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ESTIMATION FOLLOWING SEQUENTIAL TESTS INVOLVING DATA-DEPENDENT TREATMENT ALLOCATION

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Abstract: A sequential test is considered in which two treatments are compared and treatment allocation is data-dependent. Brownian motion approximations are obtained for the bias and variance of the maximum likelihood estimator of treatment difference at the end of the trial. For normal responses, simulation indicates that the approximations work well for several data-dependent allocation rules.

Key words and phrases: Brownian motion, clinical trial, correction for overshoot, data-dependent allocation rule, Gittins index, stopping time.

1. Introduction

Suppose a clinical trial is conducted in which patients can be allocated to one of two treatments A or B. We assume that the response variable for treatment i at time j, $\mathbf{X}_{ij}$ $(j = 0, 1, \ldots)$, is normally distributed with mean μ_i and variance unity. Interest lies in testing $H_0 : \mu < 0$ against $H_1 : \mu > 0$, where $\mu = \mu_B - \mu_A$. For this, Robbins and Siegmund (1974) derived the following sequential test.

Choose $b > 0$, and at stage (m, n), that is, after m patients have been allocated to treatment A and n to treatment B, let

$$z_{m,n} = \frac{mn}{(m+n)}(\overline{x}_{Bn} - \overline{x}_{Am}), \tag{1}$$

where $\overline{x}_{Am}$ and $\overline{x}_{Bn}$ are the sample means on treatments A and B, respectively. Let (M, N) be the first (m, n) such that $z_{m,n} \notin (-b, b)$. Then for $M + N < \infty$, we accept H_0 or H_1 according as $z_{m,n} \leq -b$ or $\geq b$, respectively. Robbins and Siegmund showed that for this test the error probability is approximately independent of the allocation rule used. For a generalisation of this test, see Coad (1991).

Upon termination of the test, our data consist of M responses from treatment A and N from treatment B. The maximum likelihood estimator of treatment difference is $\hat{\mu} = \overline{x}_{BN} - \overline{x}_{AM}$. If M and N were fixed sample sizes, $\hat{\mu}$ would be unbiased. However, because $M + N$ is a stopping time, $\hat{\mu}$ is biased. The purpose of this paper is to derive approximations for the bias and variance of

$\hat{\mu}$ by considering the sequential test in continuous time. The work provides a generalisation of Bather and Coad (1992), where only pairwise allocation was studied.

We begin in Section 2 by considering the sequence $\{z_{m,n}\}$ as a Brownian motion process. General expressions are then obtained for the bias and variance of a randomly stopped process. A simple modification is described which corrects for the effect of overshoot of the stopping boundaries in the discrete-time case. In Section 3, the approximations are compared with simulated values for three data-dependent allocation rules. The paper concludes with some remarks on the use of the approximations for nonnormal responses, the correction of $\hat{\mu}$ for bias and the calculation of approximations for general sequential tests.

2. Brownian Motion Approximations for the Bias and Variance

Let $\{W(t), t \geq 0\}$ be a Brownian motion with positive drift μ and variance one per unit time, and define the stopping time

$$T = \inf\{t : |W(t)| = b\}.$$

Then it is well known that the density function of T can be expressed as a linear combination of inverse Gaussian densities. This result, together with the following lemma due to Robbins and Siegmund (1974), form the basis for our approximations for the bias and variance of $\hat{\mu}$.

Lemma 1. *For any sequence of pairs (m, n) of positive integers, nondecreasing in each coordinate, the random sequences $\{z_{m,n}\}$ and $\{W(mn/(m+n))\}$ have the same joint distributions.*

The derivation of the approximate bias and variance of $\hat{\mu} = \overline{x}_{BN} - \overline{x}_{AM}$ can be simplified by using the following property.

Lemma 2. *Let $T = \inf\{t : |W(t)| = b\}$. Then $W(T)$ and T are independent.*

Proof. Let P_μ denote a probability measure on the space of paths generated by a Brownian motion with drift μ and variance one per unit time. Then we can write

$$\begin{aligned} P_\mu\{T \in dt, W(T) = b\} &= \int_{\{T \in dt, W(T)=b\}} \frac{dP_\mu}{dP_{-\mu}} dP_{-\mu} \\ &= e^{2b\mu} P_{-\mu}\{T \in dt, W(T) = b\}, \end{aligned}$$

by using the fact that $dP_\mu \propto \exp\{\mu W(t) - \frac{1}{2}\mu^2 t\}$. Now, by symmetry, $P_{-\mu}\{T \in dt, W(T) = b\} = P_\mu\{T \in dt, W(T) = -b\}$. It follows that

$$P_\mu\{W(T) = b \,|\, T \in dt\} = e^{2b\mu} P_\mu\{W(T) = -b \,|\, T \in dt\},$$

and hence $P_\mu\{W(T) = b \,|\, T \in dt\} = e^{2b\mu}/(1+e^{2b\mu})$, which does not depend on t. This completes the proof of the lemma.

In the continuous-time case, $\hat{\mu} = W(T)/T$, and the bias and variance can be calculated exactly. For discrete time, it follows from the proof of Lemma 2 that, neglecting any overshoot of the stopping boundaries, $z_{M,N}$ and $MN/(M+N)$ are independent. So our approximations for the bias and variance of $\hat{\mu} = \overline{x}_{BN} - \overline{x}_{AM}$ will be no-overshoot approximations. However, as we shall see later, a simple modification can be made to correct for the effect of overshoot.

An expression for the mean of $\hat{\mu}$ can be calculated by using a general theorem due to Woodroofe (1990). The following theorem summarises his result and gives the corresponding expression for the variance.

Theorem. *Suppose that $X_1, X_2, \ldots$ are independent random variables with a common density*

$$f(x;\theta) = \exp\{\theta x - \psi(\theta)\}.$$

This exponential form is valid for real values of the parameter θ in an open interval Ω, and ψ is an analytic function on this interval. Let $S_n = X_1 + \cdots + X_n$, and let $N \geq 1$ be any stopping time. Then

$$E_\theta\left(\frac{S_N}{N}\right) = \psi'(\theta) + \frac{\partial}{\partial\theta}E_\theta\left(\frac{1}{N}\right) \tag{2}$$

and

$$\mathrm{Var}_\theta\left(\frac{S_N}{N}\right) = \frac{\partial}{\partial\theta}E_\theta\left(\frac{S_N}{N^2}\right) - \psi'(\theta)\frac{\partial}{\partial\theta}E_\theta\left(\frac{1}{N}\right) - \left\{\frac{\partial}{\partial\theta}E_\theta\left(\frac{1}{N}\right)\right\}^2. \tag{3}$$

Proof. The first assertion is proved in Woodroofe's paper. To prove the second assertion, write

$$\mathrm{Var}_\theta\left(\frac{S_N}{N}\right) = E_\theta\left[\left\{\frac{S_N}{N} - \psi'(\theta)\right\}^2\right] - \left[E_\theta\left\{\frac{S_N}{N} - \psi'(\theta)\right\}\right]^2.$$

Let $L_n(\omega) = \exp\{\omega S_n - n\psi(\omega)\}$ for all $\omega \in \Omega$ and $n = 1, 2, \ldots$. Then we have

$$\frac{1}{n}L'_n(\omega) = \left\{\frac{S_n}{n} - \psi'(\omega)\right\}L_n(\omega) \tag{4}$$

and

$$\left\{\frac{S_n}{n} - \psi'(\omega)\right\}^2 L_n(\omega) = \frac{1}{n^2}L''_n(\omega) + \psi''(\omega)\frac{1}{n}L_n(\omega). \tag{5}$$

Further, let $\theta_0 \in \Omega$ with $\theta_0 < \theta$ and, for each $n \geq 1$, let B_n denote the set of all vectors $(x_1, \ldots, x_n)$ representing the first n observations in a sequence that stops at $N = n$. Then

$$E_\omega\left[\left\{\frac{S_N}{N} - \psi'(\omega)\right\}^2\right] = \sum_{n=1}^{\infty}\int_{B_n}\left\{\frac{S_n}{n} - \psi'(\omega)\right\}^2 L_n(\omega)dv_n,$$

where $dv_n = dx_1 dx_2 \cdots dx_n$. Thus, from (5)

$$\int_{\theta_0}^{\theta} E_\omega\left[\left\{\frac{S_N}{N} - \psi'(\omega)\right\}^2\right] d\omega = \int_{\theta_0}^{\theta} \sum_{n=1}^{\infty} \int_{B_n} \left\{\frac{S_n}{n} - \psi'(\omega)\right\}^2 L_n(\omega) dv_n d\omega$$

$$= \int_{\theta_0}^{\theta} \sum_{n=1}^{\infty} \int_{B_n} \frac{1}{n^2} L_n''(\omega) dv_n d\omega + \int_{\theta_0}^{\theta} \psi''(\omega) \sum_{n=1}^{\infty} \int_{B_n} \frac{1}{n} L_n(\omega) dv_n d\omega$$

$$= \sum_{n=1}^{\infty} \int_{B_n} \frac{1}{n^2}\{L_n'(\theta) - L_n'(\theta_0)\} dv_n + \int_{\theta_0}^{\theta} \psi''(\omega) E_\omega\left(\frac{1}{N}\right) d\omega. \tag{6}$$

Using (4), observe that the first term in (6) becomes

$$E_\theta\left(\frac{S_N}{N^2}\right) - \psi'(\theta) E_\theta\left(\frac{1}{N}\right) - E_{\theta_0}\left(\frac{S_N}{N^2}\right) + \psi'(\theta_0) E_{\theta_0}\left(\frac{1}{N}\right).$$

By differentiating (6) with respect to θ, the second assertion of the theorem follows immediately.

From Lemma 1, expressions (2) and (3) can be used as approximations for the mean and variance of $\hat{\mu} = \overline{x}_{BN} - \overline{x}_{AM}$ by replacing S_N by $z_{M,N}$ and N by $MN/(M+N)$. Using the martingale property of the sequence $\{z_{m,n} - mn\mu/(m+n),\ m, n = 1, 2, \ldots\}$ established by Robbins and Siegmund (1974) and the independence, apart from overshoot, of $z_{M,N}$ and $MN/(M+N)$ implied by Lemma 2, we obtain

$$E(\hat{\mu}) \simeq \mu + \frac{\partial}{\partial \mu} E\left(\frac{1}{\frac{MN}{M+N}}\right) \tag{7}$$

and

$$\mathrm{Var}(\hat{\mu}) \simeq \frac{\partial}{\partial \mu}\left[\mu E\left(\frac{MN}{M+N}\right) E\left\{\frac{1}{\left(\frac{MN}{M+N}\right)^2}\right\}\right] - \mu \frac{\partial}{\partial \mu} E\left(\frac{1}{\frac{MN}{M+N}}\right)$$
$$- \left\{\frac{\partial}{\partial \mu} E\left(\frac{1}{\frac{MN}{M+N}}\right)\right\}^2. \tag{8}$$

Furthermore, Robbins and Siegmund (1974) have shown that for $\mu > 0$,

$$E\left(\frac{MN}{M+N}\right) \simeq \frac{b}{\mu}\left(\frac{1 - e^{-2b\mu}}{1 + e^{-2b\mu}}\right), \tag{9}$$

where the approximation is due only to overshoot of the stopping boundaries. Approximations for the first two negative moments of $MN/(M+N)$ can be obtained by approximating the distribution of $MN\,/\,(M+N)$ by the distribution of the first time that the Brownian motion $W(t)$ exits from $(-b, b)$. Specifically, by putting $\sigma = 1.0$ in (4.8) and (4.9) of Bather and Coad (1992), we have

$$E\left(\frac{1}{\frac{MN}{M+N}}\right) \simeq \left(e^{b\mu} + e^{-b\mu}\right)\left\{\frac{\mu}{b}\sum_{i=1}^{\infty}\frac{(-1)^{i+1}}{(2i-1)}e^{-(2i-1)b\mu} + \frac{1}{b^2}\sum_{i=1}^{\infty}\frac{(-1)^{i+1}}{(2i-1)^2}e^{-(2i-1)b\mu}\right\}, \tag{10}$$

$$E\left\{\left(\frac{1}{\frac{MN}{M+N}}\right)^2\right\} \simeq \left(e^{b\mu} + e^{-b\mu}\right)\left\{\frac{\mu^2}{b^2}\sum_{i=1}^{\infty}\frac{(-1)^{i+1}}{(2i-1)^2}e^{-(2i-1)b\mu} + \frac{3\mu}{b^3}\sum_{i=1}^{\infty}\frac{(-1)^{i+1}}{(2i-1)^3}e^{-(2i-1)b\mu} + \frac{3}{b^4}\sum_{i=1}^{\infty}\frac{(-1)^{i+1}}{(2i-1)^4}e^{-(2i-1)b\mu}\right\}. \tag{11}$$

In each case, the approximation in (10) and (11) is due to the above approximation and also to overshoot of the stopping boundaries.

By substituting (10) in (7), it follows from (4.14) of Bather and Coad (1992) that

$$E(\hat{\mu}) \simeq \mu + \frac{1}{b} + 4\mu\sum_{i=1}^{\infty}\frac{(-1)^i i}{(4i^2-1)}e^{-2ib\mu} + \frac{2}{b}\sum_{i=1}^{\infty}(-1)^i\frac{(4i^2+1)}{(4i^2-1)^2}e^{-2ib\mu}.$$

The variance formula (8) can be evaluated by using (9), (10) and (11). However, in general, no simple expression is available.

The above expressions for the mean and variance of μ do not depend on the data-dependent allocation rule used. Thus, for the stopping rule considered in this paper, we can use a data-dependent allocation rule instead of equal allocation, knowing that the estimation bias and the precision of our estimator of treatment difference are approximately unchanged. These conclusions are reasonable because the error probability for the test is approximately independent of the allocation rule used.

Our expressions for the bias and variance of $\hat{\mu}$ have been derived using a continuous-time approximation. At this point, it is natural to ask whether any correction can be made for the effect of overshoot in discrete time. Results of Siegmund (1985, Chap. X) suggest that better numerical accuracy in discrete time is obtained by replacing b by $b + \rho(\mu)$, where

$$\rho(\mu) = \lim_{b\to\infty} E(z_{M,N} - b). \tag{12}$$

Now, the right-hand side of (12) can be approximated by $0.583\sqrt{\Delta(\mu)}$, where $\Delta(\mu)$ denotes the limiting interval between successive values of $mn/(m+n)$. For simplicity, we have taken $M \simeq N$, in which case $\sqrt{\Delta(\mu)} \simeq \frac{1}{2}$. As we shall see in the next section, there is a substantial improvement in accuracy of these modified approximations over the direct Brownian motion approximations.

3. Simulation Results

Three data-dependent allocation rules were considered. These are briefly described below. For details of some of their properties, see Robbins and Siegmund (1974) and Coad (1991).

The Robbins and Siegmund rule (RS). For this rule, choose a constant $c \geq b$ and initially allocate one patient to each treatment; subsequently, allocate the next patient to treatment B if $(n-m)/(m+n) \leq z_{m,n}/c$; otherwise, allocate to treatment A.

Proportionate randomisation rule (PR). This rule is based on the standardised estimated treatment difference $\hat{\mu}_s = \sqrt{\{mn/(m+n)\}}\hat{\mu}$. The rule is: initially allocate one patient to each treatment; subsequently, if $|\hat{\mu}_s| < 2$, randomise equally to the two treatments; otherwise, randomise in the proportions $1:2$ or $2:1$ to treatments A and B, respectively, according to whether $\hat{\mu}_s > 2$ or $\hat{\mu}_s < -2$.

The Gittins rule (GS). For a given discount factor $a \in (0,1)$ and given independent normal priors for the μ_i $(i = A, B)$, the Gittins index for treatment i is defined as

$$\sup_{\tau>0} \frac{E\left(\sum_{j=0}^{\tau-1} a^j X_{ij}\right)}{E\left(\sum_{j=0}^{\tau-1} a^j\right)},$$

where τ is any stopping time. The Gittins rule is based on these indices for a normal response variable with known variance. The rule is: initially, allocate one patient to each treatment; subsequently, if $m^r < n$ or $n^r < m$ $(r \geq 1)$, allocate the next patient to treatment A or B, respectively; otherwise, allocate the next patient to the treatment which currently has the larger Gittins index, randomising in the case of ties.

We performed 10,000 simulations of the sequential test defined by statistic (1) and computed the empirical bias and variance of $\hat{\mu} = \overline{x}_{BN} - \overline{x}_{AM}$ by averaging over the simulations. Results for the three data-dependent allocation rules described above are presented in Table 1. The boundary b is 6. The value of c for the Robbins and Siegmund rule is 6, and the discount factor and r for the Gittins rule are 0.99 and 1.5, respectively. The first column of approximations in Table 1 corresponds to the direct Brownian motion approximations derived in Section 2 while the second column corresponds to the modified approximations described at the end of Section 2. Note that the standard errors of the estimated biases are approximately 0.004 and the standard errors of the estimated variances are between 1% and 2%.

Table 1. Approximate and simulated values for the bias and variance of $\hat{\mu} = \overline{x}_{BN} - \overline{x}_{AM}$.

(a) Bias

μ	Brownian approximation	Modified approximation	RS	PR	GS
0.05	0.0407	0.0407	0.0394	0.0363	0.0389
0.075	0.0596	0.0593	0.0637	0.0581	0.0615
0.1	0.0768	0.0763	0.0734	0.0762	0.0760
0.17	0.1149	0.1129	0.1171	0.1111	0.1120
0.25	0.1412	0.1373	0.1385	0.1320	0.1252
0.375	0.1591	0.1529	0.1554	0.1516	0.1527
0.5	0.1646	0.1574	0.1625	0.1519	0.1606
0.75	0.1665	0.1589	0.1587	0.1579	0.1566
1.0	0.1667	0.1589	0.1572	0.1602	0.1563
2.0	0.1667	0.1589	0.1466	0.1390	0.1510

(b) Variance

μ	Brownian approximation	Modified approximation	RS	PR	GS
0.05	0.1617	0.1468	0.1465	0.1421	0.1533
0.075	0.1581	0.1433	0.1419	0.1395	0.1403
0.1	0.1538	0.1390	0.1468	0.1421	0.1359
0.17	0.1406	0.1267	0.1325	0.1244	0.1244
0.25	0.1306	0.1181	0.1208	0.1136	0.1131
0.375	0.1305	0.1199	0.1201	0.1212	0.1147
0.5	0.1430	0.1330	0.1330	0.1297	0.1333
0.75	0.1809	0.1700	0.1666	0.1625	0.1713
1.0	0.2223	0.2095	0.2068	0.2027	0.2073
2.0	0.3889	0.3684	0.3604	0.3462	0.3597

RS, Robbins and Siegmund rule; PR, proportionate randomisation rule; GS, Gittins rule.

We see from Table 1 that the direct Brownian motion approximations tend to overestimate the true values. The effect is more noticeable when μ is large. In many cases, the modified approximations provide substantial improvements. For example, when $\mu = 1.0$ the true variance is about 0.205. The direct Brownian motion approximation gives 0.2223, but the modified approximation yields 0.2095. By comparing the three allocation rules, we see that the particular data-dependent allocation rule has little effect upon the bias and variance of $\hat{\mu}$.

4. Concluding Remarks

In this paper, we have obtained approximations for the bias and variance of the maximum likelihood estimator of treatment difference following a sequential test in which response is normal. When response is nonnormal, we can use large-sample theory to construct suitable sequential tests. This has been shown for Bernoulli responses by Whitehead (1978), while exponential responses, where there is the possibility of censoring, are treated by Coad (1994). For these tests, approximations for the bias and variance can also be obtained by using formulae (2) and (3): S_N would now be replaced by the new test statistic and N by some measure of information.

It was shown in Section 3 that the approximations for the bias and variance work well. In fact, little accuracy is lost by using only the first two terms in the series in (10) and (11). Moreover, we can use these terms to correct our estimate for bias: for further details, see Whitehead (1986).

We have restricted our attention to sequential tests with horizontal stopping boundaries. Approximations for more general tests, such as those with converging or diverging stopping boundaries, may also be obtained. For some work in this direction, see Bather and Coad (1992).

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