SEQUENTIAL MEDICAL TRIALS WITH DATA DEPENDENT TREATMENT ALLOCATION

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1. Introduction

This paper is concerned with clinical trials intended to determine which, if either, of two treatments for a disease is the superior. The experimental situation is one in which patients arrive for treatment sequentially over some period of time. When a patient is admitted to the trial, he is immediately administered one of the two treatments. The effect of the treatment on the patient may be measured, either immediately, or after some delay. After a certain amount of data is collected, the trial is terminated with the conclusion that one of the two methods is superior or that there is no significant difference between them.

Emphasis in this study is on a search for protocols which assign fewer patients to the inferior treatment as compared to classical statistical methods, while retaining the error probabilities associated with these methods. In these protocols, the assignment of a patient to one of the two treatments being compared is determined by data about patients previously treated. The statistical properties (error probabilities, expected sample sizes, expected number to inferior treatment) of a variety of protocols have been explored by computer simulation, and it has been demonstrated that Wald type sequential procedures can be combined with data dependent assignment rules to reduce the expected number assigned to the inferior treatment. The Neyman-Pearson measures of significance and power remain unchanged.

2. Definition of a protocol

Treatments 1 and 2 are to be compared. The effect on the jth patient assigned to treatment i is assumed to be a random variable X_{ij} with density f_i which

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depends upon the treatment. The densities f_1 and f_2 may be characterized by parameters μ_1 and μ_2 with $\mu_1 - \mu_2 = \Delta$. The objective of the clinical trial is the acceptance of one of the following hypotheses:

$$\begin{aligned} &H_0\colon \Delta = 0, \text{ the two treatments are equally effective,} \\ &H_1\colon \Delta \geqq \Delta^*, \text{ treatment 1 is better than treatment 2,} \\ &H_2\colon \Delta \leqq -\Delta^*, \text{ treatment 2 is better than treatment 1,} \end{aligned} \tag{2.1}$$

where Δ^* is a positive constant.

A protocol consists of the following ingredients: (a) admission rule, (b) assignment rule, and (c) termination rule.

The admission rule effectively defines the population under study. It contains both the disease characteristics and the demographic properties that qualify a patient for admission to the trials. It cannot depend on knowledge of the particular treatment to be administered.

The assignment rule selects the particular treatment to be administered to a given patient. In order that bias not be introduced, it is important that the assignment be independent of the characteristics of the individual. Traditionally, this independence is achieved by randomization. In the following section, both deterministic and randomized assignment rules based on data about previous patients will be described.

The termination rule determines when the trials are ended and one of the hypotheses is accepted. This paper considers only Wald SPRT type tests which end when a generalized likelihood ratio crosses a specified boundary.

The performance of a protocol may be characterized by three surfaces, all of them functions of the two parameters μ_1 and μ_2: OC, the probability of rejecting H_0; ASN, the expected number of patients in the trial; ITN, the expected number of patients assigned to the inferior treatment.

3. Assignment rules

Both deterministic and randomized data dependent assignment rules have been thoroughly explored by simulation. All these rules require that at every patient arrival some estimate $\hat{\Delta}$ of Δ be constructed. This estimate can depend only on the effects of treatment on previous patients in the trial. Treatment 1 or 2 will be termed leading at any time according as $\hat{\Delta}$ is or is not greater than zero. The deterministic rules R_γ operate as follows.

Select $\gamma\colon 0 \leqq \gamma \leqq 1$, fixed throughout the trial. At the time of the Nth patient arrival, let M_i be the number of patients previously assigned to treatment i. If

$$\begin{aligned} &|M_1 - M_2| < \gamma N, \text{ assign the patient to the leading treatment,} \\ &|M_1 - M_2| \geqq \gamma N, \text{ assign to the treatment with fewer patients} \\ &\qquad\qquad \text{previously assigned.} \end{aligned} \tag{3.1}$$

Note that $M_1 + M_2 = N - 1$.

A few observations shed light on the operation of these rules. By a simple calculation, it can be shown that an R_γ rule sets the following bounds on the fraction of patients assigned to either treatment at every stage of the trial:

$$\frac{1-\gamma}{2} - \frac{1}{2N} \leqq \frac{M_i}{N} \leqq \frac{1+\gamma}{2} + \frac{1}{2N} \quad \text{for } i = 1, 2, \text{ all } N. \tag{3.2}$$

From (3.1), R_0 is strict alternation, while R_1 always assigns to the leading treatment. This class of rules uses as input only data generated within the trial and does not reference data on the particular patient to be assigned.

A randomized rule $\overline{R}_\gamma$ which is approximately equivalent to R_γ with respect to OC, ASN, ITN, is the following. Assign the first patient to treatment 1 or 2 with equal probability and assign the second patient to the other treatment. Assign each succeeding patient to the currently leading treatment with probability $(1 + \gamma)/2$, and to the trailing one with probability $(1 - \gamma)/2$. Here, $\overline{R}_0$ assigns to either treatment with probability $\frac{1}{2}$ throughout the trials, while $\overline{R}_1$ always selects the leading treatment.

4. Termination rules

All the protocols considered in the paper are terminated when a generalized likelihood ratio crosses a specified boundary.

The assumptions in Section 2 on treatment responses can be restated:

$$\begin{aligned} &X_{1j} \text{ has density } f(X_{1j}|\mu_1) = f(X_{1j}|\theta + \Delta/2), \\ &X_{2j} \text{ has density } f(X_{2j}|\mu_2) = f(X_{2j}|\theta - \Delta/2), \end{aligned} \tag{4.1}$$

where $\theta = (\mu_1 + \mu_2)/2$ is a nuisance parameter lying in some space Θ.

To form the generalized likelihood ratios (LR) used in termination, let

$$\begin{aligned} L_1 = \text{LR } (H_1 \textit{ versus } H_0) &= \frac{\sup_{\theta\in\Theta} \prod_{j=1}^{M_1} f(X_{1j}|\theta + \Delta^*/2) \prod_{j=1}^{M_2} f(X_{2j}|\theta - \Delta^*/2)}{\sup_{\theta\in\Theta} \prod_{j=1}^{M_1} f(X_{1j}|\theta) \prod_{j=1}^{M_2} f(X_{2j}|\theta)}, \\ L_2 = \text{LR } (H_2 \textit{ versus } H_0) &= \frac{\sup_{\theta\in\Theta} \prod_{j=1}^{M_1} f(X_{1j}|\theta - \Delta^*/2) \prod_{j=1}^{M_2} f(X_{2j}|\theta + \Delta^*/2)}{\sup_{\theta\in\Theta} \prod_{j=1}^{M_1} f(X_{1j}|\theta) \prod_{j=1}^{M_2} f(X_{2j}|\theta)}. \end{aligned} \tag{4.2}$$

To terminate the clinical trial the following rule is used. Pick A, B, such that $0 < A < 1 < B < \infty$, and if ever

$$\begin{aligned} &\max(L_1, L_2) < A, \text{ stop and accept } H_0, \\ &\max(L_1, L_2) > B, \text{ stop and accept the appropriate } H_1 \text{ or } H_2, \end{aligned} \tag{4.3}$$

otherwise continue the clinical trial.

The above procedure will be referred to as GSPRT(A, B). In any testing situation where $EX_{ij}^2 < \infty$, it is not difficult to show that ASN is finite for all R_γ, $\gamma < 1$.

5. Computational example

In general, the R_γ assignment rules coupled with GSPRT termination result in OC surfaces very close to those associated with conventional, data independent assignment rules. Appropriate choices of γ reduce the expected number of patients assigned to the inferior treatment (ITN) with only small increases in ASN.

As an example of the performance of the R_γ family of rules, we have studied, by simulation, the problem of testing for a difference in the means of two normal populations with known, equal variance. Specifically,

$$\begin{aligned} &X_{11}, X_{12}, \cdots, \text{iid } N(\mu_1, 1), \\ &X_{21}, X_{22}, \cdots, \text{iid } N(\mu_2, 1), \\ &\Delta = \mu_1 - \mu_2. \end{aligned} \tag{5.1}$$

After M_i patients have been administered treatment i, let

$$\bar{X}_i(M_i) = M_i^{-1} \sum_{j=1}^{M_i} X_{ij}, \qquad M_i > 0,\ i = 1, 2. \tag{5.2}$$

The estimate $\hat{\Delta}$ of Δ which is used in the assignment rule (Section 3) is

$$\hat{\Delta} = \bar{X}_1(M_1) - \bar{X}_2(M_2). \tag{5.3}$$

The two generalized likelihood ratios computed from (4.2) which are used in the termination rule are

$$\begin{aligned} L_1 &= \exp\left\{\Delta^* \frac{M_1 M_2}{M_1 + M_2} (\hat{\Delta} - \Delta^*/2)\right\}, \\ L_2 &= \exp\left\{\Delta^* \frac{M_1 M_2}{M_1 + M_2} (-\hat{\Delta} - \Delta^*/2)\right\}. \end{aligned} \tag{5.4}$$

Since the testing procedure is invariant under translations of θ, the three surfaces OC, ASN, and ITN are reduced to curves. For given values of Δ^*, γ, A, and B, these functions depend only on Δ, not on μ_1 and μ_2.

Simulation with 5,000 replications was carried out on an IBM 360/91 to investigate the effects of varying Δ^*, γ, A, and B on the three curves OC, ASN, and ITN. Although several pairs of stopping values were considered, $A = 0.1$ and $B = 30$ were used in the tables presented in this paper. The results for this pair are representative of the performance of the R_γ family with other stopping parameters. Simulations have been done for two values of Δ^*, three values of γ, and several values of Δ for each Δ^*, γ pair.

Table I summarizes the OC, ASN, and ITN data from these simulations and Figures 1, 2, and 3 display the curves for $\Delta^* = 0.5$ graphically. The first observation from these data concerns the remarkable constancy of the OC curve with variations of γ. Thus, within the accuracy of the simulation, the OC depends only on the termination parameters and Δ/Δ^*.

TABLE I

PERFORMANCE OF PROTOCOLS
Termination parameters: $A = 0.1$, $B = 30$.
ITN values are not applicable when $\Delta = 0$.

Δ	OC			ASN			ITN		
	$\gamma = 0$	$\gamma = .2$	$\gamma = .5$	$\gamma = 0$	$\gamma = .2$	$\gamma = .5$	$\gamma = 0$	$\gamma = .2$	$\gamma = .5$
$\Delta^* = .5$									
0	.06	.05	.05	125	127	160	—	—	—
.125	.14	.13	.14	139	141	181	70	63	66
.25	.45	.43	.43	160	164	211	80	68	62
.375	.77	.78	.77	141	146	186	71	59	50
.50	.94	.94	.94	102	107	136	51	43	36
.75	1.00	1.00	1.00	56	59	74	28	24	19
1.0	1.00	1.00	1.00	38	40	51	19	16	13
$\Delta^* = 1$									
0	.05	.05	.05	33	34	42	—	—	—
.25	.13	.13	.13	37	39	48	19	17	17
.5	.43	.45	.43	43	46	58	22	19	17
.75	.80	.78	.79	38	40	51	19	16	14
1.0	.96	.95	.96	27	28	36	14	11	10
1.5	1.00	1.00	1.00	15	16	19	8	6	5
2.0	1.00	1.00	1.00	10	10	13	5	4	4

Variations in the value of γ (for $0 \leqq \gamma \leqq 0.5$) affect only the ASN and ITN curves. In all cases simulated, ASN increases with γ. On the other hand, ITN always decreases initially as γ increases from zero. Changing γ from 0 to 0.2 causes only a small increase in ASN while markedly reducing ITN for all nonzero values of Δ considered. Thus, some of the rules in the R_γ class achieve the stated objective of reducing *ITN* without altering the error probabilities of the clinical trial, and, in fact, accomplish this end without sizable increases in ASN.

In [7] another model for comparing two treatments by data dependent assignment coupled with GSPRT termination was studied. In this model, it is assumed that the effect on a given patient can be measured by his survival time after treatment and that this time is exponentially distributed with a mean life which characterizes the treatment. Patients arrive at fixed intervals of time, so that the data about previous patients are truncated. A modification of the R_γ rule designed for this incomplete information case produced results very similar to those displayed in Table I.

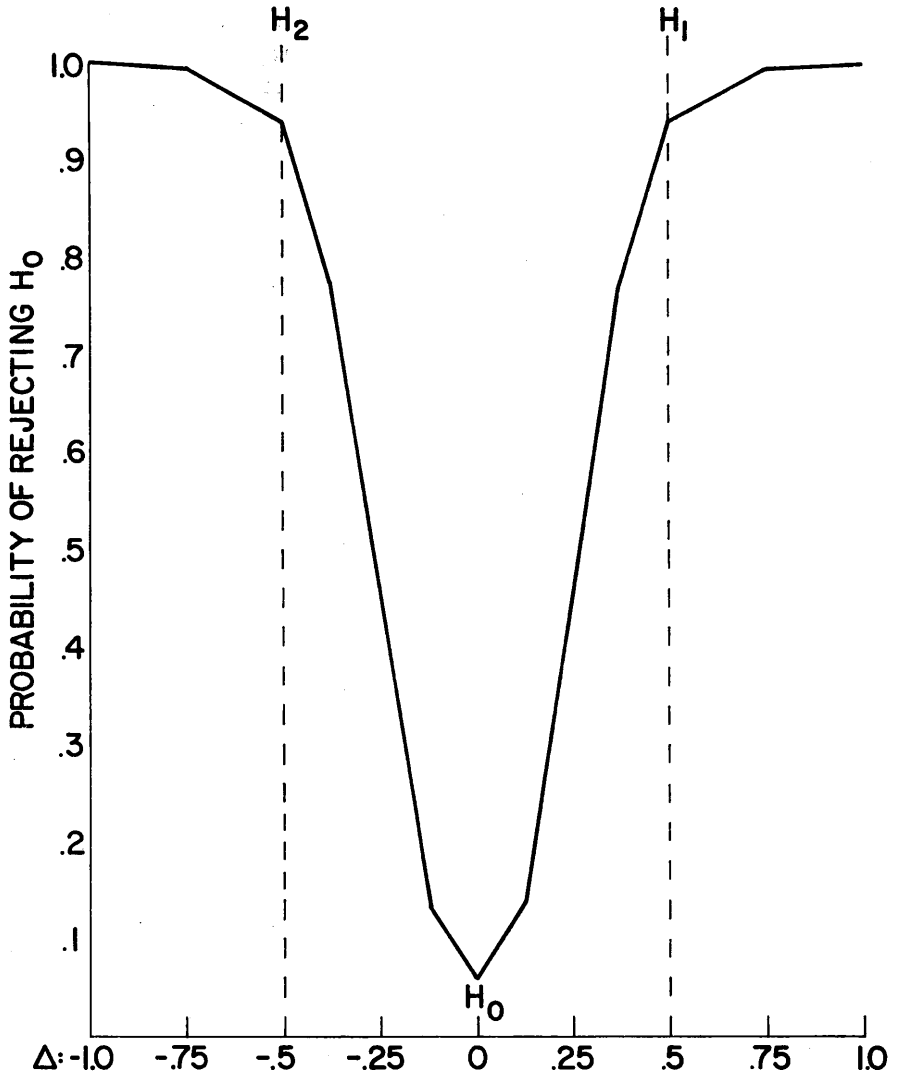

FIGURE 1

OC curves.
$A = 0.1$, $B = 30$, $\Delta^* = 0.5$.
Rules: R_γ: $\gamma = 0, 0.2, 0.5$.

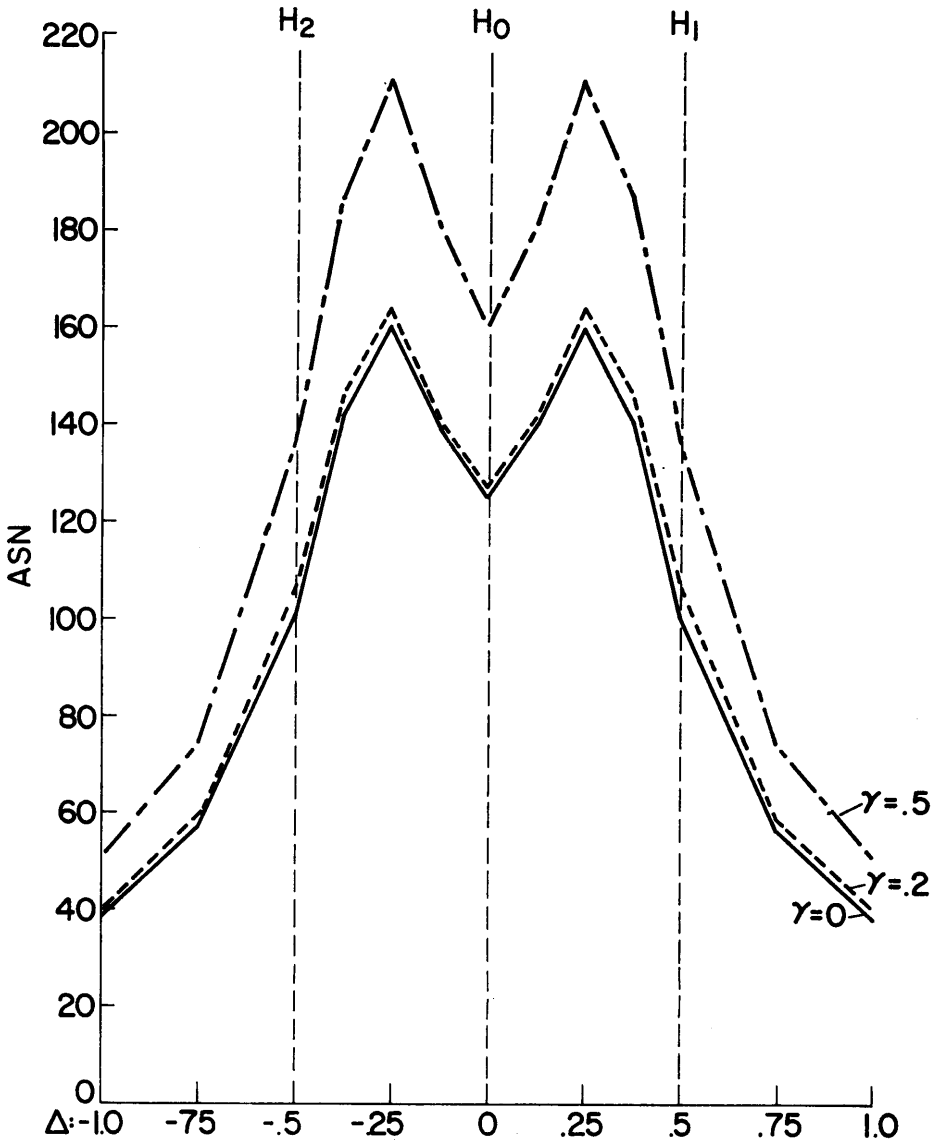

FIGURE 2

ASN curves.
$A = 0.1$, $B = 30$, $\Delta^* = 0.5$.
Rules: R_γ: $\gamma = 0, 0.2, 0.5$.

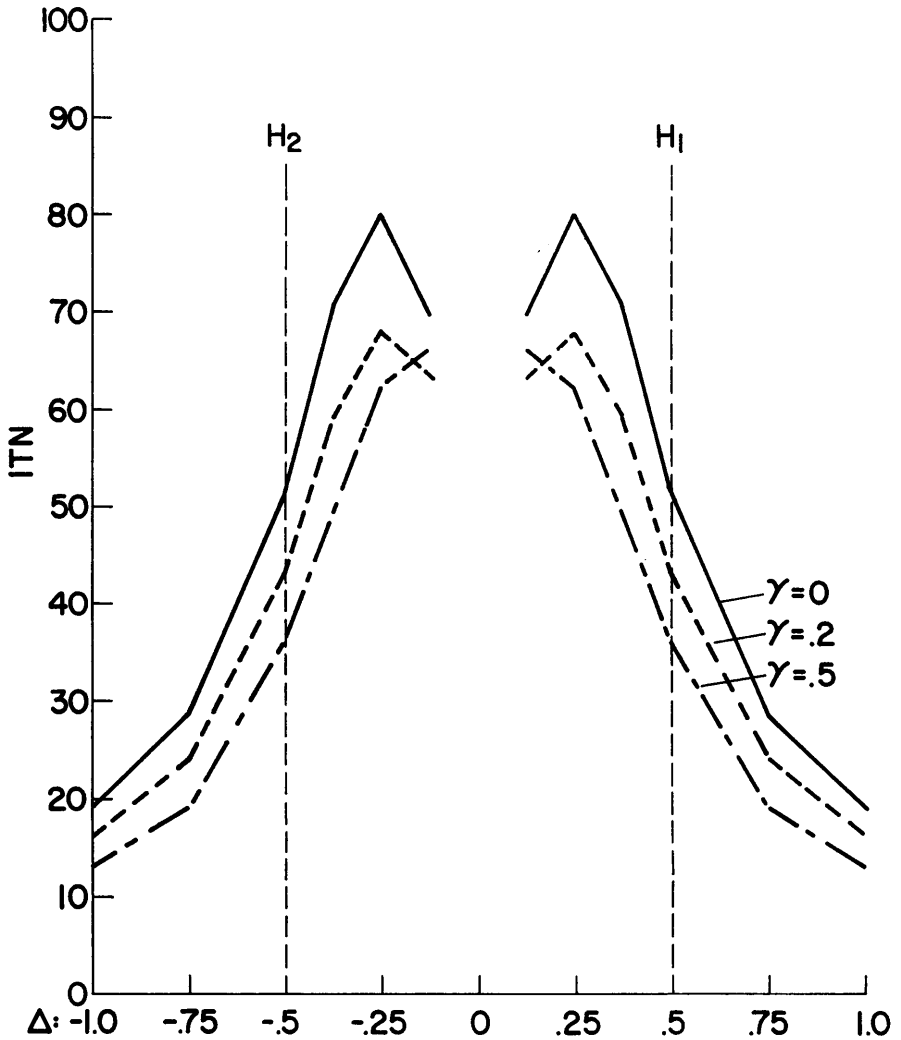

FIGURE 3

ITN curves.
$A = 0.1$, $B = 30$, $\Delta^* = 0.5$.
Rules: R_γ: $\gamma = 0, 0.2, 0.5$.

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