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Some Properties of the Randomized Play the Winner Rule

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Abstract

In clinical trials with extreme outcomes, it is ethically desirable to treat as many trial patients as possible with the superior treatment. Adaptive designs seek to achieve this goal. One such design is known as the randomized play the winner rule which has been applied in some real clinical trials. In this paper we demonstrate some interesting and desirable properties of the randomized play the winner rule.

Key Words and Phrases. Clinical trials, adaptive designs, randomized play the winner rule.

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1. Introduction

It is commonly accepted that the most reliable and efficient way to evaluate the efficacy of new medical interventions is to conduct clinical trials. Randomization has always been a key and essential feature for designing clinical trials (Rosenberger and Lachin, 2002). The traditional design of equal randomization aims at balancing covariates (known or unknown) of the patients in the alternative treatment groups, and has been regarded as the gold standard for clinical trials.

However as experiments on human subjects, clinical trials are characterized by the delicate tension between collective ethics and individual ethics. When a failure represents an extreme outcome (*i.e.* death), the traditional balanced randomization becomes ethically infeasible because of unjustifiable sacrifice of individual ethics. Instead, response adaptive randomization is ethically justified and morally required (Pullman and Wang, 2001).

Adaptive designs seek to treat the majority of patients with the superior treatment. With a response adaptive randomization, the treatment allocation probability is sequentially modified according to the information so far accumulated in the trial. The goal is to improve the efficiency and ethics of the trial without undermining the validity and integrity of the clinical research. Many types of response adaptive designs are based on various urn models, see Hu and Rosenberger (2006) and Biswas et al. (2008) for extensive reviews.

A much studied adaptive design is the randomized play the winner rule (RPWR) introduced by Wei and Durham (1978), see Rosenberger (1999) for a review and recommendations. Despite being ethically appealing, the use of adaptive designs in practice has been limited. The few reported applications of response adaptive designs, such as the Michigan extracorporeal membrane oxygenation (ECMO) trial (Bartlett et al., 1985), the fluoxetine trial (Tamura et al., 1994) and the rheumatoid arthritis trial (Biswas and Dewanji, 2004), have used the RPWR.

In this paper we investigate some attractive and desirable properties of the RPWR. Section 2 introduces the randomized play the winner rule. Main results and proofs are in Section 3. Section 4 concludes.

2. Randomized play the winner rule

Assume two treatments labeled "A" and "B", and there are n patients to be treated. Define

$$T_i = \begin{cases} 1, & \text{if the } i^{\text{th}} \text{ patient receives treatment A,} \\ 0, & \text{if the } i^{\text{th}} \text{ patient receives treatment B,} \end{cases}$$

and

$$X_i = \begin{cases} 1, & \text{if the } i^{\text{th}} \text{ patient is a success,} \\ 0, & \text{if the } i^{\text{th}} \text{ patient is a failure,} \end{cases}$$

and let $p_A = P(X_i = 1|T_i = 1)$, $p_B = P(X_i = 1|T_i = 0)$, $q_A = 1 - p_A$ and $q_B = 1 - p_B$. Some useful summary statistics are $N_A = \sum_{i=1}^{n} T_i$, $N_B = n - N_A$, $S = \sum_{i=1}^{n} X_i$, $S_A = \sum_{i=1}^{n} T_i X_i$ and $S_B = S - S_A$.

Assignment of treatments is determined by an urn which initially contains α balls of each type. A ball is randomly selected with replacement and the corresponding treatment is allocated to the current patient in the trial. After a patient's response, β balls of the appropriate type are added to the urn. To be specific, β balls of the same type are added after a success and β balls of the other type are added after a failure. The probability p_i of patient i receiving treatment "A" is given by

$$\begin{aligned} p_i &= P(T_i = 1|T_1, \ldots, T_{i-1}, X_1, \ldots, X_{i-1}) \\ &= \frac{\alpha + \beta\left(2\sum_{j=1}^{i-1} T_j X_j + (i-1) - \sum_{j=1}^{i-1} T_j - \sum_{j=1}^{i-1} X_j\right)}{2\alpha + (i-1)\beta}. \end{aligned}$$

In Rosenberger et al. (1997), it is shown that the likelihood function is proportional to the likelihood function for two independent binomial samples. Hence, the maximum likelihood estimators are $\hat{p}_A = S_A/N_A$ and $\hat{p}_B = S_B/N_B$. Using martingale limit theory, Wei et al. (1990) showed the maximum likelihood estimators are asymptotically independent and normally distributed.

3. Main results and proofs

The randomized play the winner rule has some very desirable properties from an ethical point of view. As the trial goes on, more patients are assigned to the superior treatment. This can be seen in several ways. Before going into details, some limiting results are needed.

Following Rosenberger (1996), the RPWR is a special case of the generalized Pólya urn model. This model can be embedded into a continuous time Markov branching process. Rosenberger and Sriram (1997) used this fact to show

$$\lim_{n\to\infty} \frac{N_A}{n} = v_A = \frac{q_B}{q_A + q_B} \qquad \text{a.s.}$$

and

$$\lim_{n\to\infty} p_i = v_A = \frac{q_B}{q_A + q_B} \qquad \text{a.s.}$$

A consequence of these results is that the asymptotic proportion of successes is given by

$$\frac{p_A q_B + p_B q_A}{q_A + q_B}.$$

If we had randomly assigned half the patients to A and the rest to B, the success rate would be $(p_A + p_B)/2$. If we assume $p_A > p_B$, then

$$\frac{q_B}{q_A + q_B} > \frac{1}{2} \qquad \text{and} \qquad \frac{q_A}{q_A + q_B} < \frac{1}{2}$$

hence more weight is placed on the more successful treatment, and the total success rate of the RPWR is higher.

The allocation probabilities, p_i, $i = 1, 2, \ldots$, have desirable properties as well. In Wang and Pullman (2001) it was shown how a deterministic version of the play the winner rule has many desirable properties. For the deterministic play the winner rule, the p_i's are deterministic, while for the RPWR they are random. The properties of the allocation probabilities for the deterministic play the winner rule carry over for the RPWR by taking expectations to eliminate the randomness, *i.e.* many of the results that hold for the p_i's in the deterministic case hold for $E[p_i]$ in the RPWR case. In particular, the following properties hold.

Proposition. *For the randomized play the winner rule, we have*

(a) $E[p_{i+1}] > 1/2$, $i \geq 1$, *if* $p_A > p_B$
$E[p_{i+1}] < 1/2$, $i \geq 1$, *if* $p_A < p_B$
$E[p_{i+1}] = 1/2$, $i \geq 1$, *if* $p_A = p_B$

(b) $E[p_{i+1}]$ *is increasing in* i *when* $p_A > p_B$
$E[p_{i+1}]$ *is decreasing in* i *when* $p_A < p_B$
$E[p_{i+1}]$ *is constant in* i *when* $p_A = p_B$

(c) $p = \lim_{i\to\infty} E[p_{i+1}] = E[\lim_{i\to\infty} p_{i+1}] = q_B/(q_A + q_B)$

(d) $p > 1/2$, *if* $p_A > p_B$
$p < 1/2$, *if* $p_A < p_B$
$p = 1/2$, *if* $p_A = p_B$

(e) $\lim_{p_A\to 1} p = 1$
$\lim_{\Delta\to 0} p = 1/2$, $\Delta = p_A - p_B$
$\lim_{p_B\to 1} p = 0$

The interpretation of these results is that parts (a) and (b) say the probability of being assigned the superior treatment is expected to be greater than 50% and increases as the trial goes on when using the RPWR. Properties (c), (d) and (e) show how the RPWR has good limiting allocation properties. All of these properties demonstrate how the RPWR is superior to 50-50 randomization in terms of allocating patients to the better treatment.

Proof. Property (b) will be proved first assuming $p_A > p_B$. The other cases are similar. A recursive expression for $E[p_i]$ is useful. It is obtained by noting that

$$\begin{aligned} p_{i+1} &= \frac{(2\alpha + \beta(i-1))p_i + \beta(T_i X_i + (1-T_i)(1-X_i))}{2\alpha + i\beta} \\ &= \frac{2\alpha + \beta(i-1)}{2\alpha + i\beta} p_i + \frac{\beta(T_i X_i + (1-T_i)(1-X_i))}{2\alpha + i\beta} \end{aligned}$$

from which it follows that

$$\begin{aligned}
E[p_{i+1}] &= \frac{2\alpha+\beta(i-1)}{2\alpha+i\beta}E[p_i] + \frac{\beta(E[T_iX_i]+E[(1-T_i)(1-X_i)])}{2\alpha+i\beta} \\
&= \frac{2\alpha+\beta(i-1)}{2\alpha+i\beta}E[p_i] + \frac{\beta(p_AE[p_i]+q_B(1-E[p_i])}{2\alpha+i\beta} \\
&= \frac{2\alpha+\beta(p_A-q_B+(i-1))}{2\alpha+i\beta}E[p_i] + \frac{\beta q_B}{2\alpha+i\beta} \\
&= B_{i+1}E\left[p_i\right] + A_{i+1}
\end{aligned}$$

where the second equality follows from the relationships $E[T_iX_i] = p_AE[p_i]$ and $E[(1-T_i)(1-X_i)] = q_B(1-E[p_i])$ which can be shown using successive conditioning. It now follows that

$$\frac{A_{i+1}}{1-B_{i+1}} = \frac{\beta q_B/(2\alpha+i\beta)}{\beta(q_A+q_B)/(2\alpha+i\beta)} = \frac{q_B}{q_A+q_B} = v_A.$$

This is equivalent to saying $B_{i+1}v_A + A_{i+1} = v_A$. Since $p_A > p_B$, this implies $v_A > 1/2$, and since $E[p_1] = 1/2$, $E[p_1] < v_A$. Induction will be used to show $E[p_{i+1}] < v_A$ for all $i \geq 0$.

Assume $E[p_i] < v_A$ for some $i \geq 1$. Then

$$E[p_{i+1}] = B_{i+1}E[p_i] + A_{i+1} < B_{i+1}v_A + A_{i+1} = v_A$$

and $E[p_{i+1}] < v_A$ for all $i \geq 0$.

From this,

$$\begin{aligned}
& E[p_i] < \frac{A_{i+1}}{1-B_{i+1}} \\
\Leftrightarrow \quad & E[p_i] - B_{i+1}E[p_i] < A_{i+1} \\
\Leftrightarrow \quad & A_{i+1} + B_{i+1}E[p_i] > E[p_i] \\
\Leftrightarrow \quad & E[p_{i+1}] > E[p_i]
\end{aligned}$$

for all $i \geq 1$.

Part (a) immediately follows from (b). Part (c) follows from the result stated at the beginning of the section where switching of the limit and expectation is permitted by the dominated convergence theorem since $|p_{i+1}| \leq 1$ a.s. for all i. Parts (d) and (e) are easy to verify from part (c). □

4. Conclusion

The randomized play the winner rule was proposed over 30 years ago and has been applied to some real clinical trials. This is an ad-hoc design and is subject to high variability. However understanding its important properties and characteristics helps us gaining useful insights about response adaptive designs in general. We have demonstrated some of the important properties.

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