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A SEQUENTIAL PROBABILITY RATIO TEST USING A BIASED COIN DESIGN

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Consider a sequential probability ratio test comparing two treatments, where each subject receives only one of the treatments. Each subject's treatment assignment is determined by the flip of a biased coin, where the bias serves to balance the number of patients assigned to each treatment. The asymptotic properties of this test are studied, as the sample size approaches infinity. A renewal theorem is given for the joint distribution of the sample size, the imbalance in treatment assignment at the end of the experiment, and the excess over the stopping boundary. This theorem is used to calculate asymptotic expressions for the test's error probabilities.

1. Introduction. In a clinical trial in which two treatments are to be compared, the determination of a suitable method of assigning treatments is an important design problem. It is usually desirable to assign an equal number of subjects to each treatment and to do so in a random manner, to diminish the possibility of bias in the comparison. If subjects arrive one at a time, as in a sequential test, achieving both balance and randomization may be difficult. Efron (1971) and Wei (1978) have proposed the use of a biased coin design: the treatment received by the $(n + 1)$st subject is determined by the flip of a coin which is biased in favor of the treatment to which fewer of the n previous subjects have been assigned. In this paper I study a sequential probability ratio test (SPRT) in which Wei's biased coin design is used. The SPRT's asymptotic properties are studied as the sample size approaches infinity.

The asymptotic properties of a SPRT are well known in the case of i.i.d. observations (cf. Woodroofe, 1982) and in the case of "almost" i.i.d. observations (Lai and Siegmund, 1977). However, in a biased coin design, the observations are in general not i.i.d., nor are they close enough to those in the i.i.d design (flipping a fair coin to determine treatment assignment) to apply the existing theory.

The allocation scheme and the SPRT are defined in Section 2, and the type I and type II error probabilities are expressed in terms of a type of random walk and a stopping time. Section 3 contains a local limit theorem for the joint distribution of the stopping time, the imbalance in assignment at the time of stopping, and the excess over the stopping boundary. This limit theorem is then used to calculate asymptotic expressions for the error probabilities of the SPRT. Sketches of the proofs are given. For details, see Heckman (1982).

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2. A sequential probability ratio test. Let V_i and W_i denote the ith subject's responses to the two treatments. Assume that (V_i, W_i), $i \ge 1$, are independent and identically distributed and V_1 has distribution function F and W_1 has distribution function G. By observing only one response per patient, we will test

$$H_0: F = F_0, \quad G = G_0 \quad \text{versus} \quad H_1: F = F_1, \quad G = G_1$$

where F_0 and F_1 are mutually absolutely continuous, as are G_0 and G_1, with $F_0 \neq F_1$, $G_0 \neq G_1$. The allocation procedure is defined as follows. Let U_i, $i \ge 1$, be i.i.d., uniformly distributed on $[0, 1]$ with $\{U_i\}$ $i \ge 1$ and $\{(V_i, W_i)\}$ $i \ge 1$ independent. Let h be a function from $[-1, 1]$ to $[0, 1]$ satisfying:

(i) h is nonincreasing,
(ii) $h(x) = 1 - h(-x)$,
(iii) $h(x) = ½ + h'(0)x + B(x)x^2$ where $\sup_{|x|\le 1} |B(x)| < \infty$.

Let $D_0 = 0$. Let $\delta_{n+1} = 1$ if $U_{n+1} \le h(D_n/n)$, zero otherwise, where $D_n = \sum_1^n (2\delta_i - 1)$. If $\delta_i = 1$, we observe V_i, otherwise we observe W_i. With this allocation procedure, the nth log likelihood ratio statistic for testing H_0 versus H_1 is

$$S_n = \textstyle\sum_1^n \delta_i X_i + (1 - \delta_i) Y_i \tag{2.1}$$

where $X_i = \log dF_1(V_i)/dF_0$ and $Y_i = \log dG_1(W_i)/dG_0$.

Assume that X_i and Y_i have finite positive variance under H_0 and H_1. For a and b positive, let

$$T = T(a, b) = \inf\{n: S_n > a \text{ or } S_n < -b\}.$$

Since the expectations of X_1 and Y_1 are negative under H_0 and positive under H_1, T is finite almost surely under both hypotheses. The SPRT with boundaries a and b continues testing until T subjects have entered the trial, rejecting H_0 if, at that time, $S_n > a$ and rejecting H_1 if $S_n < -b$.

Suppose that (U_i, V_i, W_i), $i \ge 1$, are defined in the probability space $(\Omega, \mathscr{F}, P)$ and that under H_0, $P = P_0$ and under H_1, $P = P_1$. Let $\mathscr{F}_\infty$ be the sigma algebra generated by $\delta_i X_i + (1 - \delta_i) Y_i$, $i \ge 1$. $\mathscr{F}_n$ is the sigma algebra generated by $\delta_i X_i + (1 - \delta) Y_i$, $1 \le i \le n$. Let

$$\mathscr{F}_T = \{A \in \mathscr{F}_\infty: A \cap \{T = n\} \in \mathscr{F}_n \text{ for all } n\}$$

and

$$P_i^T = P_i \quad \text{restricted to} \quad \mathscr{F}_T, \quad i = 0 \quad \text{or} \quad 1.$$

Then, the probability of a type I error is

$$P_0\{S_T > a\} = \int_{\{S_T > a\}} (dP_0^T/dP_1^T)\, dP_1$$

$$= \int_{\{S_T > a\}} \exp(-S_T)\, dP_1.$$

Let

$$t = t(a) = \inf\{n: S_n > a\} \quad \text{and} \quad R_a = S_t - a. \tag{2.2}$$

t is finite almost surely P_1. Since $\{S_T > a\} \subset \{t = T, S_t = S_T\}$ and $P_1\{S_T > a\} \to 1$ as a and b approach infinity,

$$P_0\{S_T > a\} \sim \exp(-a) \int \exp(-R_a)\, dP_1.$$

Thus, determination of the asymptotic distribution of R_a gives an asymptotic expression for the type I error probability. An asymptotic expression for the type II error probability can be calculated in the same way.

Let

$$\delta_i^0 = 1 \quad \text{if} \quad U_i \le 1/2, \quad \text{zero otherwise},$$

$$S_n^0 = \textstyle\sum_1^n \delta_i^0 X_i + (1 - \delta_i^0) Y_i, \tag{2.3}$$

$$\mu = (EX_1 + EY_1)/2.$$

THEOREM 1. *If $X_1 + Y_2$ is nonlattice, then*

$$P_0\{\textit{reject } H_0\} \sim \gamma_1 \exp(-a)$$

$$P_1\{\textit{reject } H_1\} \sim \gamma_0 \exp(-b)$$

as a and b approach infinity, where

$$\gamma_i = \mu^{-1} \int_0^\infty \exp(-r) P_i\{c_i S_j^0 \ge r \text{ for all } j \ge 1\}\, dr, \quad i = 0 \text{ or } 1,$$

with $c_0 = -1$ and $c_1 = 1$.

The Theorem follows directly from Theorem 2 of Section 3.

3. A renewal theorem. Let h, U_i, δ_i, and D_n be as defined in Section 2. Let (X_i, Y_i), $i \ge 1$, be i.i.d. with the expectations of X_1 and Y_1 positive, and their variances positive and finite. Suppose that $\{U_i\}_{i\ge1}$ and $\{(X_i, Y_i)\}_{i\ge1}$ are independent. Let S_n, $t(a)$, R_a, δ_i^0, S_n^0, and μ be as defined in 2.1 to 2.3. Let $\Delta = (EY_1 - EX_1)/2$, $\sigma^2 = (\text{var } X_1 + \text{var } Y_1)/2$, and $g_a(m, n, A) = P\{t(a) = n, D_t = m, R_a \in A\}$ where A is a subinterval of the reals and $m - n$ is an even integer. Suppose that m, n, and a approach infinity in such a manner that

$$\begin{aligned} n - a/\mu &\sim x(a/\mu)^{1/2} \\ m &\sim y n^{1/2} \end{aligned} \tag{3.1}$$

where $-\infty < x, y < \infty$.

THEOREM 2. *If $X_1 + Y_2$ is nonlattice, then*

$$\lim_{a\to\infty} n g_a(m, n, A) = \mu\sigma^{-1}\phi((\Delta y - \mu x)/\sigma) 2\tau^{-1}\phi(y/\tau) \int_A p(r)\, dr$$

where

$$p(r) = \mu^{-1}P\{S_j^0 \geq r \text{ for all } j \geq 1\}I\{r \geq 0\},$$

ϕ is the standard normal density, and $\tau^2 = (1 - 4h'(0))^{-1}$.

Therefore $((t - a/\mu)(a/\mu)^{-1/2}, t^{-1/2}D_t, R_a)$ converges in distribution to $((\Delta D - \sigma S)/\mu, D, R)$ where D, S, and R are independent, D and S are normally distributed with zero means and variances one and τ^2, respectively, and R has density $p(r)$.

It is now easy to see the effect of the allocation scheme on the stopping rule. For example, suppose that Δ is positive, that is $EY > EX$. Then the mean of $(\Delta D - \sigma S)/\mu$ given D is positive if and only if there has been an imbalance in favor of the X_i's. Observing an excess of the responses with smaller means causes the test to stop later than expected.

Let $0 \leq r_1 < r_2 < \infty$. Write

$$g_a(m, n, (r_1, r_2]) = P\{S_n \in a + (r_1, r_2], S_{n-j} \leq a, 1 \leq j \leq n, D_n = m\},$$

Thus,

$$\underline{f}_a(r_2) \leq g_a(m, n, r_1, r_2) \leq \bar{f}_a(r_1)$$

where

$$\bar{f}_a(r) = P\{S_n \in a + (r_1, r_2], S_n - S_{n-j} > r, 1 \leq j \leq n - 1, D_n = m\}.$$

and

$$\underline{f}_a(r) = P\{S_n \in a + (r_1, r_2], S_n - S_{n-j} \geq r, 1 \leq j \leq n - 1, D_n = m\}.$$

Theorem 2 follows directly from Proposition 1 below, the theory of Riemann integration, and the fact that

$$\int_A P\{S_j^0 \geq r \text{ for all } j \geq 1\}\, dr = \int_A P\{S_j^0 > r \text{ for all } j \geq 1\}\, dr.$$

PROPOSITION 1.

$$\begin{aligned}\lim_{a\to\infty} n\underline{f}_a(r) &= (r_2 - r_1)\mu^{-1}P\{S_j^0 \geq r \text{ for all } j \geq 1\}\\ &\quad \cdot \mu\sigma^{-1}\phi((\Delta y - \mu x)/\sigma)2\tau^{-1}\phi(y/\tau)\\ \lim_{a\to\infty} n\bar{f}_a(r) &= (r_2 - r_1)\mu^{-1}P\{S_j^0 > r \text{ for all } j \geq 1\}\\ &\quad \cdot \mu\sigma^{-1}\phi((\Delta y - \mu x)/\sigma)2\tau^{-1}\phi(y/\tau).\end{aligned}$$

The proof of the proposition is sketched here. For a more detailed proof, see Heckman (1982). Let

$$\begin{aligned}\hat{S}_j &= S_n^0 - S_{n-j}^0\\ \hat{D}_j &= \textstyle\sum_{n-j+1}^{n} (2\delta_i^0 - 1) = D_n^0 - D_{n-j}^0.\end{aligned}$$

Then

$$\underline{f}_a(r) = P\{S_{n-k} + \hat{S}_k \in a + (r_1, r_2], \hat{S}_j \geq r \text{ for all } j \leq k, D_{n-k} + \hat{D}_k = m\} + \varepsilon(a, k)$$

where $\lim_{k\to\infty} \limsup_{a\to\infty} n \mid \varepsilon(a, k) \mid = 0$.

Conditioning on $(\hat{D}_k, \hat{S}_k)$ and using the independence of $\{\hat{D}_k, \hat{S}_j, j \leq k\}$ and $\{D_{n-k}, S_{n-k}\}$ and the stationarity of the process $\{S_j^0\}$, the first term on the right-hand side of the above equation is equal to

$$\int_{s\geq r, |\ell|\leq k} P\{S_{n-k} \in a - s + (r_1, r_2] \mid D_{n-k} = m - \ell\} P\{D_{n-k} = m - \ell\} \cdot P\{S_j^0 \geq r \text{ for all } j \leq k - 1 \mid D_k^0 = \ell, S_k^0 = s\}\, dP\{D_k^0 \leq \ell, S_k^0 \leq s\}$$

By a modified version of Stone's theorem (1965) and Theorem 1 of Heckman (1985)

$$\lim_{a\to\infty} nP\{S_{n-k} \in a - s + (r_1, r_2] \mid D_{n-k} = m - \ell\} P\{D_{n-k} = m - \ell\} = (r_2 - r_1)\sigma^{-1}\phi((\Delta y - \mu x)/\sigma)2\tau^{-1}\phi(y/\tau)$$

if $n - k - (m - \ell)$ and

$$\sup_{s\geq r, |\ell|\leq k} nP\{S_{n-k} \in a - s + (r_1, r_2] \mid D_{n-k} = m - \ell\} P\{D_{n-k} = m - \ell\} < \infty$$

The proposition then follows by the dominated convergence theorem.

4. Remarks. Analogues of Theorems 1 and 2 also hold in the following case. Suppose that X_1, Y_1, and $X_1 + Y_2$ are arithmetic with the arithmetic spans of X_1 and Y_1 integer multiples of the arithmetic span of $X_1 + Y_2$. Suppose that the arithmetic and lattice span of $X_1 + Y_2$ are both equal to λ. (The arithmetic span of a random variable Z is the largest λ such that $\sum_{-\infty}^{\infty} P\{Z = k\lambda\} = 1$. The lattice span of Z is the largest λ such that $\sum_{-\infty}^{\infty} P\{Z = b + k\lambda\} = 1$ for some b. The two types of spans are not necessarily equal.) Then, if m, n, and a satisfy (3.1) and a approaches infinity through multiples of λ,

$$nP\{t = n, D_n = m, R_a = J\lambda\} \to \mu\sigma^{-1}\phi((\Delta y - \mu x)/\sigma)2\tau^{-1}\phi(y/\tau)\lambda p(J\lambda)$$

where p is as defined in Theorem 2. Thus, Theorem 1 holds with

$$\gamma_i = \lambda\mu^{-1} \sum_{J=1}^{\infty} P\{c_i S_j^0 \geq J\lambda \text{ for all } j \geq 1\}.$$

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