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Adaptive designs for sequential experiments*

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Abstract: Various adaptive designs have been proposed and applied to clinical trials, bioassay, psychophysics, etc. Adaptive designs are also useful in high cost engineering trials. More and more people have been paying attention to these design methods. This paper introduces several broad families of designs, such as the play-the-winner rule, randomized play-the-winner rule and its generalization to the multi-arm case, doubly biased coin adaptive design, Markov chain model.

Key words: Clinical trial, Adaptive designs, (Randomized) Play-the-winner rule, Biased coin design, Markov chain, Asymptotic properties, Urn model.
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INTRODUCTION

Traditional designs for clinical trials use the balanced (or 50-50) allocation of patients to treatments. For example, in a trial to compare experimental therapy (drug) to placebo (control), a standard feature of most designs is to distribute half of patients to each arm. It is reasonable that one may want to reduce the total number of failure outcomes in a trial, and keep the capability of making a comparison between experimental therapy and placebo as well. Hence the idea of adaptive designs has been proposed to serve the purpose.

Adaptive design, an important subdivision of experimental designs, are designs in which the probability a treatment assigned to the coming patient depends upon the results of the previous patients in the study. The goal is to show assignment probabilities to favor better treatment performance. This kind of design has also been applied to bioassay, psychophysics, etc. They are also useful in high cost engineering trials.

PLAY-THE-WINNER RULE AND RANDOMIZED PLAY-THE-WINNER RULE

Consider a two-arm clinical trial: two treatments (1 and 2) with dichotomous response (success and failure). Patients are recruited into the clinical trial sequentially and respond immediately to treatments. Zelen (1969) propose the following design, which is well known as the play-the-winner (PW) rule: A success on a particular treatment generates a future trial on the same treatment with a new patient. A failure on a treatment generates a future trial on the alternate treatment. Let N_{n1} and N_{n2} be the number of the patients assigned to the treatment 1 and 2, respectively, in the first n stages. And let $p_i = P\{\text{success} \mid \text{treatment } i\}$ be the success probability of a patient on the treatment i, $q_i = 1 - p_i$, $i = 1, 2$. Then

$$\frac{N_{n1}}{n} \to \frac{q_2}{q_1 + q_2} \quad a.s.$$

and

$$\sqrt{n}\left(\frac{N_{n1}}{n} - \frac{q_2}{q_1 + q_2}\right) \xrightarrow{D} N(0, \sigma^2_{\mathrm{PW}}),$$

where $\sigma^2_{\mathrm{PW}} = q_1 q_2 (p_1 + p_2)/(q_1 + q_2)^3$. This is first discussed in Zelen (1969).

As pointed out in Wei et al. (1978) and Wei (1979), the PW rule is too deterministic and is not applicable when we have delayed responses from patients to treatments. Motivated as

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an extension to Zelen's (1969) idea, Wei et al. (1978) introduced the following randomized play-the-winner (RPW) rule: We start with (α, α) balls (type 1 and 2 respectively) in the urn. If a type 1 ball is drawn, a patient is assigned to the treatment 1; If a type 2 ball is drawn, a patient is assigned to the treatment 2. The ball is replaced and the patient response is observed. A success on the treatment 1 or a failure on the treatment 2 generates a type 1 ball in the urn; A success on the treatment 2 or a failure on the treatment 1 generates a type 2 ball in the urn. The RPW rule may be regarded as a generalized Polya urn (GPU) model (Wei, 1979). Further, let Y_{n1} (Y_{n2}) be number of balls of type 1 (2) after n stage. From the results of Athreya et al. (1968), we have

$$\frac{Y_{n1}}{Y_{n1}+Y_{n2}} \to \frac{q_2}{q_1+q_2} \quad a.s. \text{ and}$$
$$\frac{N_{n1}}{n} \to \frac{q_2}{q_1+q_2} \quad a.s.$$

When $p_1 + p_2 < 1.5$ (or $q_1 + q_2 > 0.5$), we have the following asymptotic normality:

$$\sqrt{n}\left(\frac{Y_{n1}}{Y_{n1}+Y_{n2}} - \frac{q_2}{q_1+q_2}\right) \xrightarrow{D} N\left(0, \frac{q_1 q_2}{(2(q_1+q_2)-1)(q_1+q_2)^2}\right) \tag{1}$$

and

$$\sqrt{n}\left(\frac{N_{n1}}{n} - \frac{q_2}{q_1+q_2}\right) \xrightarrow{D} N(0, \sigma^2_{\mathrm{RPW}}), \tag{2}$$

where

$$\sigma^2_{\mathrm{RPW}} = \frac{q_1 q_2[5-2(q_1+q_2)]}{[2(q_1+q_2)-1](q_1+q_2)^2}.$$

The asymptotic normality was first given in Smythe et al. (1995). When $q_1 + q_2 < 0.5$, the limiting distributions of both the urn composition and the proportions of patients assigned to each treatments are unknown. The RPW rule is not deterministic and allows delayed responses by the patients.

If treatment 1 is "doing better", both PW rule and RPW rule are shown to favor treatment 1.

MULTI-ARM CASE RPW RULE AND GENERALIZED POLYA URN

One large family of randomized adaptive designs can be developed from the GPU model. Consider an urn containing balls of K types. Initially, the urn contains $Y_0 = (Y_{01}, \cdots, Y_{0K})$ balls, where Y_{0i} denotes the number of balls of type i, $i = 1, \cdots, K$. A ball is drawn at random from the urn. Its type is observed and the ball is then replaced. At the nth stage, following a type i drawn, $D_{ij}(n)$ balls of type j, for $j = 1, \cdots, K$, are added to the urn. In the most general sense, $D_{ij}(n)$ can be random and can be some function of a random process outside the urn process (in the case of adaptive designs, $D_{ij}(n)$ will be a random function of patient response). A ball must always be added at each stage (in addition to the replacement), and the expectation of the total numbers of balls added in each stage is the same (say γ), so

$$P\{D_{ij}(n) = 0, \text{ for all } j = 1, \cdots, K\} = 0,$$
$$\sum_{j=1}^{K} \mathrm{E}\{D_{ij}(n)\} = \gamma, \quad i, j = 1, \cdots, K,$$
$$n = 1, 2, \cdots.$$

Without losing generality, we can assume $\gamma = 1$. Let $\boldsymbol{H}_n$ be the matrix comprising element $\{h_{ij}(n) = \mathrm{E}\{D_{ij}(n)\}\}$. We refer to $\boldsymbol{D}_n$ as the rules and $\boldsymbol{H}_n$ as the design matrices. If $\boldsymbol{H}_n = \boldsymbol{H}$ for all n, the model is said to be homogenous. In general, it is assumed that $\boldsymbol{H}_n = \boldsymbol{H}$. Let $\boldsymbol{Y}_n = (Y_{n1}, \cdots, Y_{nK})$, where Y_{ni} represents the number of balls in the urn of type i after nth stage, and $\boldsymbol{N}_n = (N_{n1}, \cdots, N_{nK})$, where N_{ni} represents the number of times a type i ball drawn in the first n drawns. In the clinical trials, N_{ni} is the number of patients assigned to treatment i in the first n stages. Let $\boldsymbol{v} = (v_1, \cdots, v_K)$ be the left eigenvector corresponding to the largest eigenvalue of $\boldsymbol{H}$ with $v_1 + \cdots + v_K = 1$. Then v_i is just the limiting proportion of both the patients assigned to treatment i and the type i balls in the urn, i.e.,

$$\frac{N_{ni}}{n} \to v_i \quad a.s. \text{ and } \frac{Y_{ni}}{\sum_{j=1}^{K} Y_{nj}} \to v_i \quad a.s. \tag{3}$$

Athreya et al. (1968), Smyth (1996) and Bai et al. (1999; 2000*) showed the normality of $\boldsymbol{Y}_n$

* Bai, Z. D. and Hu, F., 2000. Strong consistency and asymptotic normality for urn models.

and $\boldsymbol{N}_n$: let $\lambda_1 = \gamma = 1$, $\lambda_2, \cdots, \lambda_K$ be the eigenvalues of $\boldsymbol{H}$, and $\lambda = \max\{Re(\lambda_2), \cdots, Re(\lambda_K)\}$, if $\lambda < 1/2$ and

$$\sum_{n=1}^{\infty} \frac{\| \boldsymbol{H}_n - \boldsymbol{H} \|}{\sqrt{n}} < \infty, \tag{4}$$

then

$$\sqrt{n}\left(\frac{\boldsymbol{Y}_n}{\sum_{j=1}^{K} Y_{nj}} - \boldsymbol{v} \right) \xrightarrow{D} N(0, \boldsymbol{\Sigma}) \tag{5}$$

and

$$\sqrt{n}\left(\frac{\boldsymbol{N}_n}{n} - \boldsymbol{v} \right) \xrightarrow{D} N(0, \boldsymbol{\Sigma}^*). \tag{6}$$

Under similar conditions, we showed that $\boldsymbol{Y}_n - n\boldsymbol{v}$ and $\boldsymbol{N}_n - n\boldsymbol{v}$ can be approximated by Gaussian processes:

$$\boldsymbol{G}_{n1}\boldsymbol{H} + \boldsymbol{G}_{n2} \text{ and } \boldsymbol{G}_{n1} + \int_0^n \frac{\boldsymbol{G}_{x2}}{x} \mathrm{d}x(\boldsymbol{I} - 1'\boldsymbol{v})$$

respectively (Bai et al., 2002c; 2001*), where $\boldsymbol{G}_{ti}$ are independent Gaussian processes which are solutions of the following type equation:

$$\boldsymbol{G}_t = \boldsymbol{W}_t + \int_0^t \frac{\boldsymbol{G}_s}{s}(\boldsymbol{H} - 1'\boldsymbol{v})\mathrm{d}s, \quad t > 0,$$
$$\boldsymbol{G}_0 = 0.$$

Here $\{\boldsymbol{W}(t)\}$ is a d-dimensional Brownian motion. In particular, the limiting combining distribution of $\boldsymbol{Y}_n$ and $\boldsymbol{N}_n$ was obtained. For more results, one can refer to Bai et al. (2001a; 2001b) and Rosenberger (1996).

Define $X_n = i$ if a ball of type i is drawn at nth stage; $T_n = 1$ if the response of the nth patient is a "success", 0 otherwise. Assume that $P\{T_n = 1 \mid X_j = i\}$ is independent of n, hence we can write

$$p_i = P\{T_n = 1 \mid X_n = i\}, \quad q_i = 1 - p_i. \tag{7}$$

Now we give some important special cases.

Case 1. Let $\boldsymbol{H}^{(1)} = (h_{ij}^{(1)})_{i,j=1}^{K}$, where $h_{ii}^{(1)} = p_i$ and $h_{ij}^{(1)} = q_i/(K-1)$ $(i \neq j)$. Then v_i in Eq. (3) is

$$v_i^{(1)} = \frac{1/q_K}{\sum_{j=1}^{K} q_j}.$$

This model was proposed by Wei (1979), which means that, at the nth stage, if a patient is assigned to treatment i and cured, then a type i ball is added to the urn, otherwise, if treatment i for a patient fails, then $\frac{1}{K-1}$ balls are added to each of the other $K-1$ treatments.

Case 2. Let $\boldsymbol{H}^{(2)} = (h_{ij}^{(2)})_{i,j=1}^{K}$, where $h_{ii}^{(2)} = p_i$ and $h_{ij}^{(2)} = q_i p_j/(M - p_i)$ $(i \neq j)$ and $M = \sum_{j=1}^{K} p_j$. Then v_i in Eq. (3) is

$$v_i^{(2)} = \frac{p_i(M - p_i)/q_i}{\sum_{j=1}^{K} p_j(M - p_j)/q_j}.$$

This model was proposed by Bai et al. (2002b), which means that, at the nth stage, if a patient is assigned to treatment i and cured, then a type i ball is added into the urn, otherwise, if treatment i for the patients fails, then a number of balls proportional to the success rates of the other $K-1$ treatments are added into the urn. But this design is not practicable, since the success probabilities p_j are unknown. They should be replaced by their sample estimators. This leads to the following case.

Case 3. Let $\boldsymbol{S}_n = (S_{n1}, \cdots, S_{nK})$, where S_{ni} denotes the number of successes of the ith treatment in the N_{ni} trials, $r_{ni} = (S_{ni} + 1)/(N_{ni} + 1)$ and $M_{n-1} = \sum_{j=1}^{K} r_{n-1,j}$. And let

$$\boldsymbol{H}^{(3)} = \boldsymbol{H}_n^{(3)} =$$
$$\begin{pmatrix} p_1 & \frac{r_{n-1,2}}{M_{n-1} - r_{n-1,1}} q_1 & \cdots & \frac{r_{n-1,K}}{M_{n-1} - r_{n-1,1}} q_1 \\ \frac{r_{n-1,1}}{M_{n-1} - r_{n-1,2}} q_2 & p_2 & \cdots & \frac{r_{n-1,K}}{M_{n-1} - r_{n-1,2}} q_2 \\ \cdots & \cdots & \cdots & \cdots \\ \frac{r_{n-1,1}}{M_{n-1} - r_{n-1,K}} q_K & \frac{r_{n-1,2}}{M_{n-1} - r_{n-1,K}} q_K & \cdots & p_K \end{pmatrix}$$

Case 4. The success probabilities defined in Eq. (7) are homogeneous for different stages (patients). But this assumption is not always realistic in certain situations, where patients may exhibitant drift in characteristics over time, i.e.

$$p_i(n) = P\{T_n = 1 \mid X_n = i\},$$
$$q_i(n) = 1 - p_i(n). \tag{8}$$

It is natural to assume that the treatments are sta-

* Bai, Z.D., Hu, F. and Zhang L.X., 2001. The weak and strong approximation for generalized Friedman's urn model.

ble in such case, i.e., it is assumed that $p_i(n) \to p_i$, $i = 1, \cdots, K$. In such case, the design in Case 1 becomes $\boldsymbol{H}^{(4)} = \boldsymbol{H}_n^{(4)} = (h_{ij}^{(4)})_{i,j=1}^{K}$, where $h_{ii}^{(4)} = p_i(n)$ and $h_{ij}^{(4)} = q_i(n)/(K-1)(i \neq j)$.

Both $\boldsymbol{H}^{(1)}$ and $\boldsymbol{H}^{(2)}$ are independent of n, the stage number, and so the models are homogeneous. But $\boldsymbol{H}^{(3)}$ and $\boldsymbol{H}^{(4)}$ are dependent on n, and so the models are non-homogeneous.

Remark 1. When $K = 2$, the above three adaptive designs are all governed by the RPW rule. So all of these designs are extensions of the RPW rule for K treatments.

Remark 2. For designs $\boldsymbol{H}^{(1)}$ and $\boldsymbol{H}^{(2)}$, when $K > 2$, notice that for any $i \neq j$, $1 \leqslant i, j \leqslant K$, if $p_i > p_j$, we have

$$\frac{v_i^{(2)}}{v_j^{(2)}} - \frac{v_i^{(1)}}{v_j^{(1)}} = \frac{p_i(M - p_i)/q_i}{p_j(M - p_j)/q_j} - \frac{1/q_i}{1/q_j} = \frac{(p_i - p_j)(M - p_i - p_j)/q_i}{p_j \sum_{k \neq j} p_k/q_j} > 0.$$

The design $\boldsymbol{H}^{(2)}$ is more reasonable than the design $\boldsymbol{H}^{(1)}$ because more patients will be assigned to a better treatment.

Remark 3. Let $a \geqslant 0$. An extension of the design $\boldsymbol{H}^{(3)}$ has $r_{n-1,j}^{a}$ and $M_{n-1}(a) = \sum_{j=1}^{K} r_{n-1,j}^{a}$ instead of $r_{n-1,j}$ and M_{n-1} respectively. Taking $a = 0$ and 1 yields designs $\boldsymbol{H}^{(1)}$ and $\boldsymbol{H}^{(3)}$ respectively.

Designs dependent on estimated unknown parameters: The asymptotic normality of Case 1 and Case 2 follows from Eqs.(5) and (6) immediately. In the Case 4, if

$$\sum_{n=1}^{\infty} \frac{| p_i(n) - p_i |}{\sqrt{n}} < \infty, \quad i = 1, \cdots, K, \quad (9)$$

then the condition (4) is satisfied, and so asymptotic properties also follow. But the model in Case 3 can not satisfy the condition (4), since the fastest convergence rate of $\boldsymbol{H}_n$ is that $\| \boldsymbol{H}_n - \boldsymbol{H} \| = O(\sqrt{n})$ in probability. The asymptotic normalities of such case were studied in Hu and Zhang*. We considered the general model with design matrices of the type $\boldsymbol{H}_n = \boldsymbol{H}(\hat{\boldsymbol{\Theta}}_n)$ dependent on the estimated unknown parameter, where $\hat{\boldsymbol{\Theta}}_n$ is the sample estimator of the unknown parameter $\boldsymbol{\Theta}$. Strong consistency and the asymptotic normalities are established for both the urn composition and the number of patients assigned to each treatment. It should be mentioned that the condition (4) cannot be reduced to $\| \boldsymbol{H}_n - \boldsymbol{H} \| = O(\sqrt{n})$ in general.

Designs with delay responses: Typically, clinical trials do not result in immediate outcomes, i.e., individual patient outcomes may not be immediately available prior to the randomization of the next patient. Consequently, the urn cannot be updated immediately, but can be updated only when the outcomes become available. Fortunately, it is verified that stochastic staggered entry and delay mechanisms do not affect the asymptotic properties of both the urn composition $\boldsymbol{Y}_n$ and the sample fractions $\boldsymbol{N}_n$ for a wide class of designs defined by GPU (Bai et al., 2002a).

DOUBLY BIASED COIN ADAPTIVE DESIGNS

We come back to the PW rule and RPW rule. As it is known, the PW rule is too deterministic and is not applicable when we have delayed responses from patients of treatments. The RPW rule and its generalizations seem solve this problem. However, in using the RPW rule, when $q_1 + q_2 < 0.5$, the limiting distributions of the proportions of patients assigned to each treatments are unknown. But in practice, both q_1 and q_2 are usually very small. So, the RPW rule is not practical in such cases. The asymptotic variation of the proportion becomes a big problem in using the RPW rule (even the adaptive designs based on the GPU model) for $q_1 + q_2 < 0.5$. Even in the case that $q_1 + q_2 > 0.5$, if $q_1 + q_2$ is near 0.5, σ_{RPW} is much larger than σ_{PW}. That is to say, the RPW rule is too random so that the asymptotic variance of proportion of patients assigned to each treatment is very large when the cure rates are large and so it is much less stable than the PW rule. Also, in using the multi-arm RPW, the condition that $\lambda < 1/2$ is very hard to check. Even in the 3-arm case, it is very difficult to check this condition.

Now, with keeping the desired allocation pro-

* Hu, F. and Zhang, L.X., 2001. The asymptotic theorems of adaptive designs for clinical trials with generations depending on the estimated success rates.

portions $v_1 = q_2/(q_1 + q_2)$ and $v_2 = q_1/(q_1 + q_2)$, just as in the case of the PW rule and RPW rule, our goal is to reduce the asymptotic variance. A natural way is as follows. At the $(n+1)$ th stage, we assign a patient to a certain treatment by comparing the value N_{n1}/n with v_1, or N_{n2}/n with v_2. If N_{n1}/n is larger than v_1, then we assign a patient to the treatment 1 with a probability less than v_1; If N_{n1}/n is less than v_1, then we assign a patient to the treatment 1 with a probability larger than v_1; If N_{n1}/n equals v_1, then we assign a patient to the treatment 1 with probability v_1 and to the treatment 2 with probability v_2. By choosing suitable function, we may minimize the asymptotic variance. However, v_1 and v_2 are unknown, so they should be replaced by their estimators based on the sample of the previous n stages. So, the following adaptive design of clinical trial is considered and proposed.

At the first stage, a patient is assigned to each treatment with the same probability 1/2. After m assignments, we let S_{mk} be the number of successes of all the N_{mk} patients on the treatment k in the first m assignments, $k = 1, 2$, as usual. And let $\hat{p}_{mk} = \dfrac{S_{mk} + 1/2}{N_{mk} + 1}$ be the sample estimation of p_k, and write $\hat{q}_{mk} = 1 - \hat{p}_{mk}$, $k = 1, 2$. At the $(m+1)$th stage, the $(m+1)$th patient is assigned to the treatment 1 with probability $g(\dfrac{N_{m1}}{m}, \hat{v}_{m1})$, and to the treatment 2 with probability $1 - g(\dfrac{N_{m1}}{m}, \hat{v}_{m1})$, where $\hat{v}_{m1} = \dfrac{\hat{q}_{m2}}{\hat{q}_{m1} + \hat{q}_{m2}}$ is the sample estimation of $v_1 = q_2/(q_1 + q_2)$. The functions $g(x, \rho)$ is called allocation rule. A large class of functions can be chosen as an allocation rule. If it is one of the following forms:

$$g(x,\rho) = 0 \vee \left(\frac{\rho\exp\{\alpha(\frac{\rho}{x} - 1)\} + 1 - (1-\rho)\exp\{\alpha(\frac{1-\rho}{1-x} - 1)\}}{2}\right) \wedge 1,$$

$$g(x,\rho) = 0 \vee \left(\frac{\rho(\frac{\rho}{x})^\alpha + 1 - (1-\rho)(\frac{1-\rho}{1-x})^\alpha}{2}\right) \wedge 1,$$

$$g(0,\rho) = 1,\ g(1,\rho) = 0,$$

$$g(x,\rho) = \frac{\rho(\frac{\rho}{x})^\alpha}{\rho(\frac{\rho}{x})^\alpha + (1-\rho)(\frac{1-\rho}{1-x})^\alpha},$$

where $\alpha \geqslant 0$, we have that

$$\frac{N_{n1}}{n} - v_1 = O\left(\sqrt{\frac{\log\log n}{n}}\right) \quad a.s. \quad \text{and} \quad \sqrt{n}\left(\frac{N_{n1}}{n} - v_1\right) \xrightarrow{D} N(0, \sigma^2_{DAD})$$

where

$$\sigma^2_{DAD} = \sigma^2_\alpha := \frac{q_1 q_2 (p_1 + p_2)}{(q_1 + q_2)^3} + \frac{2q_1 q_2}{(1+2\alpha)(q_1+q_2)^3}$$

It should be noted that the asymptotic normality holds for all $0 < p_1 < 1$ and $0 < p_2 < 1$ (Hu et al. 2003). It is easily seen that σ^2_α is a strictly monotonous decreasing function of $\alpha \geqslant 0$ and $\sigma^2_\alpha \to \sigma^2_{\mathrm{PW}}$ as $\alpha \to +\infty$. Also, $\sigma^2_\alpha < \sigma^2_{\mathrm{RPW}}$ for all $\alpha > 1$, whenever $q_1 + q_2 > 1/2$. Furthermore, if $q_1 + q_2$ is near 1/2, then σ_α is much smaller than σ_{RPW}. So, this adaptive design is more stable than the RPW rule. The larger α is, the more stable and less random is the design. So, this design is a compromise between the stability in the PW rule and the randomization in the RPW rule. Even when α is very large, it keeps enough randomization to avoid determinism. Such design can keep the spirit of the RPW rule in that it assigns more patients to the better treatment and allows delayed responses by the patients.

In such kind of designs, the assignments are adapted by both the results of responses and the current proportions of patients assigned, and its original idea came from Efron's (1971) biased coin design. So, they are called doubly adaptive biased coin design, first introduced by Eisele (1994) and Eisele et al. (1995) in the two-arm case with the responses which are from standard exponential families. However, the results of Eisele (1994) and Eisele et al. (1995) are not applicable since their condition (v) is impossible to be satisfied, because, if q_1 and q_2 are small, both v_1 and $v_2 = 1 - v_1$ should be very large by their (v). But this condition is a key in their proving methods.

Hu et al. (2003) studied the general multi-arm case, where the condition that $\lambda < 1/2$ in using GPU model is no longer a problem.

MARKOV CHAIN ADAPTIVE DESIGNS

In this section, we propose another class of adaptive designs, the so-called Markov chain adaptive design. Consider the two-arm case first. Suppose that at the stage n, the treatment 1 is assigned to the nth patient. Then the $(n+1)$th patient will be assigned either treatment 1 or treatment 2 according certain probabilities, which depend on the response of the nth patient. Let α_s be the probability of assigning the $(n+1)$th patient to treatment 1, when the response of the nth patient to treatment 1 is "success", and let α_f be the probability of assigning the $(n+1)$th patient to treatment 1, when the response of the nth patient to treatment 1 is "failure". Similarly define β_s and β_f with treatment 2 instead of treatment 1 in the definitions of α_s and α_f. When $\alpha_s = 1$, $\alpha_f = 0$, $\beta_s = 1$, $\beta_f = 0$, we get Zelen's PW rule. We may choose the parameters α_s, α_f, β_s and β_f for different goals.

Define $X_n = 1$ or 0 if nth patient is assigned to the treatment 1 or 2, respectively. Then $N_{n1} = \sum_{j=1}^{n} X_j$ is the number of patients assigned to treatment 1 in the first n stages. Let $p_1(n) = P\{\text{success} \mid X_n = 1\}$ and $p_2(n) = P\{\text{success} \mid X_n = 0\}$ and $\alpha_n = p_1(n)\alpha_s + (1 - p_1(n))\alpha_f$, $\beta_n = p_2(n)\beta_s + (1 - p_2(n))\beta_f$. Then $\{X_n\}$ is a Markov chain with the transition probability matrix

$$\boldsymbol{P}_n = \begin{pmatrix} \alpha_n & 1-\beta_n \\ 1-\alpha_n & \beta_n \end{pmatrix}.$$

When $p_1(n) = p_1$ and $p_2(n) = p_2$ for all n, $\{X_n\}$ is homogeneous. For this case we can write $\alpha_n = \alpha$, $\beta_n = \beta$, and we have that

$$\frac{N_{n1}}{n} \xrightarrow{P} \mu \text{ and } \sqrt{n}\left(\frac{N_{n1}}{n} - \mu\right) \xrightarrow{D} N(0, \sigma^2) \quad (10)$$

where

$$\mu = \frac{1-\beta}{2-\alpha-\beta}, \sigma^2 = \frac{(1-\alpha)(1-\beta)(\alpha+\beta)}{(2-\alpha-\beta)^2}$$

(Bai et al., 2001*). For non-homogeneous case we have similar results under the condition of type Eq. (9). Furthermore, we established the strong consistency and strong approximation of $\boldsymbol{N}_{n1}$:

$$N_{n1} - n\mu - \sigma W(n) = O((n\log\log n)^{1/4}(\log n)^{1/2}) \ a.s.,$$

where $\{W(t)\}$ is a standard Brownian motion (Lin et al. 2001**).

For the multi-arm case, we let $\boldsymbol{X}_n = (X_{n1}, \cdots, X_{nK})$, where $X_{ni} = 1$ if the nth patient is assigned to treatment i, and let $\boldsymbol{N}_n = \sum_{k=1}^{n} \boldsymbol{X}_k$ be the number of patients assigned to each treatment at the first n stages, as usual. Let $p_i(n) = P\{\text{success} \mid X_{ni} = 1\}$. Assume the transition probability matrix of the Markov chain $\{\boldsymbol{X}_n\}$ is $\boldsymbol{H}_n = \{H_{ij}(n)\}$ which is a function of $p_i(n)$, $i = 1, \cdots, K$, i.e, $\boldsymbol{E}[\boldsymbol{X}_{n+1} \mid \boldsymbol{X}_n] = \boldsymbol{X}_n\boldsymbol{H}_n$. We showed that $\boldsymbol{N}_n$ can be approximated by a multi-dimensional Browian motion:

$$\boldsymbol{N}_n - n\boldsymbol{\nu} - \boldsymbol{W}(n)\boldsymbol{\Sigma} = o(n^{1/2}) + O\left(\sum_{k=1}^{n} \| \boldsymbol{H}_k - \boldsymbol{H} \|\right) a.s.$$

where $\boldsymbol{\nu} = (v_1, \cdots, v_K)$ is the left eigenvector corresponding to the largest eigenvalue of $\boldsymbol{H}$ with $v_1 + \cdots + v_K = 1$, $\{\boldsymbol{W}(t)\}$ is a K-dimensional standard Brownian motion. In particular, we have asymptotil normality, if

$$\sum_{k=1}^{n} \| \boldsymbol{H}_k - \boldsymbol{H} \| = o(n^{1/2}). \quad (11)$$

Condition (11) is usual satisfied if $\sum_{k=1}^{n} | p_i(k) - p_i | = o(n^{1/2})$, $i = 1, \cdots, K$, which is implied by (9).

If $\boldsymbol{H}_n$ depends on estimated unknown parameters, the problen becomes more complicated. Zhang*** studied such case.

Remark 4. In Section 2, we mentioned the normality in Eqs.(1) and (2), but the condition $p_1 + p_2 < 3/2$ was imposed. But for normality in Eq.(10), this restriction is cancelled. In the multi-arm case, the restriction that $\lambda < 1/2$ is also cancelled.

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* Bai, Z.D. Chen, Y.M., Hu, F. and Lin, Z.Y., 2001. Adaptive designs based on Markov chains (Ⅰ)(Ⅱ).

** Lin, Z.Y. and Zhang L.X., 2001. Strogn approximation of a non-homogenous markov chain.

*** Zhang, L.X., 2002. A kind of multi-treatment adaptive designs with assignment probabilities depending on the estimated parameters.

Remark 5. Keeping μ we can choose α and β to minimize σ^2 so that we get more stable Markov chain adaptive designs. Also, if α and β was chosen suitably, the Markov chain adaptive designs can also keep both randomization and stability.

References

Athreya, K. B. and Karlin, S., 1968. Embedding of urn schemes into continuous time branching processes and related limit theorems. *Ann. Math. Statist.*, **39**: 1801 – 1817.

Bai, Z. D. and Hu, F., 1999. Asymptotic theorem for urn models with nonhomogeneous generating matrices. *Stochastic Process. Appl.*, **80**: 87 – 101.

Bai, Z. D., Chen, G. J. and Hu, F., 2001a. Limit theorems in an urn model with time trends in sequential experiment. *Chin. Ann. Math.*, **22**(A): 89 – 96.

Bai, Z. D., Chen, G. J. and Hu, F., 2001b. A kind of urn model for adaptive sequential design. *Acta Mathematica Scientica*, **21**(B): 224 – 228.

Bai, Z. D., Hu, F. and Rosenberger, 2002a. Asymptotic properties of adaptive designs for clinical trials with delayed response. *Ann. Statist.*, **30**: 122 – 139.

Bai, Z. D., Hu, F. and Shen, L., 2002b. An adaptive design for multi – arm clinical trials. *J. Multi. Anal.*, **81**: 1 – 18.

Bai, Z. D., Hu, F. and Zhang L. X., 2002c. The Gaussian approximation theorems for urn models and their applications. *Ann. Appl. Probab.*, **12**: 1149 – 1173.

Eisele, J., 1994. The doubly adaptive biased coin design for sequential clinical trials. *J. Statist. Plann. Inf.*, **38**: 249 – 262.

Eisele, J., 1995. Biased coin designs: some properties and applications. *In*: Adaptive Designs (Flournoy, N. and Rosenberger, W. F. eds.) Hayward, CA: Institute of Mathematical Statistics, p. 48 – 64.

Eisele, J. and Woodroofe, M., 1995. Central limit theorems for doubly adaptive biased coin designs. *Ann. Statist.*, **23**: 34 – 254.

Efron, B., 1971. Forcing a sequential experiment to be balanced. *Biometrika*, **62**: 347 – 352.

Hu, F. and Zhang, L. X., 2003. Asymptotic properties for doubly adaptive biased coin designs of multi – treatment clinical trials. accepted by Ann. *Statist.*

Rosenberger, W. F., 1996. New directions in adaptive designs. *Statist. Sci.*, **11**: 137 – 149.

Smythe, R. T. and Rosenberger, W. F., 1995. Play-the-winner designs, generalized Polya urns, and Markov branching processes. Adaptive Designs (Flournoy, N. and Rosenberger, W. F. eds.) Hayward, CA: Institute of Mathematical Statistics, p. 13 – 22.

Smythe, R. T., 1996. Central limit theorems for urn models. *Stochastic Process. Appl.*, **65**: 115 – 137.

Wei, L. J. and Durham, S., 1978. The randomized play-the-winner rule in medical trials. *J. Amer. Statist. Assoc.*, **73**: 840 – 843.

Wei, L. J., 1979. The generalized Polya's urn design for sequential medical trials. *Ann. Statist.*, **7**: 291 – 296.

Zelen, M., 1969. Play the winner rule and the controlled clinical trial. *J. Amer. Statist. Assoc.*, **64**: 131 – 146.