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ASYMPTOTIC INFERENCE WITH RESPONSE-ADAPTIVE TREATMENT ALLOCATION DESIGNS

BY WILLIAM F. ROSENBERGER

George Washington University

A response-adaptive treatment allocation design for a clinical trial attempts to place the majority of patients on the treatment that appears more successful, based on the responses of patients already treated. One example of such a design is the randomized play-the-winner rule developed by Wei and Durham, which randomizes the treatment assignment probabilities according to the outcomes of treatments previously assigned. For a trial with dichotomous treatment responses and a randomized play-the-winner assignment scheme, exact small sample permutation tests of the hypothesis of equal treatment effects and large sample tests based on a population model have previously been developed. We present a large sample permutation test statistic for this case; under certain conditions on the sequence of responses, the test statistic is shown to be asymptotically normal. For a trial with a continuous response variable, we develop a rank-based analog of the randomized play-the-winner assignment scheme. Simulation evidence in both cases suggests that a normal approximation to the test statistic works well for moderate-sized trials, with some conservatism in the extreme tails.

1. Introduction. Response-adaptive treatment allocation rules use accumulating information to assign patients to treatments in a clinical trial, with the goal of placing more patients on the more effective of two treatments. Ethical considerations make adaptive treatment assignment attractive, at least in principle.

For dichotomous responses, the randomized play-the-winner (RPW) rule [Wei and Durham (1978)] has been proposed as a form of response-adaptive treatment allocation. The design can be described in terms of an urn model. At the start of the trial, there are α balls of each color, say red and black, in the urn. When a patient is available for assignment to either of treatments A or B, a ball is drawn at random from the urn and replaced. A red ball generates an assignment to A, a black ball to B. When a response of a previously assigned patient becomes available, β red balls are added to the urn if the response is a success on treatment A or a failure on treatment B, and otherwise, β black balls are added to the urn. This rule will be denoted by RPW(α, β).

In Section 2, we present a large-sample permutation test statistic for the RPW design. This result may be regarded either as a large-sample approxima-

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tion of the exact permutation test of Wei (1988) or as a permutation test analog of the large-sample analysis of Wei, Smythe, Lin and Park (1990) under a simple population model on the responses. We show that, under certain conditions on the sequence of responses, the test statistic is asymptotically normal, and the normal approximation works well for even moderate-sized trials.

In Section 3, we introduce a nonparametric response-adaptive design for the case of general (not necessarily dichotomous) responses, in the spirit of the RPW rule. At each stage in the trial, the next treatment assignment is generated from a rank-type statistic, giving higher probability of assignment to the treatment that is "winning" at that stage. A large-sample permutation test statistic may then be calculated. Although a rigorous proof of asymptotic normality has thus far eluded us, numerical evidence for both ranks and normal scores suggests that the normal approximation is again good for moderate-sized trials.

The methods used for both the dichotomous and general cases are similar, and employ a martingale central limit theorem.

2. A permutation test statistic for dichotomous outcomes. Permutation tests are derived under the null hypothesis of no treatment effect; a patient's outcome does not depend on the treatment assigned, and hence the outcomes can be thought of as deterministic [Lehmann (1975)]. In this vein, let $z_1, \ldots, z_n$ be a sequence of outcomes treated as deterministic, which take on the value 1 if the treatment is successful and -1 if not. Let $Y_1, \ldots, Y_n$ be a sequence of dichotomous treatment assignments, where $Y_j = 1$ or 0 according to whether patient j is assigned to treatment A or B, respectively. Let $\mathscr{F}_j \equiv \sigma(Y_1, \ldots, Y_j)$, $j = 1, \ldots, n$, the sigma algebra generated by the first j treatment assignments, and let $\mathscr{F}_0$ be the trivial sigma algebra. For the design RPW(α, 1), it is easily seen that the conditional probability $P(Y_j = 1 | \mathscr{F}_{i-1})$ is given by

$$p_1 = 1/2,$$
$$p_i = \frac{\alpha + S_{i-1}}{2\alpha + i - 1}, \qquad i > 1, \tag{2.1}$$

where

$$S_i = \sum_{j=1}^{i} \left\{ z_j \left(Y_j - \tfrac{1}{2} \right) + \tfrac{1}{2} \right\}, \qquad i = 1, \ldots, n. \tag{2.2}$$

The test statistic of interest has numerator

$$\sum_{j=1}^{n} \left\{ z_j \left(Y_j - \tfrac{1}{2} \right) \right\},$$

which will take extreme values if there are a significantly larger number of

successes on one treatment than on the other treatment, leading to rejection of the hypothesis of equal treatment effects. It can also be thought of as half the difference between the number of balls of the two colors in the urn.

Let $\{b_{jn}\}$, $j = 1, \ldots, n$ be a deterministic triangular array, chosen to make

$$\sum_{j=1}^{n} z_j\left(Y_j - \tfrac{1}{2}\right) = \sum_{j=1}^{n} b_{jn} z_j (Y_j - p_j)$$

for each n. This choice of b_{jn} gives the equivalence of

$$T_n \equiv 2\frac{\sum_{j=1}^{n} z_j\left(Y_j - \frac{1}{2}\right)}{\left(\sum_{j=1}^{n} b_{jn}^2\right)^{1/2}}$$

and W_{nn}, where the array $\{W_{nk}\}$, $k = 1, \ldots, n$, with

$$W_{nk} \equiv 2\frac{\sum_{j=1}^{k} b_{jn} z_j (Y_j - p_j)}{\left(\sum_{j=1}^{n} b_{jn}^2\right)^{1/2}},$$

forms a martingale. It is not difficult to verify that the desired sequence $\{b_{jn}\}$ is given by

$$\begin{aligned} b_{nn} &= 1, \\ b_{jn} &= \prod_{k=j+1}^{n} \left(1 + \frac{z_k}{2\alpha + k - 1}\right), \end{aligned} \tag{2.3}$$

$j = 1, \ldots, n-1$. We can now apply a martingale central limit theorem to W_{nn} in order to establish the asymptotic normality of T_n.

By Corollary 3.1 of Hall and Heyde [(1980), pp. 58–59], under the following two conditions:

$$\max_{1 \le j \le n} b_{jn}^2 \Big/ \sum_{j=1}^{n} b_{jn}^2 \to 0 \quad \text{as } n \to \infty \tag{2.4}$$

and

$$S_n/n \to \tfrac{1}{2} \quad \text{in probability as } n \to \infty, \tag{2.5}$$

[S_n is defined by (2.2)], T_n converges in distribution to a standard normal variate.

Because we are treating the responses $\{z_j\}$ as a deterministic sequence, one could never discern from a finite sample whether (2.4) and (2.5) will hold. Indeed, at one extreme (all $z_j = 1$), we have a Pólya urn model, and neither condition holds; in this case, S_n/n has a beta limit [Athreya and Ney (1972), page 220]. At the other extreme (all $z_j = -1$), we have Bernard Friedman's urn [Friedman (1949)], and asymptotic normality follows from Freedman (1965).

To determine how a "typical" response sequence might behave, consider the $\{z_j\}$ to be realizations of a sample $Z_1, \ldots, Z_n$ from a sequence of centered $(1, -1)$ Bernoulli trials with parameter p. Let random variables $\{B_{jn}\}$ be

defined via (2.3) from the $\{Z_j\}$. It is easy to see, conditioning on $Z_1, \ldots, Z_n$, that under these assumptions,

$$\text{Var}(S_n) = \frac{1}{4} \sum_{i=1}^{n} \prod_{j=i+1}^{n} \left(1 + \frac{2(2p-1)}{2\alpha + j - 1}\right). \tag{2.6}$$

THEOREM 2.1. *When the $\{z_j\}$ are realizations of independent centered Bernoulli trials with success probability p, then*

$$\text{Var}(S_n/n) \to 0 \quad \text{as } n \to \infty \text{ for any } p < 1,$$

where the expectation is taken over the $\{Z_j\}$ and the $\{Y_j\}$.

PROOF. From (2.6),

$$\begin{aligned}
\text{Var}(S_n) &= \frac{1}{4} \sum_{i=1}^{n} \prod_{j=i+1}^{n} \left(1 + \frac{2(2p-1)}{2\alpha + j - 1}\right) \\
&= \frac{1}{4} \sum_{i=1}^{n} \exp\left\{ \sum_{j=i+1}^{n} \ln\left(1 + \frac{2(2p-1)}{2\alpha + j - 1}\right)\right\} \\
&\le \frac{1}{4} \sum_{i=1}^{n} \exp\left\{ 2(2p-1) \sum_{j=i+1}^{n} \left(\frac{1}{2\alpha + j - 1}\right)\right\} \\
&\le \frac{1}{4} \sum_{i=1}^{n} \left\{ \frac{2\alpha + n}{2\alpha + i} \right\}^{4p-2},
\end{aligned}$$

which is $o(n^2)$ for $p < 1$. □

REMARK 1. Note that the rate of convergence of $\text{Var}(S_n)$ is $O(n)$ for $p < 0.75$, $O(n \ln n)$ for $p = 0.75$, and $O(n^{4p-2})$ for $p > 0.75$. The value $p = 0.75$ plays an important role in the next theorem as well.

THEOREM 2.2. *Under the assumptions of Theorem 2.1, if $p < 0.75$,*

$$\max_{1 \le j \le n} B_{jn}^2 \Big/ \sum_{j=1}^{n} B_{jn}^2 \to 0 \quad \text{in probability as } n \to \infty.$$

PROOF. We have that, for $j < n$,

$$B_{jn} = \prod_{k=j+1}^{n} \left(1 + \frac{Z_k}{2\alpha + k - 1}\right),$$

so that

$$|B_{jn}| \le \exp\left\{ \sum_{k=j+1}^{n} \frac{Z_k}{2\alpha + k - 1} \right\}$$

$$= \exp(P_{jn}) \exp\left\{ (2p-1) \sum_{k=j+1}^{n} \frac{1}{2\alpha + k - 1} \right\}, \tag{2.7}$$

where

$$P_{jn} \equiv \sum_{k \equiv j+1}^{n} \frac{Z_k - (2p-1)}{2\alpha + k - 1}.$$

Consider the set

$$A_n \equiv \left\{ \max_{1 \le j < n} P_{jn} > \lambda_n \right\}.$$

By Kolmogorov's inequality, since

$$\operatorname{Var}\left(\sum_{j=a}^{n} \frac{Z_j - (2p-1)}{2\alpha + j - 1} \right) \le 2 \qquad \forall\, a = 1, \ldots, n,$$

we have $P(A_n) \le 16/\lambda_n^2$. On A_n^c, we have from (2.7) that

$$|B_{jn}| \le \exp\{\lambda_n + 1\} \left(\frac{2\alpha + n - 1}{2\alpha + j - 1} \right)^{2p-1}$$

so that

$$\max_{1 \le j \le n} B_{jn}^2 \le \frac{\exp\{2\lambda_n + 2\}}{(2\alpha)^{4p-2}} (2\alpha + n - 1)^{4p-2} + o(n). \tag{2.8}$$

Now

$$E\left\{ \max_{1 \le j \le n} B_{jn}^2 \Big/ \sum_{j=1}^{n} B_{jn}^2 \right\}$$

$$= \int_{A_n} \frac{\max_{1 \le j \le n} B_{jn}^2}{\sum_{j=1}^{n} B_{jn}^2} \, dP + \int_{A_n^c} \frac{\max_{1 \le j \le n} B_{jn}^2}{\sum_{j=1}^{n} B_{jn}^2} \, dP.$$

Let $\lambda_n = \ln(\ln n)$. Since $\max B_{jn}^2 / \sum B_{jn}^2 \le 1$, the first integral does not exceed $P(A_n) \le 16/\lambda_n^2 \to 0$. For the second integral, the numerator of the integrand can be bounded by (2.8). It follows from an argument of Wei, Smythe and Smith [(1986), pp. 272–273] that $\sum B_{jn}^2 \ge nc$ for a constant c. Hence the second integral is

$$\le \frac{1}{cn} E\left\{ \max_{1 \le j \le n} B_{jn}^2 I(A_n^c) \right\}$$

$$\le \frac{\exp\{2\lambda_n + 2\}(2\alpha + n - 1)^{4p-2}}{c(2\alpha)^{4p-2} n} + \frac{o(n)}{n}.$$

This term tends to zero as $n \to \infty$, provided $p < 0.75$. Hence the theorem holds. □

Thus for $p < 0.75$ and for almost every realization of random sequences $\{Z_j\}$ generated in the fashion above, Theorems 2.1 and 2.2 imply that T_n converges to a normal law along a subsequence.

REMARK 2. It is easy to see that the proofs of Theorems 2.1 and 2.2 remain valid for somewhat more general sequences $\{Z_j\}$. If the $\{Z_j\}$ are an independent centered Bernoulli sequence with $P\{Z_j = 1\} = p_j$, Theorem 2.1 holds, provided that, for some $p < 1$, $p_j \to p$ as $j \to \infty$; Theorem 2.2 holds if $p_j \leq p < 0.75$ for all j.

REMARK 3. It can be shown under a population model, such as the Bernoulli sampling assumption, that asymptotic normality fails when $p \geq 0.75$ [Smythe and Rosenberger (1993)].

Extensive simulations were conducted to examine the behavior of the test statistic under the Bernoulli assumption. Simulations were run in Pascal on a mainframe. One hundred sequences $\{Z_j\}$ were generated under the Bernoulli assumption for a particular p, using an algorithm by L'Ecuyer (1988), and then 1000 test statistics were calculated for each sequence $\{Z_j\}$. Values of n were 30, 50 and 100; two values of α (1 and 5) were used. Values of p used

TABLE 1
Proportion of test statistics generated with values in the extreme tails of the normal distribution (100,000 *statistics generated*), $\alpha = 5$

p	Tail probability of normal distribution	Proportion of statistics falling in left (L) or right (R) tail					
		$N = 30$		$N = 50$		$N = 100$	
		L	R	L	R	L	R
0.50	0.01	0.003	0.003	0.004	0.004	0.004	0.004
	0.05	0.024	0.023	0.024	0.023	0.024	0.023
	0.10	0.046	0.047	0.050	0.049	0.050	0.048
	0.20	0.099	0.098	0.100	0.097	0.102	0.097
0.60	0.01	0.003	0.003	0.004	0.004	0.004	0.004
	0.05	0.022	0.023	0.023	0.023	0.024	0.023
	0.10	0.048	0.049	0.048	0.048	0.048	0.049
	0.20	0.103	0.104	0.099	0.099	0.100	0.100
0.75	0.01	0.003	0.003	0.003	0.003	0.003	0.003
	0.05	0.022	0.021	0.022	0.021	0.022	0.022
	0.10	0.049	0.047	0.048	0.048	0.047	0.047
	0.20	0.103	0.101	0.099	0.098	0.099	0.097

were 0.50 to 0.80, incremented by 0.05. Coverage probabilities were calculated and are compared to the nominal significance levels of 0.01, 0.05, 0.10 and 0.20.

For $\alpha = 1$, the test statistic is conservative, very much so in the extreme tails, and only the results for $\alpha = 5$ are given in Table 1. The results are somewhat conservative in the extreme tails, but even for $n = 30$ and $n = 50$, coverage is close to nominal levels.

An attempt was made to ascertain the test statistic's behavior under "average" conditions; 100 sequences $\{Z_j\}$ were generated; for each sequence, Z_j was assumed to be a centered Bernoulli variable with parameter p_j, with p_j ranging linearly from 0.75 to 0.50. Then 1000 test statistics were calculated for each sequence $\{Z_j\}$ and coverage probabilities obtained. Again, conservatism in the extreme tails is noted, with coverage otherwise close to nominal levels.

3. A permutation test statistic for general outcomes. The use of the RPW rule is limited by the assumption of dichotomous responses. If the outcome of interest is a measure of some continuous (or at least polychotomous) quantity, it may still be desirable to use response-adaptive treatment allocation in some circumstances. In this section, we propose a response-adaptive design along with a large sample test statistic based on scores calculated from a general response variable.

For each $j = 1, \ldots, n$, let r_{ij}, for $i \le j$, be the rank of the ith patient based on some outcome variable after j outcomes are available, where a larger rank indicates a better response to treatment. Define scores a_{ij} to be some function of the r_{ij}, $1 \le i \le j \le n$, where $\sum_{i=1}^{j} a_{ij} = 0$, $j = 1, \ldots, n$. Define $a_{ij}^{+} = a_{ij} I(a_{ij} > 0)$, where I is the indicator function, and, as before, let $\mathcal{F}_j = \sigma(Y_1, \ldots, Y_j)$, with Y_j defined as in Section 2. Let

$$\tilde{p}_1 = \tilde{p}_2 = \tfrac{1}{2}$$

and

$$(3.1) \quad \tilde{p}_i = E\left(Y_j | \mathcal{F}_{i-1}\right) = \frac{1}{2}\left(1 + \frac{\sum_{j=1}^{i-1} a_{j,i-1}\left(Y_j - \frac{1}{2}\right)}{\sum_{j=1}^{i-1} a_{j,i-1}^{+}}\right), \qquad i = 3, 4, \ldots .$$

The better the responses of previous patients on treatment A, relative to those on B, the larger will be the probability that the next patient is assigned to A.

Proceeding as before, we define the array $\{\tilde{b}_{jn}\}$ to make

$$\sum_{j=1}^{n} a_{jn}\left(Y_j - \tfrac{1}{2}\right) = \sum_{j=1}^{n} \tilde{b}_{jn}\left(Y_j - \tilde{p}_j\right)$$

for each n. The test statistic

$$\tilde{T}_n \equiv 2\frac{\sum_{j=1}^{n} a_{jn}\left(Y_j - \frac{1}{2}\right)}{\left(\sum_{j=1}^{n} \tilde{b}_{jn}^2\right)^{1/2}}$$

is then equivalent to

$$\tilde{W}_{nn} \equiv 2\frac{\sum_{j=1}^{n}\tilde{b}_{jn}(Y_j - \tilde{p}_j)}{\left(\sum_{j=1}^{n}\tilde{b}_{jn}^2\right)^{1/2}}.$$

In the present case, however, the $\tilde{b}_{jn}$ depend not just on $\{a_{jn}\}$, but also on $\{a_{jk}\}$ for $k < n$. We have

$$\tilde{b}_{jn} = a_{jn} + \sum_{i=j+1}^{n} a_{jn}h_j(i), \tag{3.2}$$

$j = 1, \ldots, n$, where $h_j(i)$ is defined for $i \geq j$ by the recursion

$$h_i(i) \equiv 1,$$

$$h_j(i) = \sum_{k=j}^{i-1} \frac{a_{jk}}{2\sum_{l=1}^{k} a_{lk}^{+}} h_{k+1}(i), \qquad i > j. \tag{3.3}$$

We define

$$\tilde{S}_n \equiv \sum_{j=1}^{n} a_{jn}\left(Y_j - \tfrac{1}{2}\right).$$

The analog of conditions (2.4) and (2.5) are now given. Under the following two conditions,

$$\max_{1\leq j\leq n} \tilde{b}_{jn}^2 \Big/ \sum_{j=1}^{n} \tilde{b}_{jn}^2 \to 0 \quad \text{as } n \to \infty \tag{3.4}$$

and

$$\tilde{S}_n / \sum_{j=1}^{n} a_{jn}^{+} \to 1/2 \quad \text{in probability as } n \to \infty, \tag{3.5}$$

$\tilde{T}_n$ converges in distribution to a standard normal variate.

As before, we cannot guarantee that (3.4) and (3.5) will hold for every conceivable sequence $\{a_{ij}\}$. Thus, as in Section 2, we consider the case of responses generated by a probability mechanism to study the behavior of (3.4) and (3.5) under "average" conditions. Assume now that the responses arise from an independent sequence $X_1, X_2, \ldots$ with a continuous distribution. Let R_{ij} be the rank of the ith patient after j responses are available.

EXAMPLE 3.1 (Simple rank scores). For j even, these are defined by

$$A_{ij} \equiv 8\left(\frac{R_{ij}}{j} - \frac{j+1}{2j}\right), \quad i \leq j = 1, \ldots, n.$$

Let $\tilde{B}_{jn}$ denote the random analog of $\tilde{b}_{jn}$ in (3.2).

THEOREM 3.1. *When the responses are generated from an independent continuous sequence,* $\mathrm{Var}(\tilde{S}_n/n) \to 0$ *as* $n \to \infty$, *where the expectation is taken over both the* $\{Y_j\}$ *and the scores.*

The proof can be found in Rosenberger (1992). Thus (3.5) holds in some average sense. Due to the complicated expression for the $\{\tilde{b}_{jn}\}$ in (3.2) and (3.3), we have not been able to show that (3.4) holds in the same sense; however, as noted below, simulation evidence strongly suggests that (3.4) holds for this case. For an arbitrary rank sequence $\{a_{jn}\}$, it is easy to show that

$$\sum_{j=1}^{n} \tilde{b}_{jn}^2 \geq \delta n \quad \text{for some } \delta > 0,$$

and hence that

$$\max_{\delta n \leq j \leq n} \tilde{b}_{jn}^2 \Big/ \sum_{j=1}^{n} \tilde{b}_{jn}^2 \to 0 \quad \text{as } n \to \infty.$$

Further simulations were designed to check condition (3.4) and the rate of convergence of $\tilde{T}_n$ to normality under the distributional assumption. One hundred sequences of uniform responses were generated for $n = 30$, 50 and 100. For each of these sequences, 1000 test statistics were calculated using the design proposed in this section. The results, shown in Table 2, are conservative in the extreme tails, especially for $n = 30$, but overall, a reasonable approximation to normality is demonstrated. Condition (3.4) appears to be holding at the same rate $[O(n^{-1})]$ as $\{\max A_{jn}^2/\Sigma A_{jn}^2\}$.

EXAMPLE 3.2 (van der Waerden scores) The van der Waerden scores [Lehmann (1975), page 97] are defined by $A_{ij} \equiv \Phi^{-1}\{R_{ij}/(j+1)\}$, where Φ is the standard normal distribution function. For these scores, the behavior of $\{\max \tilde{B}_{jn}^2/\Sigma \tilde{B}_{jn}^2\}$ is even closer to that of $\{\max A_{jn}^2/\Sigma A_{jn}^2\}$ $[O(n^{-1})]$ than for simple ranks, and the analysis corresponding to Table 2 gives almost identical conclusions (not included). It can be shown that Theorem 3.1 holds for van der Waerden scores as well as simple rank scores [Rosenberger (1992)].

TABLE 2
Proportion of test statistics with values in the extreme tails of the normal distribution (100,000 *statistics generated*) *for the simple rank scores*

Tail probability of normal distribution	Proportion of statistics falling in left (L) or right (R) tail					
	$N = 30$		$N = 50$		$N = 100$	
	L	R	L	R	L	R
0.01	0.002	0.002	0.002	0.002	0.003	0.004
0.05	0.018	0.017	0.018	0.019	0.021	0.022
0.10	0.041	0.041	0.043	0.043	0.046	0.047
0.20	0.092	0.092	0.094	0.093	0.095	0.097

4. Conclusions. For dichotomous outcomes, the large-sample permutation test statistic based on the RPW treatment assignments performs well for moderate-sized or large trials when the success rate is less than 0.75. The normal approximation is improved by starting with more than one ball of each color in the urn.

For general outcomes, simple assignment schemes based on ranks leads to a permutation test which, although somewhat conservative, assigns most patients to the better treatment and, on average, gives reasonable approximations to normality in moderate-sized or large trials.

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DEPARTMENT OF STATISTICS / COMPUTER
AND INFORMATION SYSTEMS
THE BIOSTATISTICS CENTER
GEORGE WASHINGTON UNIVERSITY
6110 EXECUTIVE BOULEVARD, SUITE 750
ROCKVILLE, MARYLAND 20852