ASYMPTOTIC PROPERTIES OF ADAPTIVE DESIGNS VIA STRONG APPROXIMATIONS*

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Various adaptive designs have been proposed and applied to clinical trials, bioassay, psychophysics, etc. More and more people have been paying attention to these design methods. Via strong approximations, this paper presents asymptotic properties of 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.
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1. 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

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kind of design has also been applied to bioassay, psychophysics, etc. This paper gives some asymptotic properties of several broad families of designs via strong approximations, such as the play-the-winner rule, randomized play-the-winner rule and its generalization to the multi-arm case, the drop-the-loss rule, doubly biased coin adaptive design, Markov chain model.

We consider the K-treatment clinical trial ($K \geq 2$). Suppose the patients are recruited into the clinical trial sequential. Let $X_{nk} = 1$ if the n-th patient is assigned to the treatment k and $= 0$ if otherwise, and let $N_{nk} = \sum_{m=1}^{n} X_{mk}$ be the number of patients assigned to the treatment k after n assignments, $k = 1, \ldots, K$. Write $\mathbf{X}_n = (X_{n1}, \ldots, X_{nK})$ and $\mathbf{N}_n = (N_{n1}, \ldots, N_{nK})$. Denote $\{\boldsymbol{\xi}_n = (\xi_{n1}, \ldots, \xi_{nK}), n = 1, 2, \ldots,\}$ to be the sequence of responses of patients, where ξ_{nk} is the response of the n-th patient on the treatment k, $k = 1, \ldots, K$. $\{\boldsymbol{\xi}_n\}$ is usually assumed to be a sequence of independent random vectors. In the clinical trial, only those ξ_{nk}s for which $X_{nk} = 1$ appear. But we assume that all $\xi_{n1}, \ldots, \xi_{nK}$, $n = 1, 2, \ldots$, are there and only those non-zero ones of $X_{nk}\xi_{nk}$s are selected in the trial.

2. Play-the-Winner rule and Markov chain adaptive designs

PW 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 [34] 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 $p_i = \mathsf{P}\{\text{success} \mid \text{treatment } i\}$ 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

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

where

$$\sigma_{PW}^2 = q_1 q_2 (p_1 + p_2)/(q_1 + q_2)^3, \tag{1}$$

This is first discussed in Zelen [34].

MC adaptive design. An extension of the PW rule is the multi-treatment Markov chain adaptive design. Consider an K-treatment clinical trial. Suppose that at stage m, the m-th patient is assigned to the treatment i. Then the $(m+1)$-th patient will be assigned to the treatment j according certain probabilities, which depend on the response of the i-th patient. Denote this probability by $h_{ij}(m)$. Write $\mathbf{H}_n = \big(h_{ij}(n)\big)_{i,j=1}^K$. Obviously, $\mathbf{H}_n\mathbf{1}' = \mathbf{1}'$, where $\mathbf{1} = (1, \ldots, 1)$. Denote $\mathbf{e}_i$ be vector for which the i-th component is 1 and other components are 0, $i = 1, \ldots, K$. Then

$$\mathsf{P}(\mathbf{X}_{m+1} = \mathbf{e}_j | \mathbf{X}_m = \mathbf{e}_i) = h_{ij}(m).$$

It follows that

$$\mathsf{E}[\mathbf{X}_{m+1}|\mathcal{F}_m] = \mathbf{X}_m\mathbf{H}_m,$$

where $\mathcal{F}_m = \sigma(\mathbf{X}_1, \ldots \mathbf{X}_n)$. Obviously, $\{\mathbf{X}_n; n \geq 1\}$ is a Markov chain with transition probability matrices $\mathbf{H}_n$. If $\mathbf{H}_n = \mathbf{H}$ for all n, then $\{\mathbf{X}_n; n \geq 1\}$ is called homogenous. Otherwise, it is called non-homogeneous, and it is usually assumed that $\mathbf{H}_n \to \mathbf{H}$ a.s. for some non-random matrix $\mathbf{H}$. It is obvious that $\lambda_1 = 1$ is an eigenvalue of $\mathbf{H}$. Let $\lambda_2, \ldots, \lambda_K$ be the other $K-1$ eigenvalues of $\mathbf{H}$, and let $\lambda = \max\{Re(\lambda_2), \ldots, Re(\lambda_K)\}$. We assume that $\lambda < 1$. Notice that $|\lambda_i| \leq 1$, $i = 1, \ldots, K$. The condition that $\lambda < 1$ is not a hard condition. For example, if $\mathbf{H}$ is a regular transition probability matrix of a Markov chain, then $|\lambda_i| < 1$, $i = 2, \ldots, K$, and so $\lambda < 1$. We have the following asymptotic properties (c.f., Lin and Zhang [24] and Zhang [35]).

Theorem 2.1. *Possibly in a richer underlying probability space in which there exists an K- dimensional standard Brownian motion $\{\mathbf{B}_t\}$, we can redefine the sequence $\{\mathbf{X}_n\}$, without changing its distribution, such that*

$$\mathbf{N}_n - n\mathbf{v} - \mathbf{B}_n\mathbf{\Sigma}^{1/2}(\mathbf{I} - \widetilde{\mathbf{H}})^{-1} = o(n^{1/2-\kappa}) + O\Big(\sum_{k=1}^n \|\mathbf{H}_k - \mathbf{H}\|\Big) \quad a.s., \tag{2}$$

for some $\kappa > 0$, where $\mathbf{v} = (v_1, \cdots, v_K)$ is the left eigenvector corresponding to the largest eigenvalue $\lambda_1 = 1$ of $\mathbf{H}$ with $v_1 + \ldots + v_K = 1$, $\widetilde{\mathbf{H}} = \mathbf{H} - \mathbf{1}'\mathbf{v}$ and

$$\mathbf{\Sigma} = diag(\mathbf{v}) - \mathbf{H}'diag(\mathbf{v})\mathbf{H}.$$

In particular, if

$$\sum_{k=1}^n \|\mathbf{H}_k - \mathbf{H}\| = o(n^{1/2}) \quad a.s., \tag{3}$$

then we have the asymptotic normality:

$$n^{1/2}(\mathbf{N}_n/n - \mathbf{v}) \xrightarrow{\mathcal{D}} N(\mathbf{0}, (\mathbf{I} - \widetilde{\mathbf{H}}')^{-1}\mathbf{\Sigma}(\mathbf{I} - \widetilde{\mathbf{H}})^{-1}). \tag{4}$$

Remark 2.1. In the case $K = 2$, write $h_{11} = \alpha$ and $h_{22} = \beta$. Then it can be checked that

$$\mathbf{H} = \begin{pmatrix} \alpha & 1-\alpha \\ 1-\beta & \beta \end{pmatrix}, \quad \mathbf{v} = \left(\frac{1-\beta}{2-\alpha-\beta}, \frac{1-\alpha}{2-\alpha-\beta}\right)$$

and

$$(\mathbf{I} - \widetilde{\mathbf{H}}')^{-1}\mathbf{\Sigma}(\mathbf{I} - \widetilde{\mathbf{H}})^{-1} = \frac{(1-\alpha)(1-\beta)(\alpha+\beta)}{(2-\alpha-\beta)^3}\begin{pmatrix} 1 & -1 \\ -1 & 1 \end{pmatrix}.$$

For the PW rule, $\alpha = p_1$ and $\beta = p_2$. And so,

$$N_{n1} - nq_2/(q_1+q_2) = B_n\sigma_{PW} + o(n^{1/2-\kappa}) \quad a.s.,$$

where B_t is a one-dimensional standard Brownian motion.

The following examples are for the multi-treatment case with dichotomous response (success and failure).

Example 2.1. (**Up-and-down design**) Durham and Flournoy [8] present a response -driven up-and-down design for dose-response studies using a random walk model. Given an increasing dose-response function $p_j = F(x_j) = \mathsf{P}\{\text{"success"}|X_m = x_j\}$, $m = 1, \ldots, n$, $j = 1, \ldots, K$, and X_i taking values in the set $\{x_k = x_1 + (k-1)\Delta, k = 1, \ldots, K\}$, Durham and Flournoy [8] fix the bias of a coin $b \equiv \Gamma/(1-\Gamma)$, $0 < \Gamma < 1/2$. Given $X_m = x_j$, X_{m+1} is determined using the following allocation scheme. If the response is a failure and the coin lands heads up, assign $X_{m+1} = x_{j+1}$; if the response is a failure and the coin lands heads down, assign $X_{m+1} = x_j$; and if the response is a success, assign $X_{m+1} = x_{j-1}$ (appropriate modifications are made at the boundaries x_1 and x_K). Then they show that the distribution of administered doses centers around the unknown quantile μ, where $\Gamma = F(\mu)$. For this design,

$$\mathbf{H}_m = \mathbf{H} = \begin{pmatrix} (1-b)q_1 & bq_1 & 0 & \cdots & 0 & p_1 \\ p_2 & (1-b)q_2 & bq_2 & \ldots & 0 & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ bq_K & 0 & 0 & \cdots & p_K & (1-b)q_K \end{pmatrix}.$$

So,

$$\mathbf{N}_n - n\mathbf{v} = \mathbf{B}_n\mathbf{\Sigma}^{1/2}(\mathbf{I} - \widetilde{\mathbf{H}})^{-1} + o(n^{1/2-\kappa}) \quad a.s.$$

with $\mathbf{v} = \boldsymbol{\pi}$, where $\boldsymbol{\pi} = (\pi_1, \ldots, \pi_K)$ is defined in Durham and Flournoy [8].

When the responses $\{\boldsymbol{\xi}_n\}$ are not identical distributed, we put $p_i(n) = \mathsf{P}(\text{"success"}|X_{ni} = 1)$, and $q_i(n) = 1 - p_i(n)$, $i = 1, 2, \ldots, K$. Assume that $p_i(n) \to p_i$, $i = 1, 2, \ldots, K$. Denote $q_i = 1 - p_i$.

Example 2.2. **(PWC rule)** Suppose that the m-th patient is assigned to the i-th treatment. If the response of the m-th patient is a success, then the $(m+1)$-th patient is assigned to the same treatment i. If the response of the m-th patient is a failure, then the $(m+1)$-th patient is assigned to the treatment $(i+1)$, where the treatment $(K+1)$ means the treatment 1. This assignment scheme is called the cyclic play the winner (PWC) rule (Hoel and Sobel [14]). It is easily seen that

$$\mathbf{H}_n = \begin{pmatrix} p_1(n) & q_1(n) & 0 & \cdots & 0 \\ 0 & p_2(n) & q_2(n) & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ q_K(n) & 0 & \cdots & \cdots & p_K(n) \end{pmatrix},$$

$$\mathbf{H} = \begin{pmatrix} p_1 & q_1 & 0 & \cdots & 0 \\ 0 & p_2 & q_2 & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ q_K & 0 & \cdots & \cdots & p_K \end{pmatrix},$$

$$\mathbf{v} = \left(\frac{1/q_1}{\sum_{j=1}^K 1/q_j}, \frac{1/q_2}{\sum_{j=1}^K 1/q_j}, \cdots, \frac{1/q_K}{\sum_{j=1}^K 1/q_j} \right) \tag{5}$$

and $\|\mathbf{H}_n - \mathbf{H}\| \le C \sum_{i=1}^K |p_i(n) - p_i|$. So, by Theorem 2.1, if $0 < p_i < 1$, $j = 1, \ldots, K$, then (2) is just

$$\mathbf{N}_n - n\mathbf{v} - \mathbf{B}_n \boldsymbol{\Sigma}^{1/2} (\mathbf{I} - \widetilde{\mathbf{H}})^{-1} = o(n^{1/2-\kappa}) + O(\sum_{k=1}^n \sum_{i=1}^K |p_i(k) - p_i|) \quad a.s. \tag{6}$$

Example 2.3. Suppose that the m-th patient is assigned to the treatment i. If the response of the m-th patient is a success, then the $(m+1)$-th patient is assigned to the same treatment i. If the response of the m-th patient is a failure, then the $(m+1)$-th patient is assigned to each of other

$K-1$ treatments with probability $\frac{1}{K-1}$. It is easily seen that

$$\mathbf{H}_n = \begin{pmatrix} p_1(n) & q_1(n)/(K-1) & \cdots & q_1(n)/(K-1) \\ q_2(n)/(K-1) & p_2(n) & \cdots & q_2(n)/(K-1) \\ \cdots & \cdots & \cdots & \cdots \\ q_K(n)/(K-1) & q_K(n)/(K-1) & \cdots & p_K(n) \end{pmatrix},$$

$$\mathbf{H} = \begin{pmatrix} p_1 & q_1/(K-1) & \cdots & q_1/(K-1) \\ q_2/(K-1) & p_2 & \cdots & q_2/(K-1) \\ \cdots & \cdots & \cdots & \cdots \\ q_K/(K-1) & q_K/(K-1) & \cdots & p_K \end{pmatrix}, \tag{7}$$

$\mathbf{v}$ is the same as in (5) and $\|\mathbf{H}_n - \mathbf{H}\| \le C\sum_{i=1}^K |p_i(n) - p_i|$. So, (6) holds whenever $0 < p_i < 1$, $j = 1, \ldots, K$.

Remark 2.2. When $K = 2$, the designs in Examples 2.1-2.3 are all the PW rule.

MC adaptive design with random assignment probabilities. The PWC rule and the design in Example 2.3 tend to put more patients to better treatments. However, when there is a failure on the treatment k, it should be more reasonable to assign the next patient with higher probability to a better treatment among the other $d-1$ treatments. Thus, the following adaptive is considered.

Example 2.4. Suppose the response sequence $\{\boldsymbol{\xi}_n\}$ is an i.i.d. sequence, and so $p_k(n) = p_k$ for all n and $k = 1, \ldots, K$. If the response of the m-th patient on the treatment k is a success, we assign a coming patient to the same treatment. If the response is a failure, we assign the $(m+1)$-the patient to the treatment j with probability $\frac{\hat{p}^\alpha_{m-1,j}}{(M_{m-1,\alpha} - \hat{p}^\alpha_{m-1,k})}$ for all $j \neq k$, where $0 \le \alpha < \infty$, $M_{m-1,\alpha} = \sum_{j=1}^K \hat{p}^\alpha_{m-1,j}$, $\hat{p}_{m-1,j} = \frac{S_{m-1,j}+1}{N_{m-1,j}+1}$, and $S_{m-1,j}$ denotes the number of successes of the j-th treatment in all the $N_{m-1,j}$ trials of previous $m-1$ stages, $j = 1, \ldots, K$. Write $\widehat{\mathbf{p}}_{m-1} = (\widehat{p}_{m-1,1}, \ldots, \widehat{p}_{m-1,K})$. In this case, $\mathbf{H}_m = \mathbf{H}(\widehat{\mathbf{p}}_{m-1})$, where $\mathbf{H}(\mathbf{x}) = (h_{k,j}(\mathbf{x}), k, j = 1, \ldots, K)$ with $h_{k,k}(\mathbf{x}) = p_k$ and $h_{k,j}(\mathbf{x}) = \frac{x_j^\alpha q_k}{\sum_{i \neq k} x_i^\alpha}$ for $k \neq j$. Also,

$$\mathbf{H}_m \to \mathbf{H} = \mathbf{H}^{(\alpha)} =: \begin{pmatrix} p_1 & \frac{p_2^\alpha}{M_\alpha - p_1^\alpha} q_1 & \cdots & \frac{p_K^\alpha}{M_\alpha - p_1^\alpha} q_1 \\ \frac{p_1^\alpha}{M_\alpha - p_2^\alpha} q_2 & p_2 & \cdots & \frac{p_K^\alpha}{M_\alpha - p_2^\alpha} q_2 \\ \cdots & \cdots & \cdots & \cdots \\ \frac{p_1^\alpha}{M_\alpha - p_K^\alpha} q_K & \frac{p_2^\alpha}{M_\alpha - p_K^\alpha} q_K & \cdots & p_K \end{pmatrix}, \tag{8}$$

where $M_\alpha = \sum_{j=1}^K p_j^\alpha$, and

$$v_i = v_i^{(\alpha)} =: \frac{p_i^\alpha (M_\alpha - p_i^\alpha)/q_i}{\sum_{j=1}^K p_j^\alpha (M_\alpha - p_j^\alpha)/q_j}, \quad i = 1, \ldots, K. \tag{9}$$

If $\alpha = 0$, then $\mathbf{H}^{(\alpha)}$ is the as same as the one in (7) and $v_i^{(\alpha)}$ is the as same as the one in (6). By comparing the values of $\mathbf{v}^{(\alpha)}$s, one can find that the larger α is, the more patients will be assigned to a better treatment. So, the design Example 2.4 assigns more patients to better treatments than the PWC rule does. Also, when there is failure, the assignment is random in the design defined in this example. However, for this example, $\sum_{m=1}^n \|\mathbf{H}_m - \mathbf{H}\| = o(n^{1/2})$ dose not hold. So, the asymptotic normality is not implied by Theorem 2.1. This leads us to consider the following design (c.f., Zhang [36]).

Adaptive Design 2.1 Suppose the response sequence $\{\boldsymbol{\xi}_n\}$ is an i.i.d. sequence and each response ξ_{mi} is a random variable coming from a distribution family $\{P_{\theta_i}\}$. Without losing of generality, we assume that $\theta_i = \mathsf{E}\xi_{mi}$, $i = 1, \ldots, K$ and write $\boldsymbol{\Theta} = (\theta_1, \ldots, \theta_K)$. Suppose the previous $m-1$ patients are assigned and the responses observed. Let $\hat{\boldsymbol{\Theta}}_{m-1} = (\hat{\theta}_{m-1,1}, \ldots, \hat{\theta}_{m-1,K})$ be an estimate of $\boldsymbol{\Theta}$, where $\hat{\theta}_{m-1,k} = \frac{\sum_{i=1}^{m-1} X_{i,k}\xi_{i,k} + \theta_{0,k}}{N_{m-1,k}+1}$, $k = 1, \ldots, K$. Here, $\boldsymbol{\Theta}_0 = (\theta_{0,1}, \cdots, \theta_{0,K})$ is a guessed value of $\boldsymbol{\Theta}$, or an estimate of $\boldsymbol{\Theta}$ from other early trials.

Now, if the m-th patient is assigned to the treatment i and the response observed, then we assign the $(m+1)$-th patient to the treatment j with probability $d_{ij}(\hat{\boldsymbol{\theta}}_{m-1}, \xi_{m,i})$, $j = 1, \ldots, K$. That is

$$\mathsf{P}\big(X_{m+1,j} = 1 \big| \mathcal{F}_m, X_{m,i} = 1, \xi_{m,i}\big) = d_{ij}(\widehat{\boldsymbol{\theta}}_{m-1}, \xi_{m,i}), \tag{10}$$

$i, j = 1, \ldots, K$. Here $\mathcal{F}_n = \sigma(\mathbf{X}_1, \ldots, \mathbf{X}_n, \boldsymbol{\xi}_1, \ldots, \boldsymbol{\xi}_{n-1})$. We also let $h_{ij}(\widehat{\boldsymbol{\theta}}_{m-1}) = \mathsf{E}\big[d_{ij}(\widehat{\boldsymbol{\theta}}_{m-1}, \xi_{m,i})\big| \ \mathcal{F}_{m-1}\big]$ and write $\mathbf{H}(\widehat{\boldsymbol{\theta}}_{m-1}) = \big(h_{ij}(\widehat{\boldsymbol{\theta}}_{m-1})\big)_{i,j=1}^K$. To insure that each treatment is tested by enough patients, i.e., $N_{ni} \to \infty$ a.s., $i = 1, \ldots, K$, $d_{ij}(\hat{\boldsymbol{\theta}}_{m-1}, \xi_{m,i})$ shall be modified by $(1 - 1/m)d_{ij}(\hat{\boldsymbol{\theta}}_{m-1}, \xi_{m,i}) + 1/(mK)$ if necessary.

Theorem 2.2. *For the Adaptive Design 1, suppose* $\mathsf{E}\|\boldsymbol{\xi}_n\|^{2+\delta} < \infty$ *for some* $\delta > 0$, $\mathbf{H}(\mathbf{x}) \to \mathbf{H} =: \mathbf{H}(\boldsymbol{\Theta})$ *as* $\mathbf{x} \to \boldsymbol{\Theta}$ *and for* $\delta > 0$,

$$\mathbf{H}(\mathbf{x}) - \mathbf{H} = \sum_{k=1}^K \frac{\partial \mathbf{H}(\mathbf{x})}{\partial x_k}\Big|_{\mathbf{x}=\boldsymbol{\theta}} (x_k - \theta_k) + O(\|\mathbf{x} - \boldsymbol{\Theta}\|^{1+\delta}) \quad \textit{as} \ \ \mathbf{x} \to \boldsymbol{\Theta}.$$

Let $\lambda_1 = 1, \lambda_2, \ldots, \lambda_K$ *be the eigenvalues of* $\mathbf{H}$ *and* $\mathbf{v}$ *be the left eigenvector corresponding to* $\lambda_1 = 1$ *with* $\mathbf{v}\mathbf{1}' = 1$. *Write* $\sigma_k^2 = \mathsf{Var}(\xi_{nk})$, $k = 1, \ldots, K$. *Define* $\widetilde{\mathbf{H}} = \mathbf{H} - \mathbf{1}'\mathbf{v}$ *and*

$$\begin{aligned} \mathbf{\Sigma} &= \big(diag(\mathbf{v}) - \mathbf{H}' diag(\mathbf{v})\mathbf{H}\big), \\ \mathbf{f}_k &= \mathbf{v}\frac{\partial \mathbf{H}(\mathbf{x})}{\partial x_k}\Big|_{\mathbf{x}=\boldsymbol{\theta}}, \quad \mathbf{F} = (\mathbf{f}_1', \cdots, \mathbf{f}_K')'. \end{aligned} \tag{11}$$

If $|\lambda_i| < 1$, $i = 2, \ldots, K$, *then possibly in a richer underlying probability space in which there exist two independent d-dimensional standard Brownian motions* $\{\mathbf{B}_t\}$ *and* $\{\mathbf{W}_t\}$, *we can redefine the sequence* $\{\mathbf{X}_n, \boldsymbol{\xi}_n\}$, *without changing its distribution, such that*

$$\widehat{\mathbf{\Theta}}_n - \mathbf{\Theta} = \frac{1}{n}\mathbf{W}_n diag(\sigma_1/\sqrt{v_1}, \cdots, \sigma_d/\sqrt{v_d}) + o(n^{1/2-\kappa}) \ a.s., \tag{12}$$

$$\begin{aligned} \mathbf{N}_n - n\mathbf{v} = \big[&\mathbf{B}_n \mathbf{\Sigma}^{1/2} + \textstyle\int_0^n \frac{\mathbf{W}_t dt}{t} diag(\frac{\sigma_1}{\sqrt{v_1}}, \ldots, \frac{\sigma_K}{\sqrt{v_K}})\mathbf{F}\big](\mathbf{I} - \widetilde{\mathbf{H}})^{-1} \\ &+ o(n^{1/2-\kappa}) \ a.s., \end{aligned}$$

for some $\kappa > 0$. *In particular,*

$$n^{1/2}\Big(\frac{\mathbf{N}_n}{n} - \mathbf{v}, \ \widehat{\mathbf{\Theta}}_n - \mathbf{\Theta}\Big) \xrightarrow{\mathcal{D}} N\left(\mathbf{0}, \begin{pmatrix} \mathbf{\Lambda} & (\mathbf{I} - \widetilde{\mathbf{H}}')^{-1}\mathbf{F}'\mathbf{\Sigma}_\dagger \\ \mathbf{\Sigma}_\dagger \mathbf{F}(\mathbf{I} - \widetilde{\mathbf{H}})^{-1} & \mathbf{\Sigma}_\dagger \end{pmatrix}\right),$$

where

$$\begin{aligned} \mathbf{\Lambda} &= (\mathbf{I} - \widetilde{\mathbf{H}}')^{-1}\big(\mathbf{\Sigma} + 2\mathbf{F}'\mathbf{\Sigma}_\dagger \mathbf{F}\big)(\mathbf{I} - \widetilde{\mathbf{H}})^{-1}, \\ \mathbf{\Sigma}_\dagger &= diag(\sigma_1^2/v_1, \cdots, \sigma_d^2/v_d). \end{aligned} \tag{13}$$

3. Randomized play-the-Winner rule and generalized Polya urn

RPW rule. As pointed out in Wei and Durham [33] and Wei [32], the PW rule is too deterministic and is not applicable when we have delayed responses from patients to treatments. Motivated as an extension to Zelen's [34] idea, Wei and Durham [33] introduced the following randomized play-the-Winner (RPW) rule for a two-arm clinical trial: *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 [32]). Further, let Y_{n1} (Y_{n2}) be the number of balls of type 1 (2) after n stage. From the results of Athreya and Karlin [1], we have

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

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

$$\sqrt{n}\left(\frac{Y_{n1}}{Y_{n1}+Y_{n2}} - \frac{q_2}{q_1+q_2}\right) \xrightarrow{\mathcal{D}} N\big(0, \frac{q_1 q_2}{(2(q_1+q_2)-1)(q_1+q_2)^2}\big) \tag{14}$$

and

$$\sqrt{n}\left(\frac{N_{n1}}{n} - \frac{q_2}{q_1+q_2}\right) \xrightarrow{\mathcal{D}} N(0, \sigma^2_{RPW}), \tag{15}$$

where

$$\sigma^2_{RPW} = \frac{q_1 q_2[5 - 2(q_1+q_2)]}{[2(q_1+q_2)-1](q_1+q_2)^2}. \tag{16}$$

The asymptotic normality was first given in Smythe and Rosenberger [30]. When $q_1 + q_2 < 0.5$, the asymptotic distributions of both the urn composition and the proportions of patients assigned to each treatments are unknown.

GPU model. 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 $\mathbf{Y}_0 = (Y_{01}, \cdots, Y_{0K})$ 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 n-th 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's response $\boldsymbol{\xi}_n$). 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

$$P\{D_{ij}(n) = 0, \text{ for all } j = 1, \cdots, K\} = 0,$$

$$\sum_{j=1}^{K} \mathsf{E}\{D_{ij}(n)|\mathcal{F}_{n-1}\} = \gamma, \quad i, j = 1, \cdots, K, n = 1, 2, \cdots,$$

where $\mathcal{F}_n$ is the sigma field generated by the events up to the stage n. Without losing generality, we can assume $\gamma = 1$. Let $\mathbf{H}_n$ be the matrix comprising element $\{h_{ij}(n) = \mathsf{E}\{D_{ij}(n)|\mathcal{F}_{n-1}\}\}$. We refer to $\mathbf{D}_n$ as the **rules** and $\mathbf{H_n}$ as the **design matrices**. If $\mathbf{H}_n = \mathbf{H}$ for all n, the model is said to be homogenous. In general, it is assumed that $\mathbf{H}_n \to \mathbf{H}$. Let $\mathbf{Y}_n = (Y_{n1}, \cdots, Y_{nK})$, where Y_{ni} represents the number of balls in the urn of type i after n-th stage, and $\mathbf{N}_n = (N_{n1}, \cdots, N_{nK})$, where N_{ni} represents the number of times a type i ball drawn in the first n draws. In the clinical trials, N_{ni} is the number of patients assigned to treatment i in the first n stages. Let $\mathbf{v} = (v_1, \cdots, v_K)$ be the left eigenvector corresponding to the largest eigenvalue of $\mathbf{H}$ with $v_1 + \ldots + v_K = 1$. 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.,

$$\frac{N_{ni}}{n} \to v_i \quad a.s. \text{ and } \frac{Y_{ni}}{\sum_{j=1}^K Y_{nj}} \to v_i \quad a.s. \tag{17}$$

(c.f., Athreya and Karlin [1]). Smyth [29], Bai and Hu [3] [4] showed the normality of $\mathbf{Y}_n$ and $\mathbf{N}_n$. Bai, Hu and Zhang [7] and Hu and Zhang [18] gives the strong approximation of $\mathbf{Y}_n$ and $\mathbf{N}_n$. Let $\lambda_1 = \gamma = 1, \lambda_2, \ldots, \lambda_K$ be the eigenvalues of $\mathbf{H}$, and $\lambda = \max\{Re(\lambda_2), \ldots, Re(\lambda_K)\}$. Let $V_{qkl}(n) = \mathsf{Cov}\{D_{qk}(n), D_{ql}(n)|\mathcal{F}_{n-1}\}$ and $\mathbf{V}_{nq} = (V_{qkl}(n))_{k,l=1}^K$, $q, k, l = 1, \ldots, K$.

Theorem 3.1. *Assume that for some* $0 < \epsilon < 1$,

$$\mathsf{E}\|\mathbf{D}_n\|^{2+\epsilon} \le C < \infty, \quad n = 1, 2, \ldots, \tag{18}$$

$$\sum_{k=1}^n \|\mathbf{V}_{kq} - \mathbf{V}_q\| = o(n^{1-\epsilon}), \quad q = 1, \ldots, K,$$

$$\sum_{k=1}^n \|\mathbf{H}_k - \mathbf{H}\| = o(n^{1-\epsilon}),$$

and let $\mathbf{\Sigma}_1 = diag(\mathbf{v}) - \mathbf{v}'\mathbf{v}$ *and* $\mathbf{\Sigma}_2 = \sum_{q=1}^K v_q \mathbf{V}_q$. *If* $\lambda < 1/2$, *then on a suitably enlarged probability space with two independent* K*-dimensional standard Brownian motions* $\mathbf{B}_{t1}$ *and* $\mathbf{B}_{t2}$, *we can redefined the process* $(\mathbf{Y}_n, \mathbf{N}_n)$ *without changing the distribution, such that for some* $\kappa > 0$,

$$\mathbf{Y}_n - \mathsf{E}\mathbf{Y}_n = \mathbf{G}_n + o(n^{1/2-\kappa}) \; a.s.,$$
$$\mathbf{N}_n - \mathsf{E}\mathbf{N}_n = \mathbf{B}_{n1}\mathbf{\Sigma}_1^{1/2} + \int_0^n \frac{\mathbf{G}_x}{x}\, dx(\mathbf{I} - \mathbf{1}'\mathbf{v}) + o(n^{1/2-\kappa}) \; a.s.$$

where $\mathbf{G}_t$ *is a Gaussian process which is solution of the following type equation:*

$$\mathbf{G}_t = \mathbf{B}_{t1}\mathbf{\Sigma}_1^{1/2}\mathbf{H} + \mathbf{B}_{t2}\mathbf{\Sigma}_2^{1/2} + \int_0^t \frac{\mathbf{G}_s}{s}(\mathbf{H} - \mathbf{1}'\mathbf{v})\, ds, \quad t > 0, \quad \mathbf{G}_0 = \mathbf{0}. \tag{19}$$

Furthermore

$$\mathsf{E}\mathbf{Y}_n - n\mathbf{v} = o(n^{1/2-\kappa}) + \sum_{k=1}^{n} \mathbf{v}(\mathbf{H}_k - \mathbf{H}),$$

$$\mathsf{E}\mathbf{N}_n - n\mathbf{v} = o(n^{1/2-\kappa}) + \sum_{k=1}^{n} \mathbf{v}(\mathbf{H}_k - \mathbf{H}).$$

In particular, the asymptotic combining distribution of $\mathbf{Y}_n$ *and* $\mathbf{N}_n$ *can be obtained.*

Example 3.1. (**General RPW Rule**) Suppose $K = 2$ and the adding rule matrices are denoted by

$$\mathbf{D}_n = \begin{pmatrix} \xi_{n1} & 1-\xi_{n1} \\ 1-\xi_{n2} & \xi_{n2} \end{pmatrix},$$

where $\{\boldsymbol{\xi}_n = (\xi_{n1}, \xi_{n2}), n = 1, 2\ldots\}$ is an i.i.d. sequence with $0 \le \xi_{ni} \le 1$, $\mathsf{Var}(\xi_{ni}) = \sigma_i^2$, $\mathsf{E}\xi_{ni} = p_i$ and $q_i = 1 - p_i$ for $i = 1, 2$. For this design, one has

$$\mathbf{H} = \mathsf{E}[\mathbf{D}_n] = \begin{pmatrix} p_1 & q_1 \\ q_2 & p_2 \end{pmatrix},$$

$\lambda_1 = 1$, $\lambda_2 = p_1 + p_2 - 1$ and $\mathbf{v} = (q_2/(q_1+q_2), q_1/(q_1+q_2))$. Let $a^2 = q_1 q_2/(q_1+q_2)^2$ and $b^2 = (\sigma_1 q_2 + \sigma_2 q_1)/(q_1+q_2)$. Then there exist two independent one-dimensional standard Brownian motions B_{t1} and B_{t2} such that

$$\begin{aligned} Y_{n1} - n\mathbf{v}_1 &= \lambda_2 \sigma_1 G_{n1} + \sigma_2 G_{n2} + o(n^{1/2-\kappa}) \ a.s., \\ N_{n1} - n\mathbf{v}_1 &= \sigma_1 G_{n1} + \sigma_2 \int_0^n \frac{G_{nx}dx}{x} + o(n^{1/2-\kappa}) \ a.s. \end{aligned}$$

whenever $\lambda_2 < 1/2$, where

$$G_{ti} = t^{-\lambda_2} \int_0^t \frac{d\,B_{xi}}{x^{\lambda_2}}, \quad i = 1, 2.$$

Example 3.2. (**Wei's Rule**) Suppose $K \ge 2$ and the response sequence $\{\boldsymbol{\xi}_n\}$ is an i.i.d. sequence with $\xi_{nk} = 0$ or 1. $\xi_{nk} = 1$ or 0 corresponds to the response of the n patient on the treatment k is a success or failure, respectively, $i = 1, \ldots, K$. Let the adding rule matrices $\mathbf{D}_n = \big(D_{ij}(n)\big)_{i,j=1}^{K}$ be denoted by $D_{ii}(n) = \xi_{ni}$ and $D_{ij} = (1 - \xi_{ni})/(K-1)$ for $i \ne j$. This design is proposed by Wei [32]. For this design, the design matrix $\mathbf{H} =$

$\mathsf{E}[\mathbf{D}_n]$ is the same as the one in (7), and $\mathbf{v}$ is the same as the one in (5). If $\lambda < 1/2$, then

$$
\begin{aligned}
\mathbf{Y}_n - n\mathbf{v} &= \mathbf{G}_n + o(n^{1/2-\kappa}) \ a.s., \\
\mathbf{N}_n - n\mathbf{v} &= \mathbf{B}_{n1}\mathbf{\Sigma}_1^{1/2} + \int_0^n \frac{\mathbf{G}_x}{x}\, dx(\mathbf{I} - \mathbf{1}'\mathbf{v}) + o(n^{1/2-\kappa}) \ a.s.
\end{aligned}
$$

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 $\mathbf{Y}_n$ and the sample fractions $\mathbf{N}_n$ for a wide class of designs defined by GPU (c.f., Bai, Hu and Rosenberger [5] and Hu and Zhang [21]).

Designs dependent on estimated unknown parameters. Hu and Zhang [19] considered a general model with rules of the type $\mathbf{D}_n = \mathbf{D}(\widehat{\mathbf{\Theta}}_{n-1}, \boldsymbol{\xi}_n)$ and design matrices of the type $\mathbf{H}_n = \mathbf{H}(\widehat{\mathbf{\Theta}}_{n-1})$ dependent on the estimated unknown parameter, where $\widehat{\mathbf{\Theta}}_{n-1}$ is the sample estimator of the unknown parameter $\mathbf{\Theta}$ based on the responses of previous $n-1$ stages. Strong consistency and the asymptotic normalities are established for both the urn composition and the number of patients assigned to each treatment. For such design, we also have the following strong approximation.

Theorem 3.2. *Suppose $\{\boldsymbol{\xi}_n\}$ is an i.i.d. sequence, $\Theta = \mathsf{E}\boldsymbol{\xi}_n$ and $\widehat{\mathbf{\Theta}}_n$ is defined as in Adaptive Design 2.1. Suppose the conditions in Theorem 2.2 are satisfied and the condition (18) in Theorem 3.1 is satisfied. If $\lambda < 1$, then*

$$
\frac{\mathbf{Y}_n}{n} \to \mathbf{v} \ a.s. \ \ and \ \ \frac{\mathbf{N}_n}{n} \to \mathbf{v} \ a.s.,
$$

also, on a suitably enlarged probability space with an K-dimensional standard Brownian motion $\mathbf{W}_t$, we can redefined the process $(\mathbf{Y}_n, \mathbf{N}_n, \boldsymbol{\xi}_n)$ without changing the distribution, such that (12) holds for some $\kappa > 0$.

If $\lambda < 1/2$, then on a suitably enlarged probability space with three independent K-dimensional standard Brownian motions $\mathbf{B}_{t1}$, $\mathbf{B}_{t2}$ and $\mathbf{W}_t$, we can redefined the process $(\mathbf{Y}_n, \mathbf{N}_n, \boldsymbol{\xi}_n)$ without changing the distribution, *such that for some $\kappa > 0$, (12) holds and*

$$\mathbf{Y}_n - n\mathbf{v} = \mathbf{G}_n + o(n^{1/2-\kappa}) \ a.s.,$$
$$\mathbf{N}_n - n\mathbf{v} = \mathbf{B}_{n1}\mathbf{\Sigma}_1^{1/2} + \int_0^n \frac{\mathbf{G}_x}{x}\, dx(\mathbf{I} - \mathbf{1}'\mathbf{v}) + o(n^{1/2-\kappa}) \ a.s.$$

where $\mathbf{G}_t$ is a Gaussian process which is solution of the following type equation:

$$\mathbf{G}_t = \mathbf{B}_{t1}\mathbf{\Sigma}_1^{1/2}\mathbf{H} + \mathbf{B}_{t2}\mathbf{\Sigma}_2^{1/2} + \int_0^t \frac{\mathbf{W}_x dx}{x} diag(\frac{\sigma_1}{\sqrt{v_1}}, \dots, \frac{\sigma_K}{\sqrt{v_K}})\mathbf{F}$$
$$+ \int_0^t \frac{\mathbf{G}_s}{s}(\mathbf{H} - \mathbf{1}'\mathbf{v})\, ds, \quad t > 0, \quad \mathbf{G}_0 = \mathbf{0}, \tag{20}$$

and $\mathbf{F}$ is defined in (11).

By comparing the two equations (19) and (20), one finds that (20) has a more term than (19) has. This term is generated by the randomness of $\widehat{\mathbf{\Theta}}_n$s.

Example 3.3. (**General Wei Rule**) Suppose $K \geq 2$ and the response sequence $\{\boldsymbol{\xi}_n\}$ is the same as in Wei's rule, and $0 < p_k < 1$, $k = 1, \dots, K$. At the n-th stage, a success on the treatment k generates a particle of type k, and a failure on the treatment k generates $\frac{\hat{p}^{\alpha}_{m-1,j}}{(M_{m-1,\alpha} - \hat{p}^{\alpha}_{m-1,k})}$ particles of type j to the urn for all $j \neq k$, where $0 \leq \alpha < \infty$, where $M_{m-1,\alpha} = \sum_{j=1}^K \hat{p}^{\alpha}_{m-1,j}$, $\hat{p}_{m-1,j} = \frac{S_{m-1,j}+1}{N_{m-1,j}+1}$, and $S_{m-1,j}$ denotes the number of successes of the j-th treatment in all the $N_{m-1,j}$ trials of previous $n-1$ stages, $j = 1, \dots, K$. When $\alpha = 0$, this design model is just Wei's rule, and when $\alpha = 1$, it is the model proposed by Bai, Hu and Shen [6]. Write $\widehat{\mathbf{p}}_{m-1} = (\widehat{P}_{m-1,1}, \dots, \widehat{p}_{m,K})$. In this case, $\mathbf{H}_m = \mathsf{E}[\mathbf{D}_m|\mathcal{F}_{m-1}] = \mathbf{H}(\widehat{\mathbf{p}}_{m-1})$, where $\mathbf{H}(\mathbf{x})$ is defined as in Example 2.4. Also,

$$\mathbf{H}_m \to \mathbf{H} = \mathbf{H}^{(\alpha)}$$

and

$$\frac{\mathbf{Y}_n}{n} \to \mathbf{v} = \mathbf{v}^{(\alpha)} \quad \text{and} \quad \frac{\mathbf{N}_n}{n} \to \mathbf{v} = \mathbf{v}^{(\alpha)} \quad a.s.,$$

where $\mathbf{H}^{(\alpha)}$ and $\mathbf{v}^{(\alpha)}$ is defined as in (8) and (9), respectively. If $\lambda < 1/2$, then the conclusions in Theorem 3.2 hold. In particular,

$$n^{1/2}(\mathbf{Y}_n/n - \mathbf{v}^{(\alpha)}) \xrightarrow{\mathcal{D}} N(\mathbf{0}, \Lambda^{\dagger}) \quad \text{and} \quad n^{1/2}(\mathbf{N}_n/n - \mathbf{v}^{(\alpha)}) \xrightarrow{\mathcal{D}} N(\mathbf{0}, \Lambda^{\sharp})$$

for some $\Lambda^{\dagger}$ and $\Lambda^{\sharp}$.

4. Doubly adaptive biased coin designs

Two-arm case. 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 (near 1) and so it is much less stable than the PW rule. Also, in using the multi-arm RPW, when $K\geq 3$, the expression of λ becomes very complex, it is very hard (even impossible in more general cases) to verify the condition $\lambda<1/2$.

Now, with keeping the desired allocation proportions $v_1=q_2/(q_1+q_2)$ and $v_2=q_1/(q_1+q_2)$, just as 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 $(m+1)$-th stage, we assign a patient to a certain treatment by comparing the value N_{m1}/m with v_1, or N_{m2}/m with v_2. If N_{m1}/m is larger than v_1, then we assign a patient to the treatment 1 with a probability less than v_1; If N_{m1}/m is less than v_1, then we assign a patient to the treatment 1 with a probability larger than v_1; If N_{m1}/m 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 allocation 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 m 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 $\widehat{p}_{mk}=(S_{mk}+1/2)/(N_{mk}+1)$ be the sample estimate of p_k, and write $\widehat{q}_{mk}=1-\widehat{p}_{mk}$, $k=1,2$. At the $(m+1)$-th stage, the $(m+1)$-th patient is assigned to the treatment 1 with probability $g(N_{m1}/m,\widehat{v}_{m1})$, and to the treatment 2 with probability

$1 - g(N_{m1}/m, \widehat{v}_{m1})$, where $\widehat{v}_{m1} = \widehat{q}_{m2}/(\widehat{q}_{m1} + \widehat{q}_{m2})$ is the sample estimate of $v_1 = q_2/(q_1 + q_2)$. The function $g(x, \rho)$ is called allocation rule. A large class of functions can be chosen as a allocation rule. If it is of the following form:

$$g(0, \rho) = 1,\ g(1, \rho) = 0,\ g(x, \rho) = \frac{\rho(\frac{\rho}{x})^{\alpha}}{\rho(\frac{\rho}{x})^{\alpha_1} + (1-\rho)(\frac{1-\rho}{1-x})^{\alpha}},$$

where $\alpha \geq 0$, then we have

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

where

$$\sigma^2_{DABC} = \sigma^2_{\alpha} := \frac{q_1 q_2(p_1 + p_2)}{(q_1 + q_2)^3} + \frac{2 q_1 q_2}{(1 + 2\alpha)(q_1 + q_2)^3} \tag{21}$$

(c.f., Hu and Zhang [20]). It should be noted that the asymptotic normality holds for all $0 < p_1 < 1$ and $0 < p_2 < 1$. Recall that σ_{PW} and σ_{RPW} are defined in (1) and (16), respectively. It is easily seen that σ^2_{α} is a strictly monotonous decreasing function of $\alpha \geq 0$ and $\sigma^2_{\alpha} \to \sigma^2_{PW}$ as $\alpha \to +\infty$. Also, $\sigma^2_{\alpha} < \sigma^2_{RPW}$ 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. This design is compromise between the stability in the PW rule and the randomization in the RPW rule. 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 (c.f., Hu, Zhang, Chan and Cheung [22]).

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 [13] biased coin design. So, they are called doubly adaptive biased coin (DABC) design, first introduced by Eisele [10] and Eisele and Woodroofe [12] in the two-arm case. Hu and Zhang [20] filled a gap of their proof and studied a general multi-arm case.

Multi-arm case. Now, consider an K-treatment clinical trial. Assume the response sequence $\{\boldsymbol{\xi}_m\}$ is a sequence of i.i.d random vectors. Suppose the desired allocation proportion of patients assigned to each treatment is a function of some unknown parameters of the response $\{\boldsymbol{\xi}_n\}$. That is, the goal of the allocation scheme is to have $\mathbf{N}_m/m \to \mathbf{v} = \boldsymbol{\rho}(\boldsymbol{\Theta})$, where $\boldsymbol{\rho}(\mathbf{y}) = (\rho_1(\mathbf{y}), \ldots, \rho_K(\mathbf{y})) : \mathbb{R}^K \to (0, 1)^K$ is a vector-valued function satisfying $\boldsymbol{\rho}(\mathbf{y})\mathbf{1}' = 1$, $\boldsymbol{\Theta} = (\theta_1, \ldots, \theta_K)$ is a vector in $\mathbb{R}^K$, and θ_k is an unknown parameter of the distribution of $\xi_{1,k}$, $k = 1, \ldots, K$. Without loss of generality, we assume that $\theta_k = \mathsf{E}\xi_{1,k}$, $k = 1, \ldots, K$. Choose a $\mathbf{\Theta}_0 = (\theta_{0,1}, \ldots, \theta_{0,K}) \in \mathbb{R}^K$ as the first estimate of $\mathbf{\Theta}$. If m patients are assigned and the responses are observed, we use the sample means $\widehat{\theta}_{m,k}$, which are based on the responses observed, to estimate the parameters θ_k as we do in Adaptive Design 2.1, $k = 1, \ldots, K$, i.e.,

$$\begin{aligned} &\widehat{\theta}_{m,k} = \tfrac{\sum_{j=1}^m X_{j,k}\xi_{j,k} + \theta_{0,k}}{N_{m,k}+1}, \quad k = 1, \ldots, K, \\ &\text{and write } \widehat{\mathbf{\Theta}}_{m,k} = (\widehat{\theta}_{m,1}, \ldots, \widehat{\theta}_{m,K}). \end{aligned} \tag{22}$$

Here, adding 1 in the denominator is for avoiding the case of 0/0, and adding $\theta_{0,k}$ in the numerator is for using $\theta_{0,k}$ to estimate θ_k when no patient is assigned to the treatment k, $k = 1, \ldots, K$. Usually, the $\mathbf{\Theta}_0$ is chosen for avoiding $\rho_k(\widehat{\mathbf{\Theta}}_m) = 0$, $k = 1, \ldots, K$. In practice, $\mathbf{\Theta}_0$ is the guessed value of $\mathbf{\Theta}$, or an estimate of $\mathbf{\Theta}$ from other early trials. The following is the general BADC design.

General DABC Design Let $\mathbf{g}(\mathbf{x}, \boldsymbol{\rho}) = \big(g_1(\mathbf{x}, \boldsymbol{\rho}), \ldots, g_K(\mathbf{x}, \boldsymbol{\rho})\big) : [0,1]^K \times [0,1]^K \to [0,1]^K$ be the allocation rule with $\mathbf{g}(\mathbf{x}, \boldsymbol{\rho})\mathbf{1}' = 1$. Let $\widehat{\mathbf{\Theta}}_0 = \mathbf{\Theta}_0$ and $\widehat{\mathbf{\Theta}}_m$ be estimated as in (22) from the first m observations, $m = 1, 2, \ldots.$ Then the $(m+1)$-th patient is assigned to the treatment k with probability $p_{m,k} = g_k\big(\mathbf{N}_m/m, \widehat{\boldsymbol{\rho}}_m\big)$, $k = 1, \ldots, K$, where

$$\widehat{\boldsymbol{\rho}}_m = \boldsymbol{\rho}(\widehat{\mathbf{\Theta}}_m) \tag{23}$$

is the sample estimate of $\mathbf{v} = (v_1, \ldots, v_K) = \boldsymbol{\rho}(\mathbf{\Theta})$ based on the responses observed from the first m patients.

Theorem 4.1. *Suppose for some $\epsilon > 0$ and $0 < \delta \le 1$, $\mathsf{E}\|\boldsymbol{\xi}_n\|^{2+\epsilon} < \infty$ and*

$$\boldsymbol{\rho}(\mathbf{y}) = \boldsymbol{\rho}(\mathbf{\Theta}) + \sum_{k=1}^K (y_k - \theta_k) \frac{\partial \boldsymbol{\rho}}{\partial y_k}\Big|_{\mathbf{\Theta}} + o(\|\mathbf{y} - \mathbf{\Theta}\|^{1+\delta}) \quad \text{as} \quad \mathbf{y} \to \mathbf{\Theta}.$$

Let $\mathbf{\Sigma}_1 = diag(\mathbf{v}) - \mathbf{v}'\mathbf{v}$,

$$\sigma_k^2 = \mathsf{Var}(\xi_{1,k}), \quad k = 1, \ldots, K,$$

$$\mathbf{\Sigma}_\dagger = diag(\sigma_1^2/v_1, \ldots, \sigma_K^2/v_K),$$

$$\mathbf{\Sigma}_3 = \Big(\frac{\partial \boldsymbol{\rho}}{\partial \mathbf{\Theta}}\Big)' \mathbf{\Sigma}_\dagger \frac{\partial \boldsymbol{\rho}}{\partial \mathbf{\Theta}} = \sum_{k=1}^K \frac{\sigma_k^2}{v_k} \Big(\frac{\partial \boldsymbol{\rho}}{\partial \theta_k}\Big)' \frac{\partial \boldsymbol{\rho}}{\partial \theta_k}. \tag{24}$$

Choose the allocation function $\mathbf{g}(\mathbf{x}, \boldsymbol{\rho})$ *to be*

$$g_k(\mathbf{x}, \boldsymbol{\rho}) = \frac{\left\{\rho_k \left(\frac{\rho_k}{x_k}\right)^{\alpha}\right\} \bigwedge L}{\sum_{j=1}^{K} \left\{\rho_j \left(\frac{\rho_j}{x_j}\right)^{\alpha}\right\} \bigwedge L}, \quad k = 1, \ldots, K, \tag{25}$$

where $\alpha \geq 0$ *and* $L > 1$ *are constants.*

Then in a possibly richer underlying probability space in which there exists two independent K*- dimensional standard Brownian motions* $\{\mathbf{W}_t\}$ *and* $\{\mathbf{B}_t\}$*, we can redefine the sequence* $\{\mathbf{X}_n, \boldsymbol{\xi}_n\}$*, without changing its distribution, such that*

$$\mathbf{N}_n - n\mathbf{v} = \mathbf{G}_n + o(n^{1/2-\kappa}) \quad a.s.$$

and

$$\widehat{\boldsymbol{\rho}}_n - \mathbf{v} = \frac{\mathbf{B}_x \boldsymbol{\Sigma}_3^{1/2}}{n} + o(n^{-1/2-\kappa}) \quad a.s.,$$

where

$$\mathbf{G}_t = t^{-\alpha} \int_0^t \frac{(d\mathbf{W}_x)\boldsymbol{\Sigma}_1^{1/2}}{x^{-\alpha}} + (1+\alpha)t^{-\alpha} \int_0^t \frac{\mathbf{B}_x \boldsymbol{\Sigma}_3^{1/2}}{x^{1-\alpha}} dx$$

is a solution of the equation:

$$\mathbf{G}_t = \mathbf{W}_t \boldsymbol{\Sigma}_1^{1/2} + (1+\alpha)\frac{\mathbf{B}_t}{t}\boldsymbol{\Sigma}_3^{1/2} - \alpha \int_0^t \frac{\mathbf{G}_x dx}{x}, \quad t > 0, \mathbf{G}_0 = 0.$$

In particular,

$$\sqrt{n}\big(\mathbf{N}_n/n - \mathbf{v}, \widehat{\boldsymbol{\rho}}_n - \mathbf{v}\big) \xrightarrow{\mathcal{D}} N(\mathbf{0}, \boldsymbol{\Lambda}),$$

where

$$\boldsymbol{\Lambda} = \begin{pmatrix} \frac{1}{1+2\alpha}\boldsymbol{\Sigma}_1 + \frac{2(1+\alpha)}{1+2\alpha}\boldsymbol{\Sigma}_3 & \boldsymbol{\Sigma}_3 \\ \boldsymbol{\Sigma}_3 & \boldsymbol{\Sigma}_3 \end{pmatrix}. \tag{26}$$

5. The drop-the-loss rule

Ivanova [23] proposed a randomization procedure so called the drop-the-loss rule. He considered an urn containing balls of $K+1$ types, type k, $k = 1, \ldots, K$, and type 0. A ball is drawn at random. If it is type k, $k = 1, \ldots, K$, the corresponding treatment is assigned and the patient's response is observed. If it is a success, the ball is replaced and the urn remains unchanged. If it is a failure, the ball is not replaced. If a type 0 ball is drawn, no subject is treated, and the ball is returned to the urn together with one ball of each type k, $k = 1, \dots, K$. Ivanova [23] shows that the limiting allocation proportion of this procedure is the same as that the PWC rule and Wei's rule (see (5)). For the two-treatment case, Ivanova [23] also shows that

$$\sqrt{n}\Big(\frac{N_1(n)}{n} - \frac{q_2}{q_1+q_2}\Big) \xrightarrow{\mathcal{D}} N(0, \sigma^2),$$

where

$$\sigma^2 = q_1 q_2 (p_1 + p_2)/(q_1 + q_2)^3 = \sigma^2_{PW}.$$

The drop-the-loss rule is fully randomized. For the case of $K > 2$, the asymptotic distribution is unknown up to today. It is also an open problem whether or not the delay of responses effects the asymptotic properties.

6. The minimum asymptotic variance

Recall (1), (16) and (21). Comparing the PW rule, the RPW rule and the DABC design, one finds that, keeping the same limiting proportion $\mathbf{v} = (q_2/(q_1+q_2), q_1/(q_1+q_2))$ of assignments, the asymptotic variance in using PW rule and the drop-the-loss rule is the smallest, and the one in using RPW is the largest, i.e.,

$$\sigma_{PW} < \sigma_{DABC} = \sigma_\alpha < \sigma_{RPW}, \ \alpha > 1.$$

Hu and Rosenberger [16] points out that, if the observed allocation proportions are asymptotically normal, the asymptotic power is an decreasing function of the asymptotic variance of the allocation proportions.

Recently, Hu, Rosenberger and Zhang [17] obtains the lower bound of the asymptotic variance. Suppose the response sequence $\{\boldsymbol{\xi}_n\}$ is an i.i.d. sequence. And suppose the limiting proportion $\mathbf{v} = \boldsymbol{\rho}(\boldsymbol{\Theta})$ is a function of the parameter $\boldsymbol{\Theta} = \mathsf{E}\boldsymbol{\xi}_1$. Assume that for each $k = 1, \dots, K$, the response $\xi_{1,k}$ comes from a family of exponential distributions:

$$C(u_k)\exp\{\boldsymbol{\xi}_{1,k} u_k\} d\mu, u_k \in U_k \subset \mathbb{R}$$

and

$$\theta_k = \mathsf{E}\xi_{1,k} = \theta_k(u_k),$$

and let $I_k(u_k)$ be the Fisher information of u_k for this family. Then

$$\sigma_k^2 = \mathsf{Var}(\xi_{1,k}) = \Big(\frac{d\theta_k}{du_k}\Big)^2 / I_k(u_k).$$

Hu, Rosenberger and Zhang [17] shows the following theorem.

Theorem 6.1. *Suppose*

$$n^{1/2}\big(\mathbf{N}_n/n-\mathbf{v}\big)\xrightarrow{\mathcal{D}} N\big(\mathbf{0},\mathbf{V}(\mathbf{u})\big).$$

Under some regularity conditions, there exists a $\mathbf{U}_0\subset\mathbf{U}=\mathbf{U}_1\otimes\cdots\otimes\mathbf{U}_K$ *with Lebesgue measure* 0 *such that for every* $\mathbf{u}\in\mathbf{U}-\mathbf{U}_0$,

$$\mathbf{V}(\mathbf{u})\geq\frac{\partial\boldsymbol{\rho}\big(\boldsymbol{\Theta}(\mathbf{u})\big)'}{\partial\mathbf{u}}\mathbf{I}^{-1}(\mathbf{u},\mathbf{v})\frac{\partial\boldsymbol{\rho}\big(\boldsymbol{\Theta}(\mathbf{u})\big)}{\partial\mathbf{u}}\triangleq\mathbf{B}(\mathbf{u}),$$

where

$$\mathbf{I}(\mathbf{u},\mathbf{v})=diag(v_1I_1(u_1),\ldots,v_KI_1(u_K)).$$

Here, for two covariance matrices $\mathbf{A}$ *and* $\mathbf{B}$, $\mathbf{A}\geq\mathbf{B}$ *means that* $\mathbf{A}-\mathbf{B}$ *is non-negatively definite.*

We can rigorously define an *asymptotically best response-adaptive procedure* as one in which $\mathbf{V}(\mathbf{u})$ attains the lower bound $\mathbf{B}(\mathbf{u})$ for a particular target allocation $\boldsymbol{\rho}(\boldsymbol{\theta})$.

It is easily seen that

$$\begin{aligned}\mathbf{B}(\mathbf{u})&=\frac{\partial\boldsymbol{\rho}(\boldsymbol{\Theta})'}{\partial\boldsymbol{\Theta}}\frac{\partial\boldsymbol{\Theta}(\mathbf{u})'}{\partial\mathbf{u}}\mathbf{I}^{-1}(\mathbf{u},\mathbf{v})\frac{\partial\boldsymbol{\Theta}(\mathbf{u})}{\partial\mathbf{u}}\frac{\partial\boldsymbol{\rho}(\boldsymbol{\Theta})}{\partial\boldsymbol{\Theta}}\\ &=\frac{\partial\boldsymbol{\rho}(\boldsymbol{\Theta})'}{\partial\boldsymbol{\Theta}}diag\Big(\frac{1}{v_1I_1(u_1)}\big(\frac{d\theta_1}{du_1}\big)^2,\ldots,\frac{1}{v_KI_1(u_K)}\big(\frac{d\theta_K}{du_K}\big)^2\Big)\frac{\partial\boldsymbol{\rho}(\boldsymbol{\Theta})}{\partial\boldsymbol{\Theta}}\\ &=\frac{\partial\boldsymbol{\rho}(\boldsymbol{\Theta})'}{\partial\boldsymbol{\Theta}}diag\Big(\frac{1}{v_1}\sigma_1^2,\ldots,\frac{1}{v_K}\sigma_K^2\Big)\frac{\partial\boldsymbol{\rho}(\boldsymbol{\Theta})}{\partial\boldsymbol{\Theta}}=\boldsymbol{\Sigma}_3(\boldsymbol{\Theta}),\end{aligned}$$

where $\boldsymbol{\Sigma}_3=\boldsymbol{\Sigma}_3(\boldsymbol{\Theta})$ is defined in (24).

In the case $K=2$,

$$\boldsymbol{\Sigma}_3=\sum_{k=1}^{2}\frac{\sigma_k^2}{v_k}\big(\frac{\partial\rho_1}{\partial y_k}\big|_{\boldsymbol{\Theta}}\big)^2\begin{pmatrix}1&-1\\-1&1\end{pmatrix}=:\sigma_3^2\begin{pmatrix}1&-1\\-1&1\end{pmatrix}.$$

Further, if the responses are dichotomous (success and failure) and $\mathbf{v}=(q_2/(q_1+q_2),q_1/(q_1+q_2))$, then $\sigma_3=\sigma_{PW}$. It follows that the PW rule and the drop-the-loss rule are asymptotically best response-adaptive procedure. However, the PW rule is too deterministic. On the surface, the drop-the-loss rule would seem to give us everything we want in a response-adaptive randomization procedure: it is fully randomized and its asymptotic variance attains the lower bound. However, it can only target the PW rule allocation, which is not optimal in any formal sense, and previously reported simulations have shown that it can be slower to converge for large values of p_A and p_B and becomes more deterministic for small values of p_A and p_B (see Hu and Rosenberger [16]). The DABC procedure solve some of these deficiencies, in that they can target any desired allocation, and can approach the lower bound for large values of α. However, the procedure becomes more deterministic as α becomes larger, and hence careful tuning of α must be done in order to counter the tradeoff.

When $K \geq 3$, no of the designs mentioned above is showed asymptotically best. However, in using the general DABC design, if the allocation rule is chosen as in (25), then the asymptotic variance of $n^{1/2}(\mathbf{N}_n/n - \mathbf{v})$ satisfies

$$\frac{1}{1+2\alpha}\boldsymbol{\Sigma}_1 + \frac{2(1+\alpha)}{1+2\alpha}\boldsymbol{\Sigma}_3 \searrow \boldsymbol{\Sigma}_3 \quad \text{as} \quad \alpha \nearrow \infty.$$

If α is large enough, the asymptotic variance of $n^{1/2}(\mathbf{N}_n/n - \mathbf{v})$ is very close to the lower bound $\boldsymbol{\Sigma}_3$. So, the DABC design is nearly asymptotically most powerful if α is chosen large.

Remark 6.1. Usually, many cases, in which the parameter $\boldsymbol{\Theta}$ is not a mean of the response $\boldsymbol{\xi}_n$, can be transferred to the case we studied. In fact, if for each k, an estimate $\widetilde{\theta}_{nk} = \widetilde{\theta}_{nk}(\xi_{jk} : j = 1, 2, \cdots, n)$ of θ can be written in the following form:

$$\widetilde{\theta}_{nk} = \frac{1}{n}\sum_{j=1}^{n} f_k(\xi_{jk}) + o(n^{-1/2-\delta}), \quad \text{for some} \quad \delta > 0, \tag{27}$$

then in the adaptive designs, we can define

$$\widehat{\theta}_{m-1,k} = \widetilde{\theta}_{N_{m-1,k},k}(\xi_{jk} : X_{jk} = 1, j = 1, 2, \cdots, m-1)$$

and then

$$\widetilde{\theta}_{m-1,k} = \frac{1}{N_{m-1,k}+1}\sum_{j=1}^{N_{m-1,k}} X_{jk} f_k(\xi_{jk}) + o(N_{m-1,k}^{-1/2-\delta}).$$

Many maximum likelihood estimators and moment estimators satisfy (27).

Appendix A. Strong approximations for martingale vectors

The limiting theorems for martingales are main tools in studying the asymptotic properties of adaptive designs. We study the asymptotic properties of adaptive designs by first approximating the models to certain multi-dimensional martingale vectors and then approximating the martingales to Gaussian processes. In this appendix, we present some strong approximations for martingale vectors. We assume that $\{\mathbf{Z}_n, \mathcal{F}_n; n \geq 1\}$ is a square-integrable sequence of $\mathbb{R}^d$-valued martingale differences, defined on $(\Omega, \mathcal{F}, \mathsf{P})$, $\mathcal{F}_0$ is the trivial σ-field. The probability space $(\Omega, \mathcal{F}, \mathsf{P})$ is also assumed to be rich enough such that there is a uniformly distributed random variable U, which is independent of $\{\mathbf{Z}_n; n \geq 1\}$. Denote $\mathbf{S}_n(m) = \sum_{k=m+1}^{m+n} \mathbf{Z}_k$ and $\mathbf{S}_n = \mathbf{S}_n(0)$. Let

$$\boldsymbol{\sigma}_n = \mathsf{E}\left[\mathbf{Z}_n' \mathbf{Z}_n | \mathcal{F}_{n-1}\right],$$

also let $\boldsymbol{\Sigma}_n = \sum_{k=1}^{n} \boldsymbol{\sigma}_k$, $\boldsymbol{\Sigma}_n(m) = \sum_{k=m+1}^{m+n} \boldsymbol{\sigma}_k$ and

$$V_n = tr(\boldsymbol{\Sigma}_n) = \mathsf{E}\left[\|\mathbf{Z}_k\|^2 \big| \mathcal{F}_{k-1}\right].$$

The first strong approximation theorem for martingales can be found in Strassen's fundamental paper [31], where the strong approximation is established for one-dimensional martingale via the Skorohod embedding theorem. For $d \geq 2$, the strong approximations are also studied by many authors, though it is impossible to embed a general $\mathbb{R}^d$-valued martingale in an $\mathbb{R}^d$-valued Gaussian process (c.f., Monrad and Philipp [25]). One can refer to Morrow and Philipp [27], Eberlein [9], Monrad and Philipp [26] etc. However, in the approximations appeared in literatures, it is always assumed that the conditioned covariance matrix $\boldsymbol{\Sigma}_n$ is convergent in L_1 with some convergence rates. For example, Eberlein [9] assumed the following condition: for some $\theta > 0$

$$\|\mathsf{E}[\boldsymbol{\Sigma}_n(m)|\mathcal{F}_m] - n\mathbf{T}\|_1 = O(n^{1-\theta}), \quad \text{uniformly in } \ m,$$

and Monrad and Philipp [26] assumed that for some $0 < p \leq 1$

$$\mathsf{E} \max_{n \geq 1} \{\|\boldsymbol{\Sigma}_n - \mathbf{T} V_n\| / f(V_n)\}^p < \infty.$$

For the martingales which can approximate our adaptive design models, it is usual hard to verify that $\boldsymbol{\Sigma}_n$ converges in L_1 (or L_p) with the needed convergence rates. However, it is more easy to show that $\boldsymbol{\Sigma}_n$ converges almost surely with some convergence rates. So, we present the following approximation theorems for martingale vectors, whose proofs can be found in Zhang [35].

Theorem A.1. *Suppose that there exist constants $0 < \theta, \epsilon < 1$ and a covariance matrix $\mathbf{T}$, measurable with respect to $\mathcal{F}_k$ for some $k \geq 0$, such that*

$$\boldsymbol{\Sigma}_n - n\mathbf{T} = O(n^{1-\theta}) \quad a.s. \quad or \quad \|\boldsymbol{\Sigma}_n - n\mathbf{T}\|_1 = O(n^{1-\theta}),$$

$$\sum_{n=1}^{\infty} E\big[\|\mathbf{Z}_n\|^2 I\{\|\mathbf{Z}_n\|^2 \ge n^{1-\epsilon}\big|\mathcal{F}_{n-1}\big]/n^{1-\epsilon} < \infty \quad a.s. \tag{A.1}$$

Then there exists a sequence $\{\mathbf{Y}_n; n \ge 1\}$ *of i.i.d.* $\mathbb{R}^d$*-valued standard normal random vectors, independent of* $\mathbf{T}$*, such that*

$$\mathbf{S}_n - \sum_{m\le n} \mathbf{Y}_m \mathbf{T}^{1/2} = O(n^{1/2-\kappa}) \ a.s.$$

Here $\kappa > 0$ *is a constant depending only on* θ*,* ϵ *and* d*.*

Theorem A.2. *Suppose that there exists constants* $0 < \epsilon < 1$ *such that (A.1) is satisfied, and that* $\mathbf{T}$ *is a covariance matrix measurable with respect to* $\mathcal{F}_k$ *for some* $k \ge 0$*. Then for any* $\delta > 0$*, there exists an* $\kappa > 0$ *and a sequence* $\{\mathbf{Y}_n; n \ge 1\}$ *of i.i.d.* $\mathbb{R}^d$*-valued standard normal random vectors, independent of* $\mathbf{T}$*, such that*

$$\mathbf{S}_n - \sum_{m\le n} \mathbf{Y}_m \mathbf{T}^{1/2} = O(n^{1/2-\kappa}) + O(\alpha_n^{1/2+\delta}) \ a.s.$$

Here $\alpha_n = \max_{m\le n} \|\mathbf{\Sigma}_m - m\mathbf{T}\|$*.*

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