \int_{x_i}^{x_{i+1}} x dP .$$

If $P_j = 1$ for $j \geq k$ and $P - j = 0$ for $j \geq k$, then

$$\begin{aligned}
\mu &= \sum_{i=-k}^{k} \int_{x_i}^{x_{i+1}} x dP \\
&\doteq \sum_{i=-k}^{k} \left(x_i + \frac{d}{2} \right) (P_{i+1} - P_i) \qquad \text{by the mean-value theorem} \\
&= \sum_{i=-k}^{k} \left(x_0 + \frac{d}{2} + id \right) (P_{i+1} - P_i) \\
&= \left(x_0 + \frac{d}{2} \right) (P_{i+1} - P_i) + d \sum_{i=-k}^{k} i(P_{i+1} - P_i)
\end{aligned}$$

$$= \left(x_0 + \frac{d}{2}\right)(P_k - P_{-k}) + d\sum_{i=-k}^{k} i(P_{i+1} - P_i)$$

$$= \left(x_0 + \frac{d}{2}\right) + d\sum_{i=-k}^{0} i(P_{i+1} - P_i) + d\sum_{i=1}^{k} i(P_{i+1} - P_i)\,.$$

Now

$$\sum_{i=-k}^{0} i(P_{i+1} - P_i) = \sum_{i=-k}^{-1}(i+1)P_{i+1} - \sum_{i=-k}^{-1} P_{i+1} - \sum_{i=-k}^{0} iP_i$$

$$= -\sum_{i=-k}^{0} P_i\,.$$

Also

$$\sum_{i=1}^{k} i(P_{i+1} - P_i) = \sum_{i=1}^{k}\sum_{j=1}^{i}(P_{i+1} - P_i) = \sum_{j=1}^{k}\sum_{i=j}^{k}(P_{i+1} - P_i)$$

$$= \sum_{j=1}^{k}(P_k - P_j) = \sum_{j=1}^{k}(1 - P_j)\,.$$

Thus

(4.1)

$$\mu = \left(x_0 + \frac{d}{2}\right) - \sum_{i=-k}^{0} P_i + \sum_{j=1}^{k}(1 - P_j)\,.$$

Then a natural estimate of μ is the Spearman-Karber estimate of μ, given by

(4.2)

$$\hat{\mu} = \left(x_0 + \frac{d}{2}\right) - \sum_{i=-k}^{0} p_i + \sum_{j=1}^{k}(1 - p_j)$$

where p_j is a sample estimate of P_j, namely, the sample proportion of positive responses at the dose level x_j.

For the special case when $P(x) = \{1 + e^{-(x-\theta)/\beta}\}^{-1}$ and $p_i = r_i/n$, where r_i denotes the number of positive responses at x_i, the Spearman-Karber estimator of θ is given by

(4.3)

$$\hat{\theta}_k = \left(x_0 + \frac{d}{2}\right) - \frac{d}{n}\sum_{i=-k}^{0} r_i + \frac{d}{n}\sum_{i=1}^{k}(n - r_i)\,.$$

In a similar vein, the scale parameter is estimated by

$$\hat{\beta}_k^2 = \frac{3}{\pi^2}\left\{\left(x_0 + \frac{d}{2}\right)^2 - \frac{2d}{n}\sum_{i=-k}^{0} x_i r_i + \frac{2d}{n}\sum_{i=1}^{k} x_i(n - r_i) - \hat{\theta}_k^2\right\}.$$

4.3. Fixed-width sequential rule. Let $2m^* + 1$ denote the number of initial dose levels used and let $2D$ denote the width of the $100(1-\alpha)\%$ confidence interval for θ. We wish to choose the stopping stage k such that

$$\left(P|\hat{\theta}_k - \theta| \leq D\right) \geq 1 - \alpha.$$

If k is sufficiently large, $\hat{\theta}_k$ will be asymptotically normal so this stopping rule becomes
(4.5)

$$\Phi\left(\frac{D-B}{\sigma_{\hat{\theta}_k}}\right) + \Phi\left(\frac{D+B}{\sigma_{\hat{\theta}_k}}\right) \geq 2 - \alpha,$$

where $B = E(\hat{\theta}_k) - \theta$ and $\sigma_{\hat{\theta}_k}^2$ is the variance of $\hat{\theta}_k$. Also, for any fixed k, one can show that
(4.6)

$$B = \beta \int_{(kd+\theta)/\beta}^{(kd+d-\theta)/\beta} \{1 - G(u)\}du + o(d)$$

and
(4.7)

$$\sigma_{\hat{\theta}_k}^2 = \frac{d\beta}{n}\left\{G\left(\frac{kd-\theta}{\beta}\right) + G\left(\frac{kd+\theta}{\beta}\right) - 1\right\} + o(d^2),$$

where $G(u) = (1 + e^{-u})^{-1}$. Thus, it is reasonable to assume that B is positive when $\theta < 0$ and d is small. Thus
(4.8)

$$\Phi\left(\frac{D-B}{\sigma_{\hat{\theta}_k}}\right) \geq 1 - \alpha/2$$

implies (4.5). Using (4.6) and (4.7) in (4.8), we find that $\tilde{k}$ satisfies (4.8), where

(4.9)

$$\tilde{k}d \geq -\theta + \beta \log_e \left\{ \frac{-2\theta}{D - \left(\frac{dz^2\beta}{n}\right)^{1/2}} \right\},$$
$$z = \Phi^{-1}\left(1 - \frac{\alpha}{2}\right).$$

Similarly, when $B < 0$ (i.e. $\theta > 0$), we get an expression for $\tilde{k}d$ which is similar to that in (4.9) where θ is replaced by $-\theta$. Hence, the number of stages $\tilde{k}$ should satisfy
(4.10)

$$\tilde{k}d \geq |\theta| + \beta \log_e \left\{ \frac{2|\theta|}{D - (\frac{dz^2\beta}{n})^{1/2}} \right\}.$$

In order to use (4.10) as a stopping rule one should know the values of θ and β, but they are unknown. Thus we are led to the following adaptive stopping rule:

If experimentation has proceeded to $k+1$ stages, replace θ and β with $\hat{\theta}_k$ and $\hat{\beta}_k$, respectively, and stop at $(k+1)^{th}$ stage if (4.10) holds. That is, stop when the number of stages is K, where
(4.11)

$$K = \inf \left\{ k : k \geq m^* \text{ and } kd \geq |\hat{\theta}_k| + \hat{\beta}_k \log_e \left\{ \frac{2|\hat{\theta}_k|}{D - (\frac{dz^2\hat{\beta}_k}{n})^{1/2}} \right\} \right\},$$

where $\hat{\theta}_k$ and $\hat{\beta}_k$ are given by (4.3) and (4.4), respectively.

One can easily show that such an experiment terminates in a finite number of stages when the dose span d is bounded away from zero.

Nanthakumar and Govindarajulu (1994a) derive first order asymptotic properties of the above sequential procedure. They also show that
(4.12)

$$\frac{P\left(|\hat{\theta}_{K(d)} - \theta| \leq D\right)}{P\left(|\hat{\theta}_{\tilde{k}} - \theta| \leq D\right)} \to 1$$

as $d \to 0$, when $d = \eta D^2$ for some η such that $0 < \eta < n^2/Mz^2$ where $\beta \leq M$ and $\tilde{k}$ is given by (4.10). That is, we know, priori, that β is bounded above by a known constant M.

A simulation study has been carried out and it is surmised that the true level of confidence falls short of the nominal level at most by three percent.

4.4. Risk-efficient estimation. Here we consider the same problem with a different criterion, namely, we wish to minimize the risk plus the cost of experimentation. Towards this, we need further notation. Let c denote the cost per experimental unit where c might depend on the dose span d. Let

(4.14)

$$\begin{aligned} R_k &= \text{Risk} + \text{cost} \\ &= \text{var}\hat{\theta}_k + (\text{bias } \hat{\theta}_k)^2 + 2(k+1)cn\,, \end{aligned}$$

where $\text{var}(\hat{\theta}_k)$ and bias $(\hat{\theta}_k)$ are given by (4.7) and (4.6), respectively. Also one can easily show that (4.6) is equal to

(4.14)

$$B = \frac{e^{-(kd+\theta)/\beta} - e^{-((k+1)d-\theta)/\beta}}{1 + e^{-((k+1)d-\theta)/\beta}}.$$

The value of k for which R_k is minimum is given by

(4.15)

$$k^* = (\beta/d)\log_e J(\theta, \beta, c, d, n),$$

where

(4.16)

$$J(\theta,\beta,c,d,n) = \frac{4\beta(\Delta + \frac{4d}{\Delta})^{-1}\{\psi\gamma + (\frac{1}{\psi}) - \tilde{T}(\psi\gamma + \frac{1}{\psi})^{-1}\}}{1 + \left\{1 + \frac{16c\beta}{\Delta}(\Delta + \frac{4c}{\Delta})^{-2}[1 - \tilde{T}(\psi\gamma + \frac{1}{\psi})^{-2}]\right\}^{1/2}},$$

$$\psi = e^{\theta/\beta}, \gamma = e^{-d/\beta}, \Delta = d/n$$

$$\tilde{T} = \left(4 + \frac{2\Delta}{\beta} + \frac{4c/\beta}{\Delta}\right)\gamma + \frac{c/\beta}{\Delta}(\psi^2\gamma^2 + \psi^{-2}).$$

Since θ and β are unknown, we propose the following stopping rule. Stop taking observations at the $(K+1)^{th}$ stage, where

(4.17)

$$K = \inf\left\{k : k \geq m^*, \frac{kd}{\beta} \geq \log_e J(\hat{\theta}_k, \hat{\beta}_k, c, d, n)\right\}.$$

One can show that this sequential procedure terminates finitely with probability one when the dose span d is bounded away from zero.

If $c = 0(\Delta^{1+\delta})$, where $\delta > 1$, then (4.15) and (4.17) can be approximated by
(4.18)

$$k^* \doteq \frac{\beta}{d}\log_e\left\{2\beta^{1/2}\left(\frac{d}{n}\right)^{-\delta/2}\left(e^{|\theta|/\beta} - e^{-|\theta|/\beta}\right)\right\}$$

and
(4.19)

$$K = \inf\left\{k : k > \frac{\hat{\beta}_k}{d}\log_e\left[2\hat{\beta}_k^{1/2}\left(\frac{d}{n}\right)^{-\delta/2}\left(e^{|\hat{\theta}_k|/\hat{\beta}_k} - e^{-|\hat{\theta}_k|/\hat{\beta}_k}\right)\right]\right\}.$$

Nanthakumar and Govindarajulu (1994b) obtain first order asymptotic properties of the risk-efficient sequential procedure. They also carry out a simulation study for certain parameter configurations which indicate that EK/k^* tends to one as d goes to zero.

Consider the following alternative design. Fix the number of dose levels ahead of time and take an observation at all dose levels at every stage. Such a design would be inefficient when compared to the one considered by Nanthakumar and Govindarajulu (1994a, 1994b). See Miller (1973) for a comparison of these designs in the nonsequential case.

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