Sequential Experimental Design Procedures

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A new sequential design decision rule is proposed for a statistical multiple decision problem with finite state space and with a finite set of available experiments. Conditions are established under which the proposed rule is asymptotically optimal as c, the cost of a single experiment, tends to zero. The rule is compared to those of Chernoff [6] and Box and Hill [5]. In numerical simulations of a type of drug screening experiment, the proposed procedure yielded estimated risks no larger than, often significantly smaller than, those of procedures [6] and [5].

1. INTRODUCTION

1.1 Sequential Experimental Design

The sequential design decision problem is an extension of the usual problem of sequential analysis. In the sequential design problem there is available a set of experiments which may be conducted. After each observation, if the decision is made to continue sampling, a decision must also be made as to which experiment to conduct in the next stage. Since some experiments may be more "informative" than others, there is a potential saving in using decision rules which choose experiments rather than using decision rules which typically take one experiment of each type.

An example of such a problem is the following. Suppose a clinical examiner wishes to determine which of several drugs is the most effective in curing a particular ailment, the effectiveness of a drug being measured by its probability of cure. The examiner, employing a sequential procedure, at each stage administers a drug to a patient and observes whether or not the patient is cured. Based on the outcome of this and the preceding trials, the experimenter decides whether to continue the procedure or stop. If he decides to continue, he must then decide which drug to administer to the next patient (which experiment to perform). If he decides to stop, he must decide which drug is to be declared the most effective.

1.2 The Statistical Multiple Decision Problem

Let θ be an element in the finite set $\Theta = \{\theta_0, \theta_1, \cdots, \theta_s\}$ where θ is some parameter (state of nature) governing the outcome of a process. The experimenter, wishing to make an inference about θ is to choose an action from the set $A = \{a_0, \cdots, a_s\}$. If $\theta_j \in \Theta$ is the state of nature and the experimenter chooses action $a_i \in A$, he incurs a loss

$$\ell(\theta_j, a_i)\begin{cases} = 0 & \text{if} \quad i = j \\ > 0 & \text{if} \quad i \neq j. \end{cases}$$

There is available a finite set of experiments $E = \{e_1, e_2, \cdots, e_k\}$ any one of which may be performed at a cost of c units. The experiment selected at the nth stage of sampling will be denoted by e^n, $e^n \in E$. Upon conducting e^n the experimenter observes a random variable Y_n. It is assumed that Y_n has a density $f(y_n;\, \theta, e^n)$ with respect to a measure μ_{e^n} for each $\theta \in \Theta$. The choice of the experiment at stage n may depend on the past, i.e., $e^n = e^n(Y_1, Y_2, \cdots, Y_{n-1})$, however once it is selected its outcome is assumed independent of those of the preceding experiments.

Given these elements of the statistical decision problem, the experimenter is to sample sequentially, choosing e^n and observing Y_n, decide when to stop and what action to take when he stops. The decision rule of the statistical decision problem thus consists of three rules: the stopping rule, the terminal decision rule, and the experimentation rule.

1.3 Optimality of the Decision Rule

For the multiple decision problem defined in Section 1.2, the risk, as a function of the decision rule δ and state of nature θ, is given by

$$R(\theta, \delta) = \textstyle\sum_{i=0}^{s} l(\theta, a_i)\alpha_i(\theta) + cE_\theta(N) \qquad (1.1)$$

where $\alpha_i(\theta)$ is the probability under θ of taking action a_i, and N is the terminal sample size.

Though it is difficult to determine the expected terminal sample size and probability of error associated with a particular decision rule, asymptotic values of these quantities may be attainable, as shown by Chernoff [6] Albert [1], Bessler [2], and Kiefer and Sacks [8], among others.

Definition 1.1: A sequential design decision rule δ is said to be *asymptotically optimal* as $c \to 0$ if

$$\limsup_{c\to 0} \frac{R(\theta, \delta)}{R(\theta, \delta')} \leq 1 \quad \text{for all } \theta \in \Theta$$

for each rule δ' for which

$$\liminf_{c\to 0} \frac{R(\theta, \delta)}{R(\theta, \delta')} > 0 \quad \text{for all } \theta \in \Theta.$$

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Theory and Methods Section

The asymptotic approach results in considerable simplification of the sequential design decision problem since, as will be noted later, it is sufficient to concentrate solely on minimizing expected sampling costs and ignore losses from incorrect decisions. However, as was shown in [10], a procedure which is asymptotically optimal (e.g., that of Chernoff [6]) may yield higher risks than another which is not asymptotically optimal (e.g., that of Box and Hill [5]) in cases where c is not extremely small. From a practical point of view the criterion of asymptotic optimality is not enough to warrant use of a given rule, and practical situations in which asymptotic optimality is relevant may be rare. In this article a procedure which has exhibited excellent non-asymptotic properties is presented and compared to the procedures of Chernoff (as extended by Bessler) and Box and Hill.

2. THE PROCEDURES OF CHERNOFF AND BOX AND HILL

2.1 Chernoff's Procedure A

The Chernoff rule [6] as extended by Bessler [2], to be denoted by δ^A, is constructed as follows. Let $\hat{\theta}_n$ be the maximum likelihood estimate of θ based on the first n observations $Y_1, Y_2, \cdots, Y_n$, and let the log likelihood ratio of state θ_j to θ_l be denoted by

$$S_n(\theta_j, \theta_l) = \sum_{m=1}^{n} \log \frac{f(Y_m; \theta_j, e^m)}{f(Y_m; \theta_l, e^m)}.$$

Then δ^A is defined by the

Stopping rule: Let the terminal sample size N be the first integer n for which

$$S_n(\hat{\theta}_n, \theta_j) > -\log c$$

for all $\theta_j \neq \hat{\theta}_n$, where c is the cost of a single observation.

Terminal decision rule: If $\hat{\theta}_N = \theta_i$, accept the hypothesis H_i: $\theta = \theta_i$.

Experimentation rule: If $n < N$ choose e^{n+1} according to the maximin strategy of the experimenter in the matrix game $\Gamma[\Theta - \hat{\theta}_n, E, I(\hat{\theta}_n, \theta, e)] \equiv \Gamma(\hat{\theta}_n)$ whose $s \times k$ payoff matrix consists of Kullback-Leibler information numbers

$$I(\hat{\theta}_n, \theta_j, e) = \int \log \frac{f(y; \hat{\theta}_n, e)}{f(y; \theta_j, e)} f(y; \hat{\theta}_n, e) d\mu_e(y), \qquad \theta_j \neq \hat{\theta}_n.$$

Use of information numbers and a maximin strategy can be justified heuristically as in Chernoff [6, 7]. The maximin strategy will be denoted by

$$\lambda(\hat{\theta}_n) = [\lambda_1(\hat{\theta}_n), \lambda_2(\hat{\theta}_n), \cdots, \lambda_k(\hat{\theta}_n)].$$

The element $\lambda_i(\hat{\theta}_n)$ represents the probability of choosing experiment e_i. Hence, the actual experiment to be performed is chosen by some random mechanism corresponding to the probability measure $\lambda(\hat{\theta}_n)$ on E. The experiment space E is thus expanded to include all such linear combinations of the k individual experiments.

The Minimax Theorem assures that a value of $\Gamma(\hat{\theta}_n)$ exists. This value will be denoted $I(\hat{\theta}_n)$. By definition,

$$I(\hat{\theta}_n) = \min_{\theta \neq \hat{\theta}_n} I[\hat{\theta}_n, \theta, \lambda(\hat{\theta}_n)]$$

or as noted by Albert [1],

$$I(\hat{\theta}_n) = \min_{\theta \neq \hat{\theta}_n} \sum_{i=1}^{k} \lambda_i(\hat{\theta}_n) I(\hat{\theta}_n, \theta, e_i).$$

There are no known analytic methods for determining optimal (maximin and minimax) strategies of general matrix games. The actual calculation of such strategies may be carried out employing the simplex algorithm of linear programming. With the aid of electronic computers the calculations can often be easily made. However, if the dimensions of the payoff matrix are large, the computations may become prohibitive.

Bessler examined the asymptotic behavior of $R(\theta, \delta^A)$ as $c \to 0$. Under the mild conditions, which will be assumed to hold for the remainder of this article,

(a) there exists an $M > 0$ such that for every θ_j, $\theta_l \in \Theta$ and every $e \in E$

$$E_{\theta_l}\left(\log \frac{f(Y; \theta_l, e)}{f(Y; \theta_j, e)}\right)^2 < M \tag{2.1}$$

(b) for every θ_j, $\theta_l \in \Theta$ and every $e \in E$,

$$I(\theta_j, \theta_l, e) > 0,$$

the following were obtained:

Theorem 2.1: Using the stopping and terminal decision rules of δ^A and any experimentation procedure such that $e^n = e^n(Y_1, \cdots, Y_{n-1})$,

$$\alpha_i(\theta_j) = 0(c) \quad \text{as} \quad c \to 0,\ i,\ j = 0, 1, \cdots, s,\ i \neq j.$$

Theorem 2.2: For δ^A

$$E_{\theta_j}(N) \leqq -[1 + o(1)] \log c/I(\theta_j) \qquad \text{as } c \to 0,\ j = 0, 1, \cdots, s.$$

Theorems 2.1 and 2.2 imply that

$$R(\theta_j, \delta^A) \leqq -[1 + o(1)]c \log c/I(\theta_j) \qquad \text{as } c \to 0,\ j = 0, 1, \cdots, s.$$

The following theorem in conjunction with the two preceding theorems establishes that δ^A is asymptotically optimal.

Theorem 2.3: For any sequential design decision rule δ for which

$$R(\theta_j, \delta) = 0(-c \log c) \quad \text{as} \quad c \to 0,\ j = 0, 1, \cdots, s,$$

we have

$$R(\theta_j, \delta) \geqq -[1 + o(1)]c \log c/I(\theta_j) \qquad \text{as } c \to 0,\ j = 0, 1, \cdots, s.$$

We now note a sufficient condition for a sequential design decision rule δ to be asymptotically optimal. The proof follows from the proof of Theorem 2.2 given by Bessler [2].

Theorem 2.4: For any sequential design decision rule δ using the stopping and terminal decision rules of δ^A, if for $\epsilon > 0$, there exists a K and ρ, $K > 0$, $0 < \rho < 1$, such that

$$P_{\theta_j}[|n_i/n - \lambda_i(\theta_j)| > \epsilon] < K\rho^n$$

$j = 0, 1, \cdots, s$, $i = 1, 2, \cdots, k$, where n_i is the number of times δ chooses experiment e_i in the first n trials, then

$$E_{\theta_j}(N) \leq -[1 + o(1)] \log c/I(\theta_j) \quad \text{as} \quad c \to 0.$$

2.2 The Box-Hill Procedure

Box and Hill [5] examined the problem of discriminating among mechanistic models. From considerations involving the transfer of information in a communications systems network, Box and Hill proposed the following

Experimentation rule: Choose e^{n+1} to be the experiment $e \in E$ which maximizes

$$\sum_{l=0}^{s} \sum_{j>l}^{s} p_{nj}p_{nl}[I(\theta_l, \theta_j, e) + I(\theta_j, \theta_l, e)], \quad (2.2)$$

where p_{nj} is the posterior probability of θ_j given Y_1, Y_2, $\cdots$, Y_n. (Box and Hill utilized noninformative (uniform) prior distributions over Θ.)

Though Box and Hill do not explicitly state stopping or terminal decision rules, the decision rule consisting of the experimentation rule of (2.2) and the stopping and terminal decision rules of δ^A will be called the Box-Hill procedure and will be denoted by δ^{BH}.

3. PROCEDURE B

3.1 Defining the Rule

Decision rule δ^B was created as a rule intended to exhibit the desirable sampling characteristics of the Box-Hill rule δ^{BH}, yet behave as the asymptotically optimal δ^A for large sample sizes. In Section 4 numerical studies are presented which show that δ^B can outperform both δ^A and δ^{BH} in medium sample size situations. In this section its asymptotic behavior will be studied.

The stopping and terminal decision rules of δ^B are the same as those of δ^A. The following specifies the

Experimentation rule: Choose e^{n+1} to be that experiment $e \in E$ which maximizes

$$\sum_{j=0}^{s} p_{nj}I(\hat{\theta}_n, \theta_j, e) \quad (3.1)$$

where p_{nj} is the posterior probability of θ_j given Y_1, Y_2, $\cdots$, Y_n.

Like rule δ^A, rule δ^B attempts to maximize information between the m.l.e. $\hat{\theta}_n$ and the remaining states of nature. Whereas δ^A employs a randomized experimentation procedure maximizing a minimum of such information numbers, δ^B employs a nonrandomized experimentation procedure maximizing a linear combination of information numbers.

In [7], Chernoff proposed a new procedure M. Procedure M possesses the stopping and terminal decision rules of δ^A and the following.

Experimentation rule: Choose e^{n+1} to be that experiment $e \in E$ which maximizes

$$\sum_{j=0}^{s} p_{nj}[\sum_{l \neq j} p_{nl}I(\theta_j, \theta_l, e)/\sum_{l \neq j} p_{nl}].$$

Chernoff [7] conjectured that procedure M would ordinarily lead to asymptotically optimal results (see the Appendix for a counterexample). It was this comment which in large part stimulated our research of the asymptotic characteristics of δ^B, since, given p_{nj}, $j = 0, 1, \cdots$, s, δ^B and δ^M will choose the same experiment if $p_n(\hat{\theta}_n)$, the posterior probability of $\hat{\theta}_n$, is sufficiently close to one.

Further, if $I(\theta_j, \theta_l, e) = I(\theta_l, \theta_j, e)$ for all j, $l = 0$, $1, \cdots, s$ and for each $e \in E$, then δ^B, δ^M and δ^{BH} will all choose the same experiment for $p_n(\hat{\theta}_n)$ sufficiently close to one.

3.2 Asymptotic Behavior of δ^B

The study of the behavior of δ^B necessarily involves considerations of matrix games $\Gamma[\Theta - \hat{\theta}_n, E, I(\hat{\theta}_n, \theta, e)]$. Bessler [2] has shown that, under conditions (2.1), $\hat{\theta}_n \to \theta_0$ exponentially fast. (Here, and in the following, without loss of generality, all probabilities and expectations will be under θ_0.) Hence, only the game $\Gamma[\Theta - \theta_0$, E, $I(\theta_0, \theta, e)] = \Gamma$ need be examined for our asymptotic studies. The asymptotic optimality of δ^B will depend on the form of the payoff matrix of Γ.

A general method for determining a maximin strategy λ for an $s \times k$ matrix game Γ is to examine all square nonsingular submatrices of the payoff matrix of Γ to see if the corresponding subgames admit "simple" (see, e.g., [3] for definition) solutions. By augmenting the simple solutions of these subgames by placing zeros in positions corresponding to rows and/or columns deleted from Γ to obtain the subgame, extreme points of the set of solutions to Γ may be obtained (see, e.g., Theorem 2.7.3 of [3]). Hence, a maximin strategy of Γ may be expressed by interchanging columns until

$$\lambda = (\lambda_1', \lambda_2', \cdots, \lambda_t', 0, \cdots, 0)$$

where λ' is a maximin strategy for some $t \times t$ subgame of Γ with payoff matrix Γ'.

Only those $s \times k$ games for which the optimal (maximin and minimax strategies) solution is unique will be considered. When the maximin strategy is not unique, δ^A does not prescribe which of an infinite number of strategies to use. When the optimal solution to Γ is unique, the optimal solution to Γ' is unique. Since the solution to Γ' is a simple solution, it follows that the maximin and minimax strategies of Γ' have all nonzero components.

Let n_i represent the number of times experiment e_i is chosen by δ^B in the first n trials. If $n_i/n \to \lambda_i$ exponentially as $n \to \infty$, $i = 1, 2, \cdots, k$, then from Theorem 2.4 this is sufficient for δ^B to be asymptotically optimal. To establish that $n_i/n \to \lambda_i$, $i = 1, 2, \cdots, k$, it must be shown that $n_i/n \to \lambda'_i$ for $i = 1, 2, \cdots, t$ and $n_i/n \to 0$ for $i = t + 1, \cdots, k$.

The following lemma provides conditions on the form of the payoff matrix under which $n_i/n \to 0$. The proof is given in the appendix.

Lemma 3.1: If column i of the payoff matrix of $\Gamma[\Theta - \theta_0, E, I(\theta_0, \theta, e)]$ is dominated by a convex linear combination of other columns of Γ, then experiment e_i is not chosen by δ^B.

Hence, if columns $t+1, t+2, \cdots, k$ are each dominated by convex linear combinations of other columns of Γ, then $n_i = 0$ for $i = t+1, \cdots, k$. When columns are so dominated, it is known from the theory of games (see, e.g., [9]) that $\lambda_i = 0$, $i = t+1, \cdots, k$. (However, the columns need not be dominated for the λ_i to equal zero. In this case n_i/n does not necessarily converge to zero, and hence δ^B and δ^A are not asymptotically equivalent. An example of such a case showing that the n_i/n are bounded away from zero is given in the appendix.)

Suppose columns $t+1, t+2, \cdots, k$ satisfy the dominance relations of the conditions of Lemma 3.1. The payoff matrix of Γ can then be "reduced" to an $s \times t$ matrix by elimination of these columns. If rows $t+1$, $t+2, \cdots, s$ dominate convex linear combinations of other rows of Γ, then it may be reduced still farther to a $t \times t$ matrix as shown in

Lemma 3.2: If the vth row of Γ dominates a convex linear combination of other rows of Γ, then

$$p_{nv}/\textstyle\sum_{j=1}^{s} p_{nj} \to 0 \text{ exponentially as } n \to \infty.$$

The proof of Lemma 3.2 is given in the appendix.

If the conditions of Lemma 3.1 hold for columns $t+1$, $t+2, \cdots, k$ so that $n_i/n \to 0$ for $i = t+1, t+2, \cdots, k$, and if the conditions of Lemma 3.2 hold for rows $t+1, t+2, \cdots, s$ so that Γ can be reduced to the $t \times t$ subgame Γ', then it still needs to be shown that $n_i/n \to \lambda_i'$, $i = 1, 2, \cdots, t$, to show that δ^B is asymptotically optimal. Only the case $t = 2$ will be considered here. As shown in [4], results follow similarly for $2 < t \leqq \min(s, k)$ subject to restrictions upon the form of the $t \times t$ payoff matrix of the subgame Γ'.

Without loss of generality the 2×2 payoff matrix of Γ' may be taken to be of the form

$$\begin{bmatrix} [1] & [2] \\ [2] & [1] \end{bmatrix} \tag{3.2}$$

where $[i]$ indicates the ranking in size of the element in its row and column, $i = 1, 2$. Tied ranks cannot occur since then the maximin or minimax strategies would not have all nonzero components, or the maximin strategy would not be unique.

For the 2×2 game Γ', by (3.1) rule δ^B directs that at stage n, e^{n+1} be chosen to be e_1 if

$$p_{n1}I(\theta_0, \theta_1, e_1) + p_{n2}I(\theta_0, \theta_2, e_1) > p_{n1}I(\theta_0, \theta_1, e_2) + p_{n2}I(\theta_0, \theta_2, e_2),$$

or if

$$\frac{p_{n1}}{p_{n2}} > \frac{I(\theta_0, \theta_2, e_2) - I(\theta_0, \theta_2, e_1)}{I(\theta_0, \theta_1, e_1) - I(\theta_0, \theta_1, e_2)}, \tag{3.3}$$

since, from (3.2), both the numerator and denominator of (3.3) are positive. Denote by a the log of the right side of (3.3). Then the experimentation rule of procedure B may be characterized as follows: if

$$S_n(\theta_1, \theta_2) \begin{cases} > a, & \text{choose } e_1 \\ = a, & \text{choose either} \\ < a, & \text{choose } e_2, \end{cases} \tag{3.4}$$

where $S_n(\theta_1, \theta_2) = \log p_{n1}/p_{n2}$.

For simplicity, we will take the prior distribution over Θ to be uniform, thus the notation $S_n(\theta_1, \theta_2)$ here is identical to that used in Section 2.1 to denote a log likelihood ratio.

If experiment e_i is run at stage n, the expected change in $\langle S_n(\theta_1, \theta_2)\rangle$ is given by $I_{12}(e_i)$ where

$$I_{12}(e_i) = E\left[\log \frac{f(Y; \theta_1, e_i)}{f(Y; \theta_2, e_i)}\right] = I(\theta_0, \theta_2, e_i) - I(\theta_0, \theta_1, e_i).$$

From (3.2),

$$I_{12}(e_1) < 0 \quad \text{and} \quad I_{12}(e_2) > 0. \tag{3.5}$$

Now if $S_{m-1}(\theta_1, \theta_2) > a$, then, from (3.4), at the mth stage of experimentation an experiment e_1 is run which results in an expected decrease in the value of the process $\langle S_n(\theta_1, \theta_2)\rangle$. If $S_{m-1}(\theta_1, \theta_2) < a$, an experiment e_2 is run which results in an expected increase in the value of the process. The process $\langle S_n(\theta_1, \theta_2)\rangle$ may thus be envisioned as drifting back and forth across the value a as n increases.

The study of the asymptotic behavior of δ^B thus coincides with the study of the long range behavior of the sequence $\langle S_n(\theta_1, \theta_2)\rangle$. The lemmas given below, whose proofs are given in the appendix, establish that the sequence $S_n(\theta_1, \theta_2)$ behaves in such a way that the proportion of time it spends above the value a converges exponentially to λ_1. The lemmas hold under assumptions (2.1) as well as the following:

for every $\theta_m, \theta_j, \theta_l \in \Theta$ and every $e \in E$, there exists an h, $h > 0$, such that

$$E_{\theta_m}\left[\exp\left\{u \log \frac{f(Y; \theta_j, e)}{f(Y; \theta_l, e)}\right\}\right] < \infty \quad \text{for} \quad |u| < h. \tag{3.6}$$

Lemma 3.3: Given $\epsilon > 0$, there exists a ρ, $0 < \rho < 1$, such that

$$P[|S_n(\theta_1, \theta_2) - \textstyle\sum_{i=1}^{2} n_i I_{12}(e_i)| > n\epsilon] < \rho^n$$

where

$$I_{12}(e_i) = E\left[\log \frac{f(Y; \theta_1, e_i)}{f(Y; \theta_2, e_i)}\right] = I(\theta_0, \theta_2, e_i) - I(\theta_0, \theta_1, e_i).$$

Lemma 3.4: Given $\epsilon > 0$, there exists a ρ, $0 < \rho < 1$, such that

$$P[|S_n(\theta_1, \theta_2)| > n\epsilon] < \rho^n.$$

Lemma 3.5: Given $\epsilon > 0$, there exists a ρ, $0 < \rho < 1$, and K, $K > 0$, such that

$$P[|n_i/n - \lambda_i(\theta_0)| > n\epsilon] < K\rho^n, \quad i = 1, 2.$$

Because of Theorem 2.4, the results of Lemmas 3.1–3.5 can be summarized as

Theorem 3.6: Let the game $\Gamma(\theta_0)$ have a unique optimal solution. If each of the columns $3, 4, \cdots, k$ and each of the rows $3, 4, \cdots, s$ satisfy the dominance relations of Lemmas 3.1 and 3.2, respectively, then for such a decision problem, rule δ^B is asymptotically optimal.

Corollary 3.7: Under the conditions of Theorem 3.6, δ^M is asymptotically optimal. If also $I(\theta_0, \theta_j, e) = I(\theta_j, \theta_0, e)$ for each $e \in E$, then δ^{BH} is asymptotically optimal.

4. A DRUG SCREENING EXPERIMENT

In this section the sampling characteristics of procedures A, B and B–H are examined. The results of Monte Carlo simulations of a type of drug screening experiment mentioned in Section 1 are presented. It will be supposed that all of the drugs but one have probability $1 - p$ of success (cure) and probability p of failure. The odd drug has probability γp of failure. The parameters γ and p are known and taken to lie within the interval (0, 1). (This example is identical to the coin tossing Example 1 considered in [10]).

Suppose there are three drugs ($k = 3$). Let the state of nature θ_{j-1} correspond to the situation where drug j is the odd drug, $j = 1, 2, 3$. Let the running of experiment e_i correspond to the administering of drug i, $i = 1, 2, 3$.

Then the information numbers are given by

$$I(\theta_l, \theta_j, e_i) = \begin{cases} a & \text{if } i = l + 1 \\ b & \text{if } i = j + 1 \\ 0 & \text{if } i \neq l + 1, j + 1 \end{cases}$$

where $i = 1, 2, 3$ and $j, l = 0, 1, 2$, and where

$$a = \log\left[\gamma^{\gamma p}\left(\frac{1 - \gamma p}{1 - p}\right)^{1 - \gamma p}\right]$$

and

$$b = \log\left[\gamma^{-p}\left(\frac{1 - p}{1 - \gamma p}\right)^{1 - p}\right].$$

Note that $I(\theta_l, \theta_j, e_i)$ may be unequal $I(\theta_j, \theta_l, e_i)$. The 2×3 payoff matrix to the game $\Gamma[\Theta - \theta_0, E, I(\theta_0, \theta, e)]$, e.g., is thus of the form

$$\begin{array}{c} \\ \theta_1 \\ \\ \theta_2 \end{array} \begin{array}{c} \begin{array}{ccc} e_1 & e_2 & e_3 \end{array} \\ \begin{bmatrix} a & b & 0 \\ & & \\ a & 0 & b \end{bmatrix} \end{array}. \quad (4.1)$$

The maximin strategy $\lambda(\theta_0)$ to $\Gamma(\theta_0)$ depends on the information numbers a and b as follows:

Case 1: $a \geqq b/2$, $\lambda(\theta_0) = (1, 0, 0)$,

Case 2: $a < b/2$, $\lambda(\theta_0) = (0, \frac{1}{2}, \frac{1}{2})$.

The value of $\Gamma(\theta_0)$ is given by

$$I(\theta_0) = \max(a, b/2).$$

(Bessler [2] has shown that for this example the assumption of strictly positive information numbers is not required for $\hat{\theta}_n$ to be exponentially consistent and hence for the asymptotic optimality results of Sections 2 and 3 to hold.)

Numerical simulations of various drug screening problems have been performed. The problems differ in values of γ, p, or c. In each example 200 simulation trials were conducted. As a variance reduction technique, on even numbered trials the basic sequence of Uniform (0, 1) random numbers used in the simulation was taken to be the one's complement of the sequence used on the odd numbered trials. This produced two negatively correlated estimates each based on 100 trials which were then averaged. The true state of nature was taken to be θ_0. Listed in Tables 1–4 are the following results for each rule being compared: the estimated average sample size (ASN), the range of sample sizes, the proportion of errors committed, and the proportion of times each experiment was selected. For purposes of inference, the mean and standard deviation of the mean of the log sample sizes are also given. (It was found that the frequency distribution of N is markedly skewed.)

In addition to comparing δ^A, δ^B, and δ^{BH}, rule δ^M and also the "no design" rule δ^{NO} were considered. Rule δ^{NO} is representative of the often standard procedure of running an experiment with each of the three drugs at every trial. Procedure δ^{NO} employs the stopping and terminal decision rules of δ^A and the following

Experimentation rule: Choose e^{n+1} to be e_i with probability $\frac{1}{3}$, $i = 1, 2, 3$.

Tables 1 and 2 provide examples of Case 2, $a < b/2$. Note that the conditions of Theorem 3.6 are satisfied for Case 2. For the game $\Gamma[\Theta - \theta_0, E, I(\theta_0, \theta, e)]$, e.g., with payoff matrix (4.1), column one is dominated by a convex linear combination of columns 2 and 3 which assigns equal weight to each column. Hence δ^B is asymptotically optimal for Case 2. As noted in [10], rule δ^{BH} is such that $e^{n+1} = e_i$ if $\hat{\theta}_n = \theta_{i-1}$, $i = 1, 2, 3$. Therefore, when $\hat{\theta}_n = \theta_0$, say, δ^{BH} will always choose e_1 while δ^A and δ^B will choose between e_2 and e_3.

From Table 1 it is seen that δ^A can perform quite poorly in comparison with δ^B, δ^M and δ^{BH}. In fact the results indicate that for this example the experimenter can do just as well by randomly picking an experiment at each stage as by using δ^A. As suggested by a referee, the difficulty with δ^A in this example may be that, even though the *averaged* frequencies of e_i do not reveal this, in cases where (say) p_{n0} and p_{n1} are high and p_{n2} is low, the relative frequencies of e_1, e_2, e_3 approach $(\frac{1}{4}, \frac{1}{4}, \frac{1}{2})$. However, what is needed is many more experiments with e_2 than e_3. This is substantiated by the excellent results with a simple modification of δ^A used in [10] which always chose e_i corresponding to the *second* highest posterior probability.

Despite the fact that δ^B and δ^M sampled nearly equally from e_1, e_2, and e_3 while δ^{BH} sampled primarily e_1, there

1. SIMULATION RESULTS FOR CASE 2[a]

Rule	ASN	Range of N	Mean (of log sample sizes)	Std. dev. (of log sample sizes)	Proportion of errors	Proportion of time each exp. sampled		
A	176	24-744	4.99	.040	.015	.19	.41	.41
BH	115	40-299	4.68	.027	.010	.77	.11	.12
B	119	11-414	4.62	.043	.005	.31	.36	.33
M	124	26-378	4.69	.039	.010	.35	.33	.33
NO	175	30-455	5.03	.038	.000	.33	.34	.33

[a] $\gamma = .05$, $a = .041$,
$p = .05$, $b = .103$, $-\log c/I(\theta_0) = 89.0$.

is no significant difference in ASN or probability of error among the three.

The value $-\log c/I(\theta_0)$ is the approximation to the expected sample size derived in Theorem 2.2. All of the observed average sample sizes were significantly larger than the approximation for this example.

Table 2 again considers Case 2. The most noticeable feature of this table is the result that δ^{BH} can perform poorly. The average sample sizes attained by δ^{BH} are significantly larger than those of δ^B for $c = .01$, $.0001$, and 10^{-8}. Note that for this example the values of $I(\theta_l, \theta_j, e_i)$ and $I(\theta_j, \theta_l, e_i)$ are substantially different for $i = l + 1, j + 1$.

Even for values of c as small as 10^{-8}, δ^B yields significantly smaller average sample sizes than δ^A.

In Tables 3 and 4 simulation studies of Case 1 are presented. Case 1 can be subdivided into Case 1a, $b/2 \leqq a < b$, and Case 1b, $a \geqq b$. For Case 1a the conditions of Theorem 3.6 fail to hold. However, when $\hat{\theta}_n = \theta_0$, once experiment e_1 is chosen δ^B will always thereafter choose only e_1 since the log likelihood ratio $S_n(\theta_1, \theta_2)$ remains constant. For Case 1b, column one of (4.1) strictly dominates columns two and three, so that

2. FURTHER SIMULATION RESULTS FOR CASE 2[a]

Rule	ASN	Range	Mean (of log sample sizes)	Std. dev. (of log sample sizes)	Proportion of errors	Proportion of time each exp. sampled		
			$c = .01$		$-\log c/I(\theta_0) = 25.0$			
A	59.2	2-222	3.83	.057	.010	.23	.38	.39
BH	44.4	2-97	3.68	.043	.015	.74	.14	.12
B	36.1	3-122	3.36	.052	.015	.41	.30	.29
M	40.4	3-94	3.56	.042	.015	.38	.32	.30
			$c = .0001$		$-\log c/I(\theta_0) = 50.1$			
A	102	18-280	4.51	.035	.000	.15	.42	.42
BH	93.5	49-181	4.52	.014	.000	.88	.06	.06
B	69.7	7-214	4.11	.038	.000	.23	.40	.36
M	66.1	13-168	4.10	.029	.000	.24	.37	.39
			$c = 10^{-8}$		$-\log c/I(\theta_0) = 100$			
A	148	47-379	4.92	.028	.000	.10	.45	.46
BH	184	135-279	5.20	.009	.000	.94	.03	.03
B	121	44-298	4.73	.025	.000	.13	.44	.43
M	118	41-235	4.72	.023	.000	.14	.42	.44

[a] $\gamma = .01$, $a = .100$,
$p = .10$, $b = .367$.

3. SIMULATION RESULTS FOR CASE 1a[a]

Rule	ASN	Range of N	Mean (of log sample sizes)	Std. dev. (of log sample sizes)	Proportion of errors	Proportion of time each exp. sampled		
			$c = .01$		$-\log c/I(\theta_0) = 18.4$			
A,BH	21.3	10-58	2.99	.026	.005	.77	.12	.11
B	21.6	7-61	2.98	.033	.010	.45	.28	.27
M	21.8	9-57	2.99	.027	.010	.48	.22	.29
NO	32.1	7-107	3.33	.035	.005	.32	.35	.33
			$c = 10^{-7}$		$-\log c/I(\theta_0) = 64.4$			
A,BH	68.6	45-127	4.21	.015	.000	.93	.04	.03
B	67.7	29-160	4.18	.018	.000	.60	.20	.20
M	67.7	40-123	4.18	.017	.000	.67	.17	.16
NO	86.1	35-218	4.41	.020	.000	.34	.34	.33

[a] $\gamma = .1$, $a = .247$,
$p = .3$, $b = .462$.

when $\hat{\theta}_n = \theta_0$, δ^B will always choose e_1. Since $\lambda_1(\theta_0) = 1$ for Case 1, δ^B is asymptotically optimal.

For Case 1 δ^A and δ^{BH} are identical.

In Tables 3 and 4 no evidence of significant differences between δ^A and δ^B is detected. Note that in Table 4 $c = .05$, as compared to $c \leqq .01$ of the previous tables. With this higher cost have come higher proportions of error.

The following general features of the simulation studies presented in Tables 1–4 are evident (generalizations beyond the present examples are not valid): The decision rule δ^B consistently performed as well as or better than the decision rules δ^A and δ^{BH} regardless of the classifications Case 2, 1a, or 1b; in every case the "no design" rule δ^{NO} yielded results which were significantly inferior to those of δ^B; nowhere were significant differences in error rates among δ^A, δ^{BH}, δ^B and δ^M recorded; only for the first example of Table 2 were significant differences in average sample sizes between δ^B and δ^M recorded.

5. DISCUSSION

A sequential design decision rule δ^B has been presented. Under rather restrictive conditions it has been shown to be asymptotically optimal. Numerical studies for several specific examples have shown it may yield lower observed risks in comparison with other sequential design rules. Based on these findings, admittedly limited, we have suggested that the rule is a good one.

Rule δ^B, as well as δ^A, judges experiments as a function of information numbers which measure the usefulness of

4. SIMULATION RESULTS FOR CASE 1b[a]

Rule	ASN	Range of N	Mean (of log sample sizes)	Std. dev. (of log sample sizes)	Proportion of errors	Proportion of time each exp. sampled		
A,BH	102	11-848	4.33	.059	.090	.57	.22	.21
B	104	14-410	4.40	.051	.090	.56	.21	.23
M	110	7-486	4.39	.054	.085	.55	.21	.24
NO	160	21-532	4.87	.046	.055	.34	.34	.33

[a] $\gamma = .9$, $a = .0366$, $c = .05$,
$p = .9$, $b = .0306$, $-\log c/I(\theta_0) = 82.0$.

experiments in discriminating between states $\hat{\theta}_n$ and θ_j when $\hat{\theta}_n$ is the true state of nature. For small samples this may not be a sufficiently adequate criterion. In the small sample case, adjustment for the crudeness of $\hat{\theta}_n$ may be made by considering posterior probabilities (δ^M, and in certain cases δ^{BH}, is such an adjustment for δ^B), but even so perhaps experiments should not be compared only on the basis of information numbers (and posterior probabilities). The relative importance of losses from incorrect decisions is increased when c is not small. Exact (Bayes) rules incorporating both kinds of losses can be constructed [11], but are unwieldy and can require excessive computation even for extremely small sample sizes [4]. Hence, our primary objective has been to find, within a class of "large sample" rules, a rule which produces desirable small sample results.

APPENDIX

An example where δ^B is such that $n_i/n \longrightarrow \lambda_i(\theta_0)$.

Let $\Theta - \theta_0 = \{\theta_1, \theta_2\}$, $E = \{e_1, e_2, e_3, e_4\}$. Let the payoff matrix to $\Gamma(\theta_0)$ be given by

$$\begin{array}{c} \\ \theta_1 \\ \theta_2 \end{array} \begin{array}{c} \begin{array}{cccc} e_1 & e_2 & e_3 & e_4 \end{array} \\ \begin{pmatrix} 6 & 1 & 3 & 5 \\ 1 & 6 & 5 & 3 \end{pmatrix} \end{array}.$$

For this 2×4 matrix game $\lambda(\theta_0) = (0, 0, \frac{1}{2}, \frac{1}{2})$.

For sufficiently large n (when $\hat{\theta}_n = \theta_0$), procedure B says choose $e^{n+1} = e_1$ if

$$6p_{n1} + p_{n2} > p_{n1} + 6p_{n2}$$
$$6p_{n1} + p_{n2} > 3p_{n1} + 5p_{n2}$$
$$6p_{n1} + p_{n2} > 5p_{n1} + 3p_{n2}.$$

Dividing by $p_{n1} + p_{n2}$, and letting $p'_{n1} = p_{n1}/(p_{n1} + p_{n2})$, these inequalities reduce to $p'_{n1} > \frac{1}{2}$, $p'_{n1} > 4/7$, and $p'_{n1} > 2/3$, respectively. Hence, δ^B chooses e_1 if $p'_{n1} > 2/3$. Similarly it can be obtained that δ^B chooses e_2 if $p'_{n1} < 1/3$, e_3 if $1/3 < p'_{n1} < 1/2$ and e_4 if $1/2 < p'_{n1} < 2/3$. Or δ^B chooses

$$\begin{array}{lll} e_1 & \text{if} & \log p_{n1}/p_{n2} > \log 2 \\ e_2 & \text{if} & \log p_{n1}/p_{n2} < -\log 2 \\ e_3 & \text{if} & -\log 2 < \log p_{n1}/p_{n2} < 0 \\ e_4 & \text{if} & 0 < \log p_{n1}/p_{n2} < \log 2. \end{array} \tag{A.1}$$

For n_1/n and n_2/n to converge to zero wpl as $n \to \infty$, from (A.1) it must be that

$$P_{\theta_0}[|\log p_{n1}/p_{n2}| > \log 2] \to 0 \quad \text{as} \quad n \to \infty.$$

For this to be true it must be that

$$\left|\log \frac{f(Y;\theta_1, e_i)}{f(Y;\theta_2, e_i)}\right| < \left| 2\log 2 \text{ wpl} \right. \tag{A.2}$$

for both $i = 3$ and 4. But

$$E_{\theta_0}\left[\left|\log \frac{f(Y;\theta_1, e_i)}{f(Y;\theta_2, e_i)}\right|\right] \geq \left|I(\theta_0, \theta_2, e_i) - I(\theta_0, \theta_1, e_i)\right|$$
$$= 2 > 2\log 2$$

for both $i = 3$ and 4.

Hence, (A.2) is violated. Thus n_1/n and n_2/n are each bounded away from zero wpl as $n \to \infty$ whereas $\lambda_1(\theta_0) = \lambda_2(\theta_0) = 0$.

Proof of Lemma 3.1:

By hypothesis, suppose

$$\sum_{u=1}^k b_u(\theta_0, \theta_j, e_u) \geqq I(\theta_0, \theta_j, e_i)$$

for all θ_j (with strict inequality for at least one θ_j), where $b_u \geqq 0$,

$$\sum_{u=1}^k b_u = 1, \quad b_i = 0.$$

Hence

$$\sum_{j=1}^s p_{nj} \sum_{u=1}^k b_u I(\theta_0, \theta_j, e_u) > \sum_{j=1}^s p_{nj} I(\theta_0, \theta_j, e_i)$$

for any posteriors p_{nj} such that the prior probability of each state is positive. Rearranging,

$$\sum_{u=1}^k b_u[\sum_{j=1}^s p_{nj} I((\theta_0, \theta_j, e_u)] > \sum_{j=1}^s p_{nj} I(\theta_0, \theta_j, e_i).$$

But this implies there exists some integer $v \neq i$ for which

$$\sum_{j=1}^s p_{nj} I(\theta_0, \theta_j, e_v) > \sum_{j=1}^s p_{nj} I(\theta_0, \theta_j, e_i)$$

for any positive p_{nj}, $j = 1, 2, \cdots, s$.

Therefore, the e that maximizes $\sum_{j=1}^s p_{nj} I(\theta_0, \theta_j, e)$ is never e_i.

Proof of Lemma 3.2:

Suppose columns $t+1, t+2, \cdots, k$ are each dominated by convex linear combinations of other columns of $\Gamma(\theta_0)$ and have been eliminated from the payoff matrix. Suppose that

$$\sum_{j=1}^s b_j I(\theta_0, \theta_j, e_i) < I(\theta_0, \theta_v, e_i) \tag{A.3}$$

$i = 1, 2, \cdots, t$ where $b_j \geq 0$, $j = 1, 2, \cdots, s$, $\sum_{j=1}^s b_j = 1$, $b_v = 0$.

Now by Lemma 3.3, for all $j \neq v$,

$$P[S_n(\theta_v, \theta_j) - \sum_{i=1}^t n_i I_{vj}(e_i) \leqq n\epsilon] > 1 - \rho^n \tag{A.4}$$

for some constant ρ, $0 < \rho < 1$, where $S_n(\theta_v, \theta_j) = \log(p_{nv}/p_{nj})$ and $I_{vj}(e_i) = I(\theta_0, \theta_j, e_i) - I(\theta_0, \theta_v, e_i)$. It follows from (A.4) that

$$P\Big[\exp\{\sum_{j=1}^s b_j \log(p_{nv}/p_{nj})\} < \exp\Big\{n\Big(\sum_{i=1}^t \frac{n_i}{n}[\sum_{j=1}^s b_j I(\theta_0, \theta_j, e_i) - I(\theta_0, \theta_v, e_i)] + \epsilon\Big)\Big\}\Big] > 1 - \rho^n. \tag{A.5}$$

Applying inequality (A.3) to (A.5) yields that

$$\exp\{\sum_{j=1}^s b_j \log(p_{nv}/p_{nj})\} \to 0 \text{ exponentially as } n \to \infty.$$

Now

$$\begin{aligned} \exp\{\sum_{j=1}^s b_j \log(p_{nv}/p_{nj})\} &= \prod_{j=1}^s [p_{nv}/p_{nj}]^{b_j} \\ &\geq p_{nv}/\prod_{j=1}^s [\max_j p_{nj}]^{b_j} \\ &= p_{nv}/\max_j p_{nj} \\ &\geq p_{nv}/\sum_{j=1}^s p_{nj}, \end{aligned}$$

and the desired result follows.

Proof of Lemma 3.3:

Let $L(e)$ denote $\log\{f(Y;\theta_1, e)/f(Y;\theta_2, e)\}$. For any random variable X, $P(X \leq 0) \leq E[\exp(uX)]$ for $u < 0$. Hence

$$\begin{aligned} &P[\sum_{m=1}^n [L_m(e^m) - I_{12}(e^m) + \epsilon] \leq 0] \\ &\quad \leq E[\exp\{u\sum_{m=1}^n [L_m(e^m) - I_{12}(e^m) + \epsilon]\}] \quad \text{for} \quad u < 0. \end{aligned} \tag{A.6}$$

Now

$$L(e_i) - I_{12}(e_i) + \epsilon$$

is a random variable with positive mean and finite moment generating function in neighborhood about zero for each $i = 1, 2$. Hence, there exists a $u_1 < 0$ and a ρ, $0 < \rho < 1$ such that

$$E[\exp\{u_1[L(e_i) - I_{12}(e_i) + \epsilon]\}] < \rho \tag{A.7}$$

for each experiment e_i, $i = 1, \cdots, t$. Applying (A.7) to the $n-1$ conditional expectations with respect to the distribution of Y_m given $Y_1, Y_2, \cdots, Y_{m-1}$ in (A.6), we obtain that there exists a $u^* < 0$ and a ρ, $0 < \rho < 1$ for which

$$E[\exp\{u^* \sum_{m=1}^n [L_m(e^m) - I_{12}(e^m) + \epsilon]\}] < \rho^n. \tag{A.8}$$

From (A.6) and (A.8)

$$P[S_n(\theta_1, \theta_2) - \sum_{i=1}^{t} n_i I_{12}(e_i) \leq -n\epsilon] < \rho^n.$$

In a similar manner it can be shown that there exists a γ, $0 < \gamma < 1$ such that

$$P[S_n(\theta_1,\theta_2) - \sum_{i=1}^{t} n_i I_{12}(e_i) \geq n\epsilon] < \gamma^n,$$

and the desired result follows.

Proof of Lemma 3.4:

Without loss of generality, assume $S_n(\theta_1, \theta_2) \geq a$. Now

$$S_n(\theta_1, \theta_2) = S_{n^*}(\theta_1, \theta_2) + \sum_{m=n^*+1}^{n} L_m(e_1),$$

where $n^* - 1$ is the largest integer m, $0 \leq m < n$, for which $S_m < a$ and L is defined in the previous lemma. Now

$$P[S_n(\theta_1, \theta_2) > n\epsilon] \leq P[S_n{}^*(\theta_1, \theta_2) > n\epsilon/2] + P[\sum_{m=n^*+1}^{n} L_m(e_1) > n\epsilon/2]. \quad \text{(A.9)}$$

But

$$S_{n^*}(\theta_1,\theta_2) = S_{n^*-1}(\theta_1, \theta_2.) + L_{n^*}(e_2).$$

By definition of n^*, $S_{n^*-1}(\theta_1,\theta_2)$ is bounded above by a. Now

$$\begin{aligned} P[L_{n^*}(e_2) > n\epsilon/2] &= P[L(e_2) > n\epsilon/2 | L(e_2) > a - S_{n^*-1}(\theta_1, \theta_2)] \\ &= P[L(e_2) > \max\{n\epsilon/2, a - S_{n^*-1}(\theta_1, \theta_2)\}]/ \\ &\qquad P[L(e_2) > a - S_{n^*-1}(\theta_1, \theta_2)]. \end{aligned}$$

Hence, for any possible value of S_{n^*-1}, for sufficiently large n, there exist constants K_1 and u, $K_1 > 0$, $u < 0$, such that

$$P[L_{n^*}(e_2) > n\epsilon/2] \leq K_1 \exp\{un\epsilon/2\} E[\exp\{-uL(e_2)\}]. \quad \text{(A.10)}$$

The expectation on the right side of (A.10) is finite by (3.6). Letting $\rho_1 = \exp\{u\epsilon/2\}$, we then have that there exists a constant K for which

$$P[S_{n^*}(\theta_1, \theta_2) > n\epsilon/2] < K\rho_1^n. \quad \text{(A.11)}$$

Also

$$P[\sum_{m=n^*+1}^{n} L_m(e_1) > n\epsilon/2] \leq \exp\{un\epsilon/2\} E[\exp\{-u \sum_{m=n^*+1}^{n} L_m(e_1)\}] \quad \text{(A.12)}$$

for $u < 0$. But from (3.5) $E[-L(e_1)] > 0$ and hence there exists a ρ_2, $0 < \rho_2 < 1$ such that for each possible value of n^*

$$E[\exp\{-u_2 \sum_{m=n^*+1}^{n} L_m(e_1)\}] < \rho_2^{n-n^*}. \quad \text{(A.13)}$$

Hence, from (A.12) and (A.13) letting $\rho_3 = \exp\{u\epsilon/2\}$ we have

$$P[\sum_{m=n^*+1}^{n} L_m(e_1) > n\epsilon/2] < \rho_3^n. \quad \text{(A.14)}$$

From (A.11) and (A.14), there exist constants $K > 0$ and ρ, $0 < \rho < 1$ such that

$$P[S_n(\theta_1, \theta_2) > n\epsilon] < K\rho^n.$$

Similarly it can be shown that $P[S_n(\theta_1, \theta_2) > -n\epsilon]$ is also exponentially bounded, and the conclusion of the Lemma follows.

Proof of Lemma 3.5:

The maximin strategy α of a simple solution to the 2×2 game $\Gamma[\Theta - \theta_0, E, I(\theta_0, \theta, e)]$ with value $I(\theta_0)$ satisfies

$$\sum_{i=1}^{2} \alpha_i I(\theta_0, \theta_j, e_i) = I(\theta_0)$$

for $j = 1, 2$. Since λ is the unique maximin strategy of Γ, noting that $\alpha_2 = 1 - \alpha_1$, we have that $\alpha_1 = \lambda_1$ is the unique solution to

$$\alpha_1 I_{12}(e_1) + (1 - \alpha_1) I_{12}(e_2) = 0.$$

As a consequence of Lemmas 3.3 and 3.4, for $\epsilon > 0$ there exist constants K and ρ, $K > 0$, $0 < \rho < 1$ such that

$$P\left[\left|\frac{n_1}{n} I_{12}(e_1) + \left(1 - \frac{n_1}{n}\right) I_{12}(e_2)\right| > \epsilon\right] < K\rho^n,$$

and hence it follows that

$$P[|n_1/n - \lambda_1| > \epsilon] < K\rho^n.$$

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