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Generalized Delayed Response in Randomized Play-the-Winner Rule

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ABSTRACT

In clinical trials, a particular patient's response may be delayed in the sense that it is not obtained before the entrance of the next patient. Delayed responses are particularly important in the context of adaptive trials where the allocations are done on the basis of the available responses. Bandyopadhyay and Biswas (Bandyopadhyay, U., Biswas, A. (1996). Delayed response in randomized play-the-winner rule: a decision theoretic outlook. *Calcutta Statistical Association Bulletin* 46:69–88) and Biswas (Biswas, A. (1999). Delayed response in randomized play-the-winner rule revisited. *Comm. Statist. Simul. Comput.* 28:715–731) have studied a simple delayed response model in the context of the randomized play-the-winner rule (RPW), a popular adaptive design, originally developed by Wei and Durham (Wei, L. J., Durham, S. (1978). The randomized play-the-winner rule

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in medical trials. *J. Am. Statist. Assoc.* 73:838–843) and Wei (Wei, L. J. (1979). The generalized Polya's urn for sequential medical trials. *Ann. Statist.* 7:291–296). The present article provides a generalized model for the delayed response in the RPW rule. The model is then theoretically developed and the exact and limiting proportion of patients allocated to the two treatments are obtained. The exact expression of the variance of the proportion of allocation is also obtained.

Key Words: Delayed response; Markov chain; Proportion of allocation; Randomized play-the-winner rule.

1. INTRODUCTION

1.1. Randomized Play-the-Winner Rule

For comparing two treatments in a clinical trial with a sequential chain of patient entry, the problem of allocating the entering patients among the two competing treatments is of great importance. In a clinical trial with human beings as experimental subjects the ethical question is prime and it is necessary to have a sampling design which allocates a larger number of patients to the better treatment during the course of sampling. Recently Yao and Wei (1996) described a clinical trial by Connor et al. (1994) that was intended to compare the antiviral therapy AZT to the placebo group to measure the risk of maternal-to-infant HIV transmission. By a standard randomization scheme, 238 pregnant women received AZT and 238 received placebo. As a result 60 newborns were HIV-positive in the placebo group and only 20 newborns were HIV-positive in the AZT group. The feeling is that many newborns would have been saved if they were treated by AZT which could easily be done if an appropriate adaptive design were adopted.

Zelen (1969) made the first major breakthrough towards this direction. He introduced the concept of the "play-the-winner" (PW) rule for dichotomous responses of the study subjects. By this PW rule a success by a treatment results in the next patient being assigned to the same treatment. The first patient is treated by either treatment by tossing a fair coin. Modifying Zelen's (1969) PW rule, Wei and Durham (1978) and Wei (1979) introduced the concept of "randomized play-the-winner" (RPW) rule. Let us illustrate the rule by an urn model as follows:

Initially the urn contains α balls of type A and α balls of type B. Every entering patient is treated by drawing a ball from the urn. If the response is a success we add an additional β balls of the same kind by

which the patient is treated. On the other hand, if the response is a failure we add an additional β balls of the opposite kind. For a given (α, β), this rule is denoted by RPW(α, β). Clearly, the urn composition is skewed in favor of A if treatment A is doing better, and a larger proportion of patients is treated by the better treatment in the course of sampling (see Bandyopadhyay and Biswas, 1997a; 1997b). Some recent work on the RPW rule is due to Matthews and Rosenberger (1997), Rosenberger (1993), and Rosenberger and Lachin (1993), among others.

Some practical applications of the RPW rule are of course there. Bartlett et al. (1985) reported the use of RPW in the Michigan extra-corporeal membrane oxygenation (ECMO) trial to treat newborns with respiratory failure. The RPW rule was recently used in a trial of fluoxetine in depression by Tamura et al. (1994).

1.2. Scope of the Present Paper

In much of the work concerning clinical trials authors have assumed instantaneous patient response. But, in practice, we may often face a delayed response, i.e., a particular patient's response may not be obtained before the entry of the next patient. Tamura et al. (1994) described an actual clinical trial with delayed response. Delayed response is particularly important and of interest in the settings of an adaptive clinical trial. In an adaptive trial any patient is allocated to either of the competing treatments on the basis of the past responses, and if some of the past responses are not available the task becomes more difficult as we are to decide how the available information can be used in an optimal manner.

Both in Bandyopadhyay and Biswas (1996) and Biswas (1999) a simple probability model for the distribution of delay was assumed where the delay is independent of the treatment or the final response. If π_t is the probability of obtaining a response within t time lags, they assumed the sequence $\{\pi_t, t \geq 1\}$ is non-decreasing with $\pi_t \to 1$ as $t \to \infty$. That model is, of course, a very crude assumption. In practice, π_t's may well be a function of the particular treatment applied and the ultimate response, and this should be incorporated into the model. In the present article a more generalized model for π_t is considered and it is shown that every general function can be reduced to our assumed form. In Sec. 2, we find the expression for the exact and limiting proportion of patients treated by each of the treatments. The expression for the exact variance of the proportion of patients treated by the treatments is also obtained. In Sec. 3, we provide a note on the delayed response indicator variables, and the theoretical construction of their probability distributions. Finally Sec. 4 ends with a discussion.

2. MODELING THE PROBABILITIES OF RESPONSE

2.1. Two Different Models in Delayed Response

First, corresponding to the i-th entering patient we define a set $\{\delta_i, Z_i, \epsilon_{1i}, \epsilon_{2i}, \ldots, \epsilon_{i-1i}\}$ of indicator variables as follows:

$\delta_i = 1$ if treatment A is assigned or 0 if treatment B is applied following a delayed response RPW(α, β) scheme of sampling,

$Z_i = 1$ if the i-th patient experiences a success or 0 if a failure occurs, and $\epsilon_{ji} = 1$ if the response of the j-th patient is obtained before the entry of the i-th patient, $j = 1, \ldots, i-1$, and 0 otherwise.

There are two existing models for possible application of delayed response. First, based on the Wei (1988) model, the conditional probability that $\delta_{i+1} = 1$ given all of the previous assignments $\{\delta_j, 1 \le j \le i\}$, responses $\{Z_j, 1 \le j \le i\}$ and all of the indicator response statuses $\{\epsilon_{ji+1}, 1 \le j \le i\}$ is:

$$P(\delta_{i+1} = 1 | \delta_1, \ldots, \delta_i, Z_1, \ldots, Z_i, \epsilon_{1i+1}, \ldots, \epsilon_{ii+1}) = \left\{ \alpha + \beta \left(2 \sum_{j=1}^{i} \epsilon_{ji+1} \delta_j Z_j + \sum_{j=1}^{i} \epsilon_{ji+1} - \sum_{j=1}^{i} \epsilon_{ji+1} \delta_j - \sum_{j=1}^{i} \epsilon_{ji+1} Z_j \right) \right\} \Bigg/ \left(2\alpha + \beta \sum_{j=1}^{i} \epsilon_{ji+1} \right). \tag{2.1}$$

As the denominator of Eq. (2.1) is random, it is not easy to handle the model mathematically to compute the unconditional probabilities. To circumvent this difficulty Bandyopadhyay and Biswas (1996) (henceforth we call it BB) introduced a delayed response model where we add $\beta/2$ balls of both kinds into the urn for a non-response (somewhat similar to the idea of adding fractional balls of Andersen et al., 1994). When the corresponding response is obtained in a subsequent stage we withdraw these $\beta/2$ balls of each kind and add β balls accordingly by noting the success or failure and the treatment by which the patient was treated. By this rule we have

$$P(\delta_{i+1} = 1 | \delta_1, \ldots, \delta_i, Z_1, \ldots, Z_i, \epsilon_{1i+1}, \ldots, \epsilon_{ii+1}) = \left\{ \alpha + \beta \left(2 \sum_{j=1}^{i} \epsilon_{ji+1} \delta_j Z_j + \frac{1}{2} \left(i + \sum_{j=1}^{i} \epsilon_{ji+1} \right) - \sum_{j=1}^{i} \epsilon_{ji+1} \delta_j - \sum_{j=1}^{i} \epsilon_{ji+1} Z_j \right) \right\} \Big/ (2\alpha + i\beta), \tag{2.2}$$

which has a non-random denominator. Biswas (1999), while revisiting BB (1996), has shown that there is no significant difference between the performances of these two models in the exact set-up and that they are asymptotically equivalent. Hence in the present article we consider the BB (1996) model only.

In both in BB (1996) and Biswas (1999) it was assumed that

$$P(\epsilon_{jj+t} = 1 | \delta_j, Z_j) = \pi_t,$$

which is independent of δ_j, Z_j.

2.2. The Model

In many situations it is reasonable to assume different pattern of delay in response for different treatments—some treatments provide quicker responses than other treatments. Similarly, often a failure can be quickly obtained than a success. Here we consider the generalized model:

$$q_t(j) = P(\epsilon_{jj+t} = 1 | \delta_j, Z_j) = \pi_t^{(1)} - \delta_j \pi_t^{(2)} - Z_j \pi_t^{(3)} - \delta_j Z_j \pi_t^{(4)} = x_j' \theta, \tag{2.3}$$

where

$$x_j' = (1, \delta_j, Z_j, \delta_j Z_j), \theta' = (\pi_t^{(1)}, -\pi_t^{(2)}, -\pi_t^{(3)}, -\pi_t^{(4)}).$$

Here we assume that $q_t(j) \to 1$ as $t \to \infty$, and $\{q_t(j), t \geq 1\}$ is a non-decreasing sequence, which is ensured if $\{\pi_t^{(1)}, t \geq 1\}$ is a non-decreasing sequence and

$$\pi_t^{(1)} \to 1 \text{ as } t \to \infty \text{ along with } \pi_t^{(s)} \to 0 \text{ as } t \to \infty, \quad s = 2, 3, 4. \tag{2.4}$$

Writing

$$P(\delta_j = 1) = \frac{1}{2} + d_j,$$
$$P(Z_j = 1 | \delta_j = k) = p_{2-k}, \quad k = 1, 0,$$

the unconditional probability is

$$P(\epsilon_{jj+t} = 1) = E(\epsilon_{jj+t}) = A_{1t} + B_{1t} d_j, \tag{2.5}$$

where

$$A_{1t} = \pi_t^{(1)} - \frac{1}{2}\pi_t^{(2)} - \frac{1}{2}(p_1 + p_2)\pi_t^{(3)} - \frac{1}{2}p_1\pi_t^{(4)},$$
$$B_{1t} = -\pi_t^{(2)} - (p_1 - p_2)\pi_t^{(3)} - p_1\pi_t^{(4)}.$$

Subsequently in Sec. 3, it is shown that any other functional form of $q_t(j)$ can be reduced as in Eq. (2.3).

2.3. Expected Proportion of Allocation

As in Eq. (2.6) we obtain

$$E(\epsilon_{jj+t}\delta_j) = A_{2t} + B_{2t}d_j,$$
$$E(\epsilon_{jj+t}Z_j) = A_{3t} + B_{3t}d_j,$$
$$E(\epsilon_{jj+t}\delta_j Z_j) = A_{4t} + B_{4t}d_j,$$

where

$$A_{2t} = \frac{1}{2}\left\{\pi_t^{(1)} - \pi_t^{(2)} - p_1\pi_t^{(3)} - p_1\pi_t^{(4)}\right\},$$
$$A_{3t} = \frac{1}{2}(p_1 + p_2)\left(\pi_t^{(1)} - \pi_t^{(3)}\right) - \frac{1}{2}p_1\pi_t^{(2)} - \frac{1}{2}p_1\pi_t^{(4)},$$
$$A_{4t} = \frac{1}{2}p_1\left(\pi_t^{(1)} - \pi_t^{(2)} - \pi_t^{(3)} - \pi_t^{(4)}\right),$$
$$B_{2t} = \pi_t^{(1)} - \pi_t^{(2)} - \pi_t^{(3)} - \pi_t^{(4)},$$
$$B_{3t} = (p_1 - p_2)\left(\pi_t^{(1)} - \pi_t^{(3)}\right) - p_1\pi_t^{(2)} - p_1\pi_t^{(4)},$$
$$B_{4t} = p_1\left(\pi_t^{(1)} - \pi_t^{(2)} - \pi_t^{(3)} - \pi_t^{(4)}\right).$$

Hence, using model (2.2), it can be recursively shown that for $i \geq 1$,

$$P(\delta_{i+1} = 1) = \frac{1}{2} + d_{i+1},$$

where

$$d_{i+1} = \frac{\beta}{2\alpha + i\beta}\sum_{j=1}^{i}\left(2A_{4i+1-j} + \frac{1}{2}A_{1i+1-j} - A_{2i+1-j} - A_{3i+1-j}\right)$$
$$+ \frac{\beta}{2\alpha + i\beta}\sum_{j=1}^{i}\left(2B_{4i+1-j} + \frac{1}{2}B_{1i+1-j} - B_{2i+1-j} - B_{3i+1-j}\right)d_j, \quad (2.6)$$

with $d_1 = 0$, from the initial composition of the urn. If n patients are treated by a delayed response RPW rule, the proportion of patients treated by treatment A is $n^{-1}\sum_{i=1}^{n}\delta_i$, and the expected proportion is

$$P_A = \frac{1}{n}E\left(\sum_{i=1}^{n}\delta_i\right) = \frac{1}{2} + \frac{1}{n}\sum_{i=1}^{n}d_i.$$

It is to be noted that $P_B = 1 - P_A$. Figures 1 and 2 provide the computation of P_A for different (p_1, p_2) and two different delayed response models to be described in Sec. 3. Some computational results are also presented in Table 1. Note that as $q_t(j)$ is a function of δ_j, P_A may not be equal to P_B even when $p_1 = p_2$ (which is supported by our computation). However, the difference is very small, and this slender discrepancy is due to the fact that the response pattern of the two treatments is unequal, and hence for one treatment the urn contains $\beta/2$ balls of both kinds for a long time while the other treatment modifies the urn combination at a faster rate. If $q_t(j)$ is only a function of Z_j (and free of δ_j) we have that $P_A = P_B$ when $p_1 = p_2$.

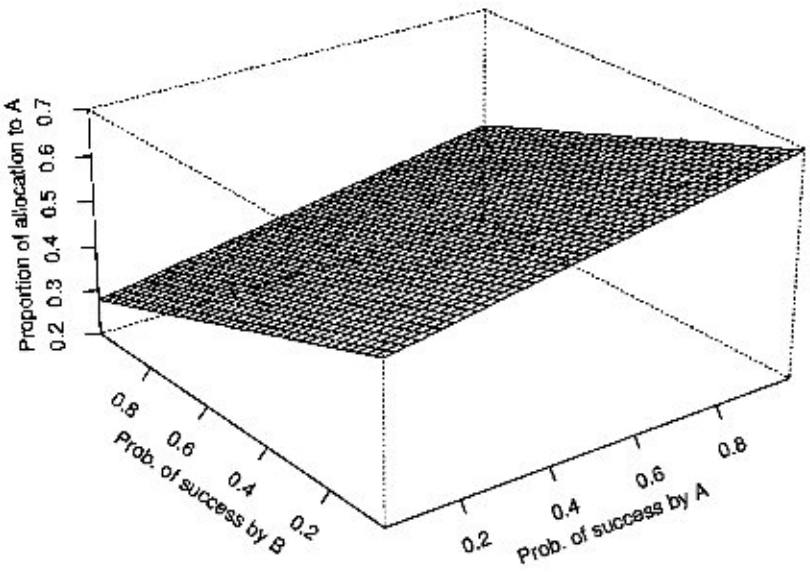

Figure 1. Proportion of allocation to A using functional form (i).

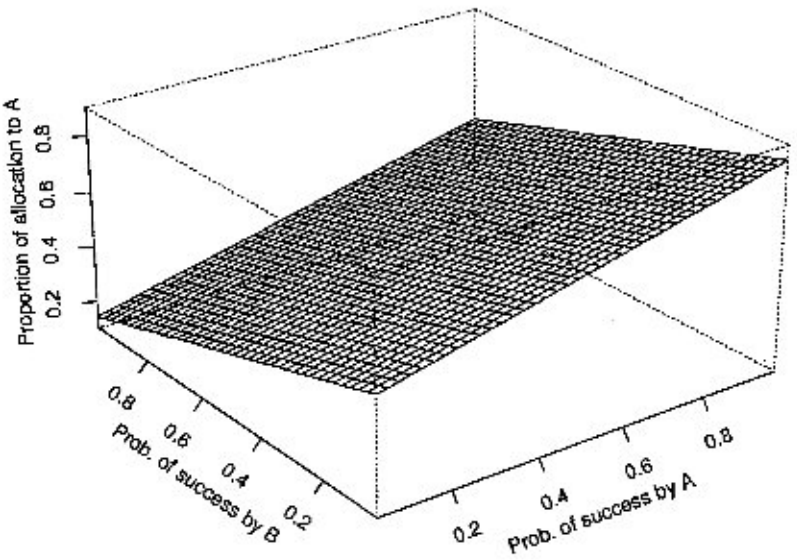

Figure 2. Proportion of allocation to A using functional form (ii).

2.4. Variance of the Proportion of Allocation

Writing

$$P(\delta_i = 1 | \delta_k = 1) = \frac{1}{2} + \bar{d}_i^{(k)}, \quad i > k,$$

it can be recursively shown that

$$\begin{aligned}\bar{d}_i^{(k)} = {} & \frac{\beta}{2\alpha + (i-1)\beta} \sum_{j=1, j\neq k}^{i-1} \left(2A_{4i-j} + \frac{1}{2}A_{1i-j} - A_{2i-j} - A_{3i-j}\right) \\ & + \frac{\beta}{2\alpha + (i-1)\beta}\left[\sum_{j=1}^{k-1}\left(2B_{4i-j} + \frac{1}{2}B_{1i-j} - B_{2i-j} - B_{3i-j}\right)\bar{d}_j^{(k)}\right. \\ & \left. + \sum_{j=k+1}^{i-1}\left(2B_{4i-j} + \frac{1}{2}B_{1i-j} - B_{2i-j} - B_{3i-j}\right)\bar{d}_j^{(k)}\right] \\ & + \frac{\beta}{2\alpha + (i-1)\beta}\left[\left(p_1 - \frac{1}{2}\right)\left(\pi_{i-k}^{(1)} - \pi_{i-k}^{(2)}\right) - \frac{1}{2}p_1\left(\pi_{i-k}^{(3)} + \pi_{i-k}^{(4)}\right)\right].\end{aligned}$$

Table 1. Expectation and variance of the proportion of allocation to treatment A.

	Functional form (i)		Functional form (ii)	
(p_1, p_2)	P_A	$\sqrt{V_A}$	P_A	$\sqrt{V_A}$
(0.2, 0.3)	0.4709	0.0494	0.4720	0.0500
(0.2, 0.2)	0.5007	0.0409	0.5011	0.0416
(0.2, 0.1)	0.5276	0.0311	0.5274	0.0320
(0.3, 0.4)	0.4672	0.0590	0.4684	0.0593
(0.3, 0.3)	0.5004	0.0504	0.5006	0.0508
(0.3, 0.2)	0.5302	0.0407	0.5297	0.0414
(0.3, 0.1)	0.5570	0.0294	0.5560	0.0304
(0.4, 0.5)	0.4626	0.0692	0.4639	0.0691
(0.4, 0.4)	0.5000	0.0600	0.5000	0.0602
(0.4, 0.3)	0.5332	0.0501	0.5323	0.0505
(0.4, 0.2)	0.5629	0.0390	0.5613	0.0397
(0.4, 0.1)	0.5894	0.0252	0.5874	0.0265
(0.5, 0.6)	0.4569	0.0801	0.4583	0.0796
(0.5, 0.5)	0.4993	0.0703	0.4990	0.0702
(0.5, 0.4)	0.5367	0.0597	0.5352	0.0599
(0.5, 0.3)	0.5698	0.0481	0.5674	0.0487
(0.5, 0.2)	0.5992	0.0345	0.5961	0.0356
(0.5, 0.1)	0.6252	0.0147	0.6219	0.0174
(0.6, 0.7)	0.4496	0.0922	0.4513	0.0911
(0.6, 0.6)	0.4983	0.0816	0.4975	0.0809
(0.6, 0.5)	0.5408	0.0699	0.5383	0.0698
(0.6, 0.4)	0.5780	0.0572	0.5743	0.0577
(0.6, 0.3)	0.6107	0.0430	0.6062	0.0441
(0.6, 0.2)	0.6395	0.0245	0.6346	0.0269
(0.7, 0.8)	0.4402	0.1057	0.4423	0.1037
(0.7, 0.7)	0.4966	0.0940	0.4952	0.0927
(0.7, 0.6)	0.5454	0.0810	0.5415	0.0805
(0.7, 0.5)	0.5877	0.0669	0.5822	0.0672
(0.7, 0.4)	0.6245	0.0511	0.6180	0.0524
(0.7, 0.3)	0.6566	0.0316	0.6494	0.0345
(0.8, 0.9)	0.4281	0.1209	0.4308	0.1177
(0.8, 0.8)	0.4940	0.1079	0.4918	0.1057
(0.8, 0.7)	0.5506	0.0933	0.5449	0.0922
(0.8, 0.6)	0.5992	0.0773	0.5912	0.0775
(0.8, 0.5)	0.6410	0.0594	0.6315	0.0610
(0.8, 0.4)	0.6770	0.0374	0.6667	0.0414
(0.9, 0.95)	0.4528	0.1312	0.4526	0.1270
(0.9, 0.9)	0.4902	0.1237	0.4868	0.1202
(0.9, 0.8)	0.5564	0.1071	0.5482	0.1053
(0.9, 0.7)	0.6127	0.0886	0.6012	0.0886
(0.9, 0.6)	0.6606	0.0678	0.6471	0.0700
(0.9, 0.5)	0.7015	0.0422	0.6868	0.0479

Then, we have

$$V(\delta_i) = P(\delta_i = 1) - (P(\delta_i = 1))^2 = \frac{1}{4} - d_i^2, \quad i = 1, \ldots, n,$$

and, for $i < j$,

$$\begin{aligned}\mathrm{Cov}(\delta_i, \delta_j) &= P(\delta_i = 1)\{P(\delta_j = 1 | \delta_i = 1) - P(\delta_j = 1)\} \\ &= \left(\frac{1}{2} + d_i\right)\left(\bar{d}_j^{(i)} - d_j\right),\end{aligned}$$

and hence the variance of the proportion of allocation to treatment A is

$$V_A = \frac{1}{n^2} V\left(\sum_{i=1}^{n} \delta_i\right) = \frac{1}{n^2}\left[\sum_{i=1}^{n}\left(\frac{1}{4} - d_i^2\right) + 2\sum_{i<j}\left(\frac{1}{2} + d_i\right)\left(\bar{d}_j^{(i)} - d_j\right)\right].$$

It is easy to note that $V_B = V_A$. Table 1 also provides results for the computation of $\sqrt{V_A}$. The calculations of Table 1 are done with $n = 50$, $a = b = 0.2$ and $k_1 = k_2 = 0.2$, $k_3 = 0.1$. Note that the computations are exact and the functional forms (i) and (ii) are given in Eq. (3.1).

2.5. Limiting Proportions of Allocations

Here we have the following theorem:

Theorem 2.1. *Under assumption Eq.* (2.4), *the limiting proportion of patients treated by treatment A is*

$$(1 - p_2)/(2 - p_1 - p_2).$$

Proof. Using the fact that the sequence $\{d_i\}$ is monotonic and bounded, as in the proof of Theorem 4.2 of Biswas (1999) it can be shown that $n^{-1}\sum_{i=1}^{n} \delta_i$ converges in probability to

$$\lim_{n \to \infty} \frac{1}{n} E\left(\sum_{i=1}^{n} \delta_i\right) = \frac{1}{2} + d,$$

where $\lim_{n \to \infty} d_i = d$ (exists). Again, as $(2B_{4t} + B_{1t}/2 - B_{2t} - B_{3t}) \to (p_1 + p_2 - 1)$ if $t \to \infty$, the Cauchy product $i^{-1}\sum_{j=1}^{i}(2B_{4i+1-j} + B_{1i+1-j}/2 - B_{2i+1-j} - B_{3i+1-j})d_j$ converges to $(p_1 + p_2 - 1)d$ as $i \to \infty$. Hence, from Eq. (2.6), we get

$$d = \left(p_1 + \frac{1}{2} - \frac{1}{2} - \frac{1}{2}(p_1 + p_2)\right) + (p_1 + p_2 - 1)d,$$

which implies

$$d = (p_1 - p_2)/(2(2 - p_1 - p_2)).$$

Thus the limiting proportion of patients receiving treatment A is

$$\frac{1}{2} + d = (1 - p_2)/(2 - p_1 - p_2). \qquad \square$$

Note 1. This limiting proportion is independent of any choice of (α, β).

Note 2. This limiting proportion is same as the limiting proportion in an RPW rule or the limiting proportion obtained by using the simpler model of π_t in BB (1996) or Biswas (1999).

Note 3. In a similar fashion, it can be easily shown that as $n \to \infty$, we have $V_A \to 0$.

3. A NOTE ON THE DELAYED RESPONSE INDICATOR VARIABLE

There may be many functional forms satisfying the basic requirements. For illustration we present the following forms:

$$\text{(i)} \quad q_t(j) = 1 - e^{-at} - k_1 e^{-at}\delta_j - k_2 e^{-at} Z_j - k_3 e^{-at}\delta_j Z_j, \quad a > 0,$$

$$\text{(ii)} \quad q_t(j) = 1 - \left(\frac{b}{a+b}\right)^t - k_1\left(\frac{b}{a+b}\right)^t \delta_j - k_2\left(\frac{b}{a+b}\right)^t Z_j - k_3\left(\frac{b}{a+b}\right)^t \delta_j Z_j, \quad a, b > 0. \tag{3.1}$$

The parameters involved in (i) and (ii) are either known or can be estimated from past data. Figures 1 and 2 are drawn taking $k_1 = k_2 = 1$, $k_3 = 0.5$ and $a = b = 0.2$. In Table 1, the functional form $q_t(j)$'s exhibit slower responses for treatment A. A detailed computation is also carried out using $q_t = 1 - e^{-at}$ and $q_t = 1 - (a/(a+b))^t$, which are free of δ_j and Z_j, where the distributions of delay are same for both the treatments. Denoting the corresponding proportion of allocation by P_A^*, we observe that the P_A^*-values are slightly less than the corresponding P_A-values, in general. We skip the detailed computational figures of P_A^*, for the sake of brevity.

The general form $\pi_t^{(1)} - \delta_j \pi_t^{(2)} - Z_j \pi_t^{(3)} - \delta_j - Z_j \pi_t^{(4)}$ or the functional forms of $q_t(j)$ are proposed heuristically. Actually here the $q_t(j)$'s,

at least in theory, could be built up starting from more basic data. Thus one could assume that, along with the i-th observation variable (X_i, if it is treated by treatment A, or Y_i, if it is treated by treatment B; we observe $\delta_i X_i + (1-\delta_i)Y_i$ and consider the indicator variable Z_i which is a function of $\delta_i X_i + (1-\delta_i)Y_i$), there is another random variable representing response time, say, U_i. Here we assume that the U_i's are not independent of the X_i's or Y_i's. (Generally, however, if the X_i's or Y_i's are survival times, the U_i's may be equal to the X_i's or Y_i's). Then one can assume a random interarrival time, W_i, between the i-th and the $(i+1)$-st arrivals. Thus

$$\epsilon_{j|j+t} = 1 \text{ iff } U_j < \sum_{k=0}^{t-1} W_{j+k}, \quad t \geq 1.$$

Assuming a distribution for the U_i's and another for the W_j's and independence of these, one could conceptually build up $q_t(t)$.

Assuming that given (δ_j, Z_j), U_j has the probability density function (p.d.f.) $(a_1 + a_2\delta_j + a_3 Z_j + a_4\delta_j Z_j)\exp\{-(a_1 + a_2\delta_j + a_3 Z_j + a_4\delta_j Z_j)\,u\}$, $u > 0$, and taking $W_j = c_0$, a constant, i.e., assuming a constant interarrival time (which is, of course, a crude assumption), we get

$$\begin{aligned}
q_j(t) &= 1 - e^{-(a_1+a_2\delta_j+a_3Z_j+a_4\delta_jZ_j)tc_0} \\
&= 1 - e^{-a_2c_0t\delta_j}e^{-a_3c_0tZ_j}e^{-a_4c_0t\delta_jZ_j}e^{-a_1tc_0} \\
&= 1 - \left\{\left(e^{-a_2c_0t}-1\right)\delta_j + 1\right\}\left\{\left(e^{-a_3c_0t}-1\right)Z_j + 1\right\} \\
&\quad \times \left\{\left(e^{-a_4c_0t}-1\right)\delta_jZ_j + 1\right\}e^{-a_1c_0t} \\
&= 1 - e^{-at} - k_1e^{-at}\delta_j - k_2e^{-at}Z_j - k_3e^{-at}\delta_jZ_j,
\end{aligned}$$

where $a = a_1c_0$, $k_1 = (e^{-a_2c_0t}-1)$, $k_2 = (e^{-a_3c_0t}-1)$ and $k_3 = \{(e^{-a_2c_0t}-1)(e^{-a_3c_0t}-1) + e^{-(a_2+a_3)c_0t}(e^{-a_4c_0t}-1)\}$. Instead, if we assume that the interarrival time, W_j, has the p.d.f. $b\exp\{-bw\}$, $w > 0$, we get

$$\begin{aligned}
q_j(t) &= 1 - \left(\frac{b}{a_1a_2\delta_j + a_3Z_j + a_4\delta_jZ_j + b}\right)^t \\
&= 1 - \left(1 + a_1' + a_2'\delta_j + a_3'Z_j + a_4'\delta_jZ_j\right)^{-t}, \\
&\quad a_s' = a_s/b, \quad s = 1(1)4 \\
&= 1 - (1+a_1')^{-t}\left(1 + a_2''\delta_j + a_3''Z_j + a_4''\delta_jZ_j\right)^{-t}, \\
&\quad a_s'' = a_s'/(1+a_1'), \quad s = 2(1)4 \\
&= 1 - (1+a_1')^{-t}\left(1 + k_1\delta_j + k_2Z_j + k_3\delta_jZ_j\right)^{-t},
\end{aligned}$$

as δ_j, Z_j are indicator variables, which is of the form (ii) when $a = a_1$.

If, instead, $U_i = a(\delta_j, Z_j)\exp\{-a(\delta_j, Z_j)u\}, u > 0$, for some general functional form $a(\delta_j, Z_j)$ of (δ_j, Z_j), we can write

$$\begin{aligned} a(\delta_j, Z_j) &= \{a(1, Z_j) - a(0, Z_j)\}\delta_j + a(0, Z_j) \\ &= \{(a(1,1) - a(1,0))Z_j + a(1,0) - (a(0,1) - a(0,0))Z_j - a(0,0)\}\delta_j \\ &\quad + (a(0,1) - a(0,0))Z_j + a(0,0) \\ &= a(0,0) + (a(1,0) - a(0,0))\delta_j + (a(0,1) - a(0,0))Z_j \\ &\quad + (a(1,1) - a(1,0) - a(0,1) + a(0,0))\delta_j Z_j, \end{aligned}$$

which is a linear function in δ_j, Z_j and $\delta_j Z_j$ and is the same as the form that we have considered to develop $q_i(j)$. Thus, as δ_j and Z_j are indicator variables, every general function can be transformed into this linear form. Exactly in the same way it can be shown that every general functional form of $q_i(j)$ (say, logistic function, see Cox, 1980) can be reduced to the linear form given in Eq. (2.3).

But at the present moment we observe that

$$P(\epsilon_{ji+1} = 1 | \epsilon_{ji} = 1) = 1,$$

and hence

$$P(\epsilon_{ji+1} = 1 | \epsilon_{ji} = 0) = \frac{q_{i+1-j}(j) - q_{i-j}(j)}{1 - q_{i-j}(j)}. \tag{3.2}$$

Now, for $q_i(j)$ given by (i) and (ii) the right hand member of Eq. (3.2) reduces to $1 - e^{-a}$ and $1 - (b/(a+b))$, which is independent of $i - j$. Thus, for (i), the ϵ_{ji} follow a two-state Markov Chain with the transition probability matrix P given by

$$\begin{array}{c} \\ \text{states of } \epsilon_{ji} \end{array} \begin{array}{c} \begin{array}{cc} \text{states of } \epsilon_{ji+1} & \\ 0 & 1 \end{array} \\ \begin{array}{c} 0 \\ 1 \end{array} \begin{pmatrix} e^{-a} & 1 - e^{-a} \\ 0 & 1 \end{pmatrix} \end{array}.$$

It is easy to check that

$$P^k = \begin{pmatrix} e^{-ka} & 1 - e^{-ka} \\ 0 & 1 \end{pmatrix},$$

whence we get that

$$\lim_{k \to \infty} P^k = \begin{pmatrix} 0 & 1 \\ 0 & 1 \end{pmatrix}.$$

Similarly, for the functional form given in (ii), the ϵ_{ji}'s follow a two-state Markov Chain with the transition matrix P given by

$$\begin{array}{c} \\ \text{states of } \epsilon_{ji} \end{array} \begin{array}{c} \text{states of } \epsilon_{ji+1} \\ \begin{array}{cc} 0 & 1 \end{array} \\ \begin{array}{c} 0 \\ 1 \end{array} \begin{pmatrix} \frac{b}{a+b} & 1-\frac{b}{a+b} \\ 0 & 1 \end{pmatrix} \end{array}.$$

Note that Eq. (3.3) also holds in this case.

4. DISCUSSION

BB (1996) and Biswas (1999) have considered a decision-making problem along with allocation. A similar analysis can also be carried out under the general delayed response model. Actually this is a routine development and hence we ignore the details.

In the present article we have assumed that the patients are homogeneous. But, in practice, patients may be heterogeneous with respect to some prognostic factor(s) like age, blood sugar, blood pressure etc. The treatment allocation problem in the presence of prognostic factors is considered by Begg and Iglewicz (1980). They used optimum design theory to suggest a deterministic design criterion, which is then modified for computational convenience. The presence of prognostic factors is also considered by Atkinson (1982) who used optimum design theory to provide a procedure based on the biased coin for an arbitrary number of treatments. This problem is also considered by BB (1999). Clearly, the delayed response model discussed in the present article needs to be modified to incorporate the presence of prognostic factors.

Suppose there is only one prognostic factor u_j which has $(T+1)$ levels $0, 1, 2, \ldots, T$ and which is non-stochastic. We assume that $P(Z_j = 1 | \delta_j = k, u_j) = p_{2-k,\, u_j}, k = 1, 0$. Then we consider the linear model:

$$\begin{aligned} q_j(t) &= P(\epsilon_{jj+t} = 1 | \delta_j, Z_j, u_j) \\ &= \pi_t^{(1)} - \delta_j \pi_t^{(2)} - Z_j \pi_t^{(3)} - \delta_j Z_j \pi_t^{(4)} \\ &\quad - u_j \pi_t^{(5)} - \delta_j u_j \pi_t^{(6)} - Z_j u_j \pi_t^{(7)} - \delta_j Z_j u_j \pi_t^{(8)}, \end{aligned} \tag{4.1}$$

where $\pi_t^{(s)} \to 0$ as $t \to \infty, s = 5(1)8$. Clearly, Eq. (4.1) can be expressed as

$$q_j(t) = \pi_t^{*(1)} - \delta_j \pi_t^{*(2)} - Z_j \pi_t^{*(3)} - \delta_j Z_j \pi_t^{*(4)},$$

where $\pi_t^{*(1)} = \pi_t^{(1)} - u_j \pi_t^{(5)}$, $\pi_t^{*(s)} = \pi_t^{(s)} + u_j \pi_t^{(s+4)}$, $s = 2, 3, 4$. Thus we have a similar analysis and similar expression to that of d_j as in Sec. 2, where A_{st} and $B_{st}, s = 1(1)4$, are replaced by A_{st}^* and B_{st}^* with $\pi_t^{(l)}, l = 1(1)4$ and p_{2-k} is replaced by $p_{2-k,u_j}, k = 1, 0$.

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