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A BAYESIAN APPROACH FOR AN EXPONENTIAL PARAMETER WITH DELAYED OBSERVATIONS

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Abstract

The Mady model for the choice between two medical treatments is studied, with the additional assumption that there is a time lag between the administration of the treatments and the availability of the responses. Two simple procedures are suggested for dealing with patients who arrive during the waiting period, caused by the lag, between the trial and treatment stages of the model. The relative performance of the procedures in the Bayesian framework is discussed when the responses to the treatments are exponentially distributed.

Introduction

The Mady model for clinical trials is appropriate in certain situations where two competing treatments for the same disease are being compared (Mady [7], Hardwick et al. [5], Langenberg and Srinivasan [6], Colton [4], Anscombe [1] and Armitage [2]). The central assumption in the model is that there exists a known finite patient horizon, N, representing the total number of patients who will ever be receiving one of the two treatments under study. A decision rule, according to the simplest version of the model, consists of the "trial stage" when n patients are assigned to each of the two treatments, leading to the choice of one of the treatments as the

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better, and the "treatment stage" when the remaining $N - 2n$ patients receive the treatment so chosen. Then the problem of clinical trials is the determination of optimal decision rules (i.e., optimal n), optimality being defined in terms of appropriate loss functions. For the sake of definiteness we shall assume, along with Mady [7], that the response to treatment i, $i = 1, 2,$ is exponentially distributed with unknown mean $(1/\theta_i)$ and that its quality is characterized by $(1/\theta_i)$, so that the treatment with the larger mean is considered the better. Also, let the treatment with the larger observed sample mean be chosen as the better at the end of the trial stage.

In the context of clinical trials it is reasonable to suppose that the only loss is the ethical loss incurred in treating a patient with the inferior treatment. *Optimality* may therefore be defined in terms of the expected regret, R, which represents the difference between the total expected response if one were to treat all the N patients with the better treatment and the expected response achieved by following a decision rule. In our case it turns out that $(1/\theta_1)$ and $(1/\theta_2)$ enter R only through the true difference between the treatments, $\delta = 1/\theta_1 - 1/\theta_2$. Under the Bayesian formulation, Mady [7] assumed that the prior distribution of $(1/\theta_i)$ is gamma with parameters $(\alpha = 2, \lambda_0)$ and she determined the optimal value of n [i.e., the one which minimizes the Bayes average regret, $E(R)$] for given specifications of the parameters of the model.

An important assumption implicit in the Mady model is that the response to the treatments is instantaneous, or that there is no time lag between the treatment of the patients during the trial stage and the availability of all the treatment results. In practice, however, the response to the treatments is often delayed, causing a 'waiting period' between the two stages, and an accumulation of new patients who have to be treated before the beginning of the treatment stage. The allocation of treatments to these patients is an important issue, especially when their number is large relative to N (see Mendoza and Iglewicz [8], Nomachi [9] and Choi and Clark [3] for some work with delayed observations in sequential analysis).

Our purpose is to incorporate the assumption of delayed response into the Mady model and examine some Bayes optimal procedures for dealing with the patients who arrive during the waiting period. Now, the nature of the delay could, in general, be quite complicated. For instance, as happens naturally when the response is survival time, the delay might not only be dependent on the treatment given, but be a variable for each treatment. However, to make the analysis manageable and to be specific, we shall assume that

(i) patients arrive sequentially, one per unit time, and are to be assigned to one of the two treatments, and

(ii) there is a delay of T time units (T is taken to be an even integer for convenience) in obtaining the response to either treatment.

Two procedures for treating the T patients who arrive during the waiting period will now be investigated.

Results

For the two procedures described below, the trial stage consists of the first $2n$ patients to arrive, with n patients assigned to each of the two treatments randomly within pairs, the treatment stage consists of the $N - 2n - T$ patients arriving after the waiting period, who are given the treatment with the larger sample mean based on the observations made during the trial stage. The treatment allocations during the waiting period are as follows:

Procedure 1. The patients are assigned randomly within pairs, as they arrive, to the two treatments, $T/2$ to each.

Procedure 2. All the T patients are assigned to that treatment with the larger sample mean based on $n - T/2$ available observations on each treatment from the trial stage.

Note that Procedure 2 is meaningful only when $n \geq 1/2,$ while there are no such restrictions placed on Procedure 1. Also, when $T = 0$ both procedures lead to Mady's decision rule with the delay outlined in the Introduction omitted. We shall now derive the Bayes optimal value of n for the two procedures.

In Procedure 1, let P denote the probability that the inferior treatment (i.e., treatment 2 if $\delta < 0$, and treatment 1 if $\delta \geq 0$) is chosen as the better on the basis of the n observations on each treatment available at the end of the waiting period, that is,

$$P = F_{2n, 2n}(\theta_1/\theta_2), \quad \theta_1 < \theta_2$$

$$= 1 - F_{2n, 2n}(\theta_1/\theta_2), \quad \theta_2 < \theta_1,$$

where F denotes the Fisher cumulative distribution function with $(2n, 2n)$ degrees of freedom. The expected regret function for Procedure 1 can then be given by

$$R_1/N = |\delta|[p + t/2 + (1 - 2p - t)P], \tag{1}$$

where $p = n/N$ and $t = T/N$.

Averaging R_1 over the prior distribution of θ_i (recall that θ_i follows gamma with parameters $(\alpha = 2, \lambda_0)$), we get

$$\overline{R}_1 = E(R_1/N) = (\lambda_0/2)[2p + t + (1 - 2p - t)/(2Np + 1)]. \tag{2}$$

The value of p which minimizes the right hand side of (2), that is, the optimal p for Procedure 1, will be denoted by p_1 and is easily seen to be

$$p_1 = p_1(t) = \frac{(1 - t)}{2[1 + \sqrt{1 + N(1 - t)}]}. \tag{3}$$

The optimal average regret denoted by $\overline{R}_1^*$, is obtained by substituting $p = p_1$ in (2).

In Procedure 2, let P_1 and P_2 denote the probabilities of choosing the inferior treatment based, respectively, on the $n - T/2$ observations available on each of the two treatments at the end of the trial stage and the n such observations available at the end of the waiting period. Clearly, then

$$P_1 = F_{2(n-T/2), 2(n-T/2)}(\theta_1/\theta_2), \quad \theta_1 < \theta_2$$

$$= 1 - F_{2(n-T/2), 2(n-T/2)}(\theta_1/\theta_2), \quad \theta_2 < \theta_1$$

and

$$P_2 = F_{2n,2n}(\theta_1/\theta_2), \quad \theta_1 < \theta_2$$

$$= 1 - F_{2n,2n}(\theta_1/\theta_2), \quad \theta_2 < \theta_1.$$

The expected regret function for Procedure 2 is given by

$$R_2/N = |\delta|[p + tP_1 + (1 - 2p - t)P_2] \tag{4}$$

and the Bayes average regret is

$$\overline{R}_2 = E(R_2/N) = (\lambda_0/2)\{2p + t/[2N(p - t/2) + 1] + (1 - 2p - t)/(2Np + 1)\}. \tag{5}$$

The optimal value of p, say p_2, is obtained by minimizing $\overline{R}_2$ with respect to p. We shall denote the average regret corresponding to $p = p_2$ by $\overline{R}_2^*$. It can be shown from (5) that p_2 satisfies

$$(2Np_2 + 1)^2[N(2p_2 - t) + 1]^2$$

$$= Nt(2Np_2 + 1)^2 + [N(1 - t) + 1][N(2p_2 - t) + 1]^2. \tag{6}$$

We have not been able to derive a closed form expression for p_2, only numerical solutions for various values of N and t are obtained.

Comparing (1) and (4), we see that if $p > t/2$, then $R_2 < R_1$ for all δ. Consequently we have $\overline{R}_2^* < \overline{R}_1^*$ provided that $p_1 > t/2$. Now, it is clear from (3) that $p_1(t)$ is a decreasing function of t, this, plus the fact that $p_1(0) > 0$, shows that there exists a value of $t^* > 0$ which is such that $p_1(t) > t/2$ for $t < t^*$ and $p_1(t) < t/2$ for $t > t^*$ [t^* is the solution to $p_1(t) = t/2$]. We have thus shown that, for any given N, Procedure 2 is superior to Procedure 1 for all values of t less than t^*, where t^* depends on N.

Numerical results on the relative performance of the two procedures are presented in Table 1 for selected values of N and t. Note that under Procedure 2, since $n \geq T/2$ and $2n + T \leq N$, we have $t \leq (1/2)$, hence we have included t values only up to $(1/2)$.

Table 1. Relative performance of the two procedures*

N	t	p_1	p_2	R'_1	R'_2	I
100	.00	.0452	.0452	.1810	.1810	0
	.01	.0450	.0453	.1900	.1811	5
	.05	.0440	.0483	.2260	.1855	22
	.07	.0435	.0536	.2439	.1922	27
	.09	.0430	.0616	.2618	.2031	29
	.10	.0427	.0663	.2708	.2099	29
	.20	.0400	.1190	.3600	.3023	19
	.30	.0371	.1732	.4485	.4095	10
	.45	.0324	.0330	.5797	.1177	80
200	.00	.0329	.0329	.1318	.1318	0
	.01	.0328	.0330	.1411	.1319	7
	.05	.0321	.0378	.1782	.1380	29
	.07	.0317	.0458	.1967	.1482	33
	.09	.0313	.0556	.2153	.1628	32
	.10	.0311	.0607	.2245	.1711	31
	.20	.0292	.0301	.3169	.1095	65
	.30	.0272	.0240	.4087	.3779	8
	.45	.0238	.2452	.5359	.0897	83
400	.00	.0238	.0238	.0951	.0951	0
	.01	.0237	.0239	.1046	.0952	10
	.05	.0231	.0320	.1426	.1049	36
	.07	.0229	.0417	.1616	.1191	36
	.09	.0226	.0521	.1805	.1366	32
	.10	.0225	.0238	.1900	.0851	55
	.20	.0211	.0214	.2846	.0814	71
	.30	.0197	.1626	.3788	.3551	7
	.45	.0173	.0174	.5193	.0666	87

* $R'_i = 2\overline{R}_i^*/\lambda_0$ and $I = 1 - (R'_2/R'_1)$ denotes the percent increase in R'_1 over R'_2.

The most striking feature in the table is the uniform superiority of Procedure 2, this adds confirmation to our conjecture. The percentage increase I in $\overline{R}_1^*$ over $\overline{R}_2^*$, given in the last column, shows that this superiority could be quite pronounced. The values of I indicate that the reduction in regret afforded by Procedure 2 is strongly dependent upon the patient horizon and the delay. Therefore, in any given application the value of I for the specific N and t involved should be taken into consideration before the choice between the two procedures is attempted. Then the improvement in performance of Procedure 2 should be weighed against the operational simplicity of Procedure 1. In addition, any realistic comparison of the two procedures should take into account another important aspect: the duration of the trial phase. The table indicates that Procedure 1 has the definite advantage of a shorter trial stage for all N and t. Note also that the percentage increase in p_2 over p_1 increases with t for any fixed N. Both of these properties can be shown to be true in general since p_2 is an increasing function of t, and p_1 is already known to decrease with t and $p_1 = p_2$ when $t = 0$.

Finally, let us note some asymptotic (large N) properties of p_1 and p_2, which would also be helpful in making the choice between the two procedures. With t held constant, if we let $N \to \infty$, then $p_1 \to 0$ and $p_2 \to 0$. The first result follows immediately from (3), the second is deduced from (6). Using these results along with (2) and (5), we can show that, for fixed t as $N \to \infty$, $2\overline{R}_1^*/\lambda_0$ converges to t and $2\overline{R}_2^*/\lambda_0$ converges to zero.

References

[1] F. Anscombe, Sequential medical trials, J. Amer. Statist. Assoc. 58 (1963), 365-383.

[2] P. Armitage, Sequential Medical Trials, 2nd ed., Blackwell, Oxford, 1975.

[3] S. Choi and V. Clark, Sequential decision for a binomial parameter with delayed observations, Biometrics 26 (1970), 411-420.

[4] T. Colton, A model for selecting one of two medical treatments, J. Amer. Statist. Assoc. 58 (1963), 388-400.

[5] J. Hardwick, R. Oehmke and Q. Stout, New adaptive designs for delayed response models, J. Sequent. Plann. Infer. 136 (2006), 1940-1955.

[6] P. Langenberg and R. Srinivasan, On the Colton model for clinical trials with delayed observations normally distributed responses, Biometrics 37 (1981), 143-148.

[7] A. Mady, Fixed and sequential treatment allocation in clinical trials, Far East. J. Theo. Stat. (2009), to appear.

[8] G. Mendoza and B. Iglewicz, A three-phase sequential model for clinical trials, Biometrika 64(2) (1977), 201-205.

[9] Y. Nomachi, A Bayesian approach for testing hypotheses with continuation of observations from a population in a family of populations with one parameter exponential distributions, Bull. Math. Statist. 12 (1967), 21-37.

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