Adaptive Allocation Theory in Clinical Trials
–A Review *

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Abstract

Various adaptive randomization procedures (adaptive designs) have been proposed to clinical trials. This paper discusses several broad families of procedures, such as the play-the-winner rule and Markov chain model, randomized play-the-winner rule and urn models, drop-the-loser rule, doubly biased coin adaptive design. Asymptotic theories are presented with several pivotal proofs. The effect of delayed responses, the power and variability comparison of these designs are also discussed.

1 Introduction.

As reported by the World Health Organization (Global Summary of the AIDS Epidemic, December 2006), the estimated number of people living with HIV is 39.5 million, causing 2.9 million deaths in 2006 and 13% are children under 15 years. The alarming magnitude of AIDS epidemic and outbreaks of other fetal contagious diseases such as SARS reveal how vulnerable our health care system is. In order to search for more effective treatments, efficient clinical studies are urgently needed. In clinical trials, the traditional balanced (or 50%-50%) treatment allocation rule been challenged due to its possible unethical consequences. A frequently quoted clinical trial is the study of the drug AZT in reducing risk of maternal-infrac HIV transmission. While half of the pregnant women (239) are given the AZT drug, the remaining mothers (238) receive the placebo when 50%-50% allocation scheme is used. Only 20 infants are HIV-positive in AZT group and 60 in the placebo group. (c.f., Connor et al., New England J. Medicine, 1994). Balanced allocation resulted in many failures in the placebo group.

Yao and Wei (1996) redesigned the AZT trial using an adaptive allocation rule, the randomized play-the-wiener rule proposed by Wei and Durham (1978), and showed a reduction of several treatment failures under adaptive allocation. Adaptive designs, an important subdivision of experimental designs nowadays, are allocation rules in which the probability a treatment assigned to the coming patient depends upon the

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results of the previous patients in the study. The basic goal is to skew allocation probabilities to favor better treatment performance.

Early important work on adaptive designs was carried out by Thompson (1933) and Robbins (1952). Since then, a steady stream of research (Zelen (1969), Wei and Durham (1978), Wei (1979), Eisele and Woodroofe (1995), etc) in this area has generated various treatment allocation schemes for clinical trials. This paper provides the recent theories of several broad families of designs. In Section 2 we state some limit results on martingale, which are the basic tools to derive the asymptotic properties of adaptive designs. In Section 3 we consider Zelen’s play-the-winner rule and its generations by Lin, et al (2003). In Section 4 we derive the asymptotic properties of the adaptive designs based on urn models, a large family of randomization procedures. In Section 5 the drop-the-loser rule is introduced. In Section 6 an important family of target-driven designs, the doubly adaptive biased coin designs, are discussed. In Section 7, the effect of the delay of treatment results is discussed. In Section 8, we compare the variabilities of different type of adaptive designs. The lower bound of the asymptotic variability for a pre-specified allocation proportion is established, and asymptotic best adaptive designs are provided. Finally, further discussion and future topics are mentioned in Section 9. For the convenience of reading, we also give several pivotal proofs. The principle ideas of deriving asymptotic properties can be found from these proofs. Those who are not interested in the theoretical results can skip these proofs and go quickly to the last two sections.

The following notations and definitions are introduced to describe the randomized treatment allocation schemes. Given a clinical trial with \( K \) treatments. Let \( X_1, X_2, \ldots \) be the sequence of random treatment assignments. For the \( m \)-th subject, \( X_m = (X_{m,1}, \ldots , X_{m,K}) \) represents the assignment of treatment such that if the \( m \)-th subject is allocated to treatment \( k \), then all elements in \( X_m \) are 0 except for the \( k \)-th component, \( X_{m,k} \), which is 1. Let \( N_{n,k} \) be the number of subjects assigned to treatment \( k \) in the first \( n \) assignments and write \( N_n = (N_{n,1}, \ldots , N_{n,K}) \). Then \( N_n = \sum_{m=1}^{n} X_m \). We are interested in the statistical behavior of proportions \( N_{n,k}/n \), \( k = 1, \ldots , K \).

2 Preliminaries, limit theorems on martingales.

The martingale approach is the basic tool to investigate the asymptotic properties of adaptive designs. In this section, we state some limit theorems on martingales. For more results, one can refer to Hall and Heyde (1980) and Stout (1974) or other text books. Let \( \{M_n, \mathcal{F}_n; n \geq 1\} \) be a real martingale sequence with \( \Delta M_n = M_n - M_{n-1} \) being its difference.

**Theorem A (LLN)** Let \( \eta_n > 0 \) be a sequence of random variables such \( \eta_n \) is \( \mathcal{F}_{n-1} \) measurable and \( \eta_n \not\nearrow \) a.s., and \( p \) is a real number in \((0, 2]\).

(a) Then with probability one, \( M_n/\eta_n \to 0 \) on the event \( \{\eta_n \to \infty, \sum_{m=1}^{\infty} \mathbb{E}[(\Delta M_m)^p|\mathcal{F}_{m-1}]/\eta_m^p < \infty\} \).

(b) If \( \sum_{m=1}^{n} \mathbb{E}[(\Delta M_m)^2|\mathcal{F}_{m-1}] \leq \eta_n \) a.s., then with probability one \( M_n/\eta_n \to 0 \) on the event \( \{\eta_n \to \infty\} \).
Theorem B (LIL) Suppose \( \sup_m E[|\Delta M_m|^p] < \infty \) for some \( p > 2 \), then \( M_n = O(\sqrt{n \log \log n}) \) a.s.

Theorem C (CLT) Suppose there is a constant \( \sigma \geq 0 \) such that \( \sum_{m=1}^n E([\Delta M_m]^2 | F_{m-1})/n \stackrel{p}{\to} \sigma^2 \). Further assume that the conditional Lindberg condition

\[
\frac{1}{n} \sum_{m=1}^n E[(\Delta M_m)^2 I\{|\Delta M_m| \geq \epsilon \sqrt{n}|F_{m-1})] \stackrel{P}{\to} 0, \quad \forall \epsilon > 0
\]

is satisfied. Then \( M_n/\sqrt{n} \overset{d}{\to} N(0, \sigma^2) \). Further, \( M[nt]/\sqrt{n} \overset{d}{\to} \sigma W(t) \) in \( D[0, \infty) \), where \( W(t) \) is a standard Brownian motion.

Theorem D (Skorokhod embedding theorem) In a possibly enlarged probability space in which there is a standard motion \( B(t) \), we can redefine the martingale sequence \( \{M_n, F_n; \geq 1\} \) without changing its distribution and define a non-decreasing sequence of random variables \( \{\tau_n\} \) such that \( \tau_n \) is \( F_n \) measurable, \( M_n = B(\tau_n) \) and \( E[\Delta \tau_m | F_{m-1}) = E[(\Delta M_m)^2 | F_{m-1}) \) a.s., \( E[|\Delta \tau_m|^p | F_{m-1}) \leq C_p E[|\Delta M_m|^{2p}] | F_{m-1}) \) a.s. for \( p \geq 1 \).

Theorem E (Strong approximation) Let \( \{M_n, F_n; \geq 1\} \) be a martingale sequence in \( R^d \) space, \( \Sigma_n = \sum_{m=1}^n E[(\Delta M_m)' \Delta M_m | F_{m-1}) \). Suppose that there exists constants \( 0 < \epsilon < 1 \) such that

\[
\sum_{n=1}^\infty E[\|\Delta M_n\|^2 I\{\|\Delta M_n\|^2 \geq n^{1-\epsilon} | F_{n-1})]/n^{1-\epsilon} < \infty \quad a.s., \quad (2.1)
\]

and that \( T \) is a covariance matrix which is measurable with respect to \( F_k \) for some \( k \geq 0 \). Then for any \( \delta > 0 \), (possibly in an enlarged probability space with \( \{M_n\} \) being redefined) there exist \( \kappa > 0 \) and a \( d \)-dimensional standard Brownian \( W(t) \), independent of \( T \), such that

\[
S_n = W(n)T^{1/2} = O(n^{1/2-\kappa}) + O(\alpha_n^{1/2+\delta}) \quad a.s.
\]

Here \( \alpha_n = \max_{m \leq n} \|\Sigma_m - mT\| \).

If \( \sup_n \alpha_n E[|\Delta M_n|^{2+\delta_0}] < \infty \) for some \( \delta_0 > 0 \), then the condition (2.1) is satisfied. The proofs of Theorem A (a), Theorem C and Theorem D can be found in Hall and Heyde (1980). The proof of Theorem A (b) can be found in Stout (1974). Theorem B can be proved by Theorem D and the LIL of a Brownian motion. The proof of Theorem E is given in Zhang (2004). Also, Theorems A-C remain true for martingales in a \( R^d \) space with some necessary notations changed.

3 Play-the-winner rule and Markov chain adaptive design

Consider a two-arm clinical trial: two treatments (1 and 2) with dichotomous response (success and failure). Patients (subjects) are recruited into the clinical trial sequentially and respond immediately to treatments. Zelen (1969) proposed 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 \( p_i \) be the success probability of a patient on the treatment \( i, q_i = 1 - p_i, i = 1, 2 \). Then

\[
\frac{N_{n,1}}{n} \sim \frac{q_2}{q_1 + q_2} \quad \text{and} \quad \sqrt{n}(\frac{N_{n,1}}{n} - \frac{q_2}{q_1 + q_2}) \overset{D}{\rightarrow} N(0, \sigma^2_{PW}),
\]

where \( \sigma^2_{PW} = q_1 q_2 (p_1 + p_2)/(q_1 + q_2)^3 \). Notice that \( q_2/(q_1 + q_2) > 1/2 \) if \( p_1 > p_2 \). So, if treatment 1 is “doing better”, the PW rule favors treatment 1.

Lin, Bai, Chen and Hu (2003) extended the PW rule to a general Markov Chain adaptive design. Suppose that at the stage \( m \), the treatment 1 is assigned to the \( m \)th patient. Then the \((m+1)\)th patient will be assigned either treatment 1 or treatment 2 according certain probabilities, which depend on the response of the \( m \)th patient. Let \( \alpha_s \) be the probability of assigning the \((m+1)\)th patient to treatment 1, when the response of the \( m \)th patient to treatment 1 is “success”, and let \( \alpha_f \) be the probability of assigning the \((m+1)\)th patient to treatment 1, when the response of the \( m \)th patient to treatment 1 is “failure”. Similarly define \( \beta_s \) and \( \beta_f \) with treatment 2 instead of treatment 1 in the definitions of \( \alpha_s \) and \( \alpha_f \). When \( \alpha_s = 1, \alpha_f = 0, \beta_s = 1, \beta_f = 0 \), we get Zelen’s PW rule. A clinical application disadvantage of the PW rule is that it is fully deterministic, i.e., when the previous results are known, the assignment of the next subject is fully determined. The Markov chain adaptive design is not fully deterministic except when the parameter \( \alpha_s, \alpha_f, \beta_s \) and \( \beta_f \) take extreme values 0 and 1. When taking \( \alpha_s = \alpha_f = \beta_s = \beta_f = 1/2 \), we get the fully randomization procedure which allocates patients to each treatment with a probability 1/2. The more are the parameters near extreme values, the more is the procedure being deterministic. When \( \alpha_s < \alpha_f \) and \( \beta_s < \beta_f \), the Markov chain adaptive design is less ethical than the balanced allocation (c.f., Equation (3.1)). The parameters \( \alpha_s, \alpha_f, \beta_s \) and \( \beta_f \) can be chosen to reflect the trade-off between the degree of randomness and ethic.

Let \( p_1(m) = P\{\text{success } | X_{m,1} = 1\} \) and \( p_2(m) = P\{\text{success } | X_{m,1} = 0\} \) and \( \alpha_m = p_1(m)\alpha_s + (1 - p_1(m))\alpha_f, \beta_m = p_2(m)\beta_s + (1 - p_2(m))\beta_f \). Then \( \{X_{m,1}\} \) is a Markov chain with the transition probability matrix

\[
P_m = \begin{pmatrix}
\alpha_m & 1 - \alpha_m \\
1 - \beta_m & \beta_m
\end{pmatrix}.
\]

When \( p_1(m) = p_1 \) and \( p_2(m) = p_2 \) for all \( m \), \( \alpha_n \equiv \alpha, \beta_n \equiv \beta \), and \( \{X_{m,1}\} \) is a homogeneous Markov chain with a stationary distribution \((\mu, 1 - \mu)\), where \( \mu = (1 - \beta)/(2 - \alpha - \beta) \). Following from the central limit theorem for Markov chains we have that

\[
\frac{N_{n,1}}{n} \sim \mu \quad \text{and} \quad \sqrt{n}(\frac{N_{n,1}}{n} - \mu) \overset{D}{\rightarrow} N(0, \sigma^2) \tag{3.1}
\]

where

\[
\sigma^2 = \text{Var}_{\mu}\{X_{1,1}\} + 2 \sum_{j=2}^{\infty} \text{Cov}_{\mu}\{X_{1,1}, X_{j,1}\} = \frac{(1 - \alpha)(1 - \beta)(\alpha + \beta)}{(2 - \alpha - \beta)^3}.
\]
For non-homogeneous case, Lin, Bai, Chen and Hu (2003) proved (3.1) under the condition that
\[ \sum_{m=1}^{\infty} \frac{|p_1(m) - p_1| + |p_2(m) - p_2|}{\sqrt{m}} < \infty. \]

Lin, Zhang, Cheung and Chan (2005) established the strong approximation for $N_{n,1}$, from which (3.1) follows immediately.

**Theorem 3.1** In a possibly enlarged probability space, we can redefine the sequence \( \{N_{n,1}\} \) without changing its distribution, such that
\[ N_{n,1} - n\mu - \sigma W(n) = O((n \log \log n)^{1/4}(\log n)^{1/2}) + O(\Delta_n) \quad a.s., \]
where \( \{W(t)\} \) is a standard Brownian motion and \( \Delta_n = \sum_{m=1}^{n} (|\alpha_m - \alpha| + |\beta_m - \beta|). \)

**Proof.** Write \( \Delta m_n = X_{m,1} - E[X_{m,1}|\mathcal{F}_{m-1}] \), where \( \mathcal{F}_{m-1} \) is the history sigma field generated by \( X_{m,1}, \ldots, X_{m-1,1} \). Then \( X_m = \Delta m_m + E[X_{m,1}|\mathcal{F}_{m-1}] = \Delta m_m + 1 - \beta_m - (1 - \alpha_m - \beta_m)X_{m-1,1} \). It follows that \( N_{n,1} = m_n + 1 - \beta - (1 - \alpha - \beta)N_{n-1,1} + O(\Delta_n) + O(1) \).

So,
\[ N_{n,1} = n\mu + m_n/(2 - \alpha - \beta) + O(\Delta_n). \]

For the martingale \( m_n \), we have \( E[(\Delta m_m)^2|\mathcal{F}_{m-1}] = (1 - \beta_m)\beta_m + (\alpha_m - \beta_m)(1 - \alpha_m - \beta_m)X_{m-1,1} \) and \( |\Delta m_m| \leq 1 \). It follows that
\[ \sum_{m=1}^{n} E[(\Delta m_m)^2|\mathcal{F}_{m-1}] = n(1 - \beta)\beta + (\alpha - \beta)(1 - \alpha - \beta)N_{n-1,1} + O(\Delta_n) \]
\[ = n(1 - \beta)\beta + n(\alpha - \beta)(1 - \alpha - \beta)\mu + (\alpha - \beta)(1 - \alpha - \beta)\frac{m_n}{2 - \alpha - \beta} + O(\Delta_n) \]
\[ = n\frac{(1 - \alpha)(1 - \beta)(\alpha + \beta)}{2 - \alpha - \beta} + O(\Delta_n) + O(\sqrt{n \log \log n}) \]
\[ = n\sigma_M^2 + O(\Delta_n) + O(\sqrt{n \log \log n}) \quad a.s. \]

due to the LIL (Theorem B). Applying the Skorokhod embedding theorem (Theorem D), we can write \( m_n = B(\tau_n) \). Notice \( \sum_{m=1}^{n} (\Delta \tau_m - E[\Delta \tau_m|\mathcal{F}_{m-1}]) \) is also a martingale sequence. By the LIL, we conclude that
\[ \tau_n = \sum_{m=1}^{n} E[\Delta \tau_m|\mathcal{F}_{m-1}] + O(\sqrt{n \log \log n}) \]
\[ = \sum_{m=1}^{n} E[(\Delta m_m)^2|\mathcal{F}_{m-1}] + O(\sqrt{n \log \log n}) \]
\[ = n\sigma_M^2 + O(\Delta_n) + O(\sqrt{n \log \log n}) \quad a.s. \]

It follows that
\[ m_n = B(\tau_n) = B(n\sigma_M^2 + O(\sqrt{(\Delta_n + \sqrt{n \log \log n}) \log n})) \]
\[ = B(n\sigma_M^2) + O(\Delta_n) + O((n \log \log n)^{1/4}(\log n)^{1/2}) \quad a.s. \]
by the sample properties of a Brownian motion (c.f., Csörgő and Révész (1980)). The proof is now completed by letting \( W(t) = B(t\sigma_M^2)/\sigma_M \) and noticing that \( \sigma_M^2/(2 - \alpha - \beta)^2 = \sigma^2 \). \( \square \).

For the multi-treatment case, we let \( p_i(m) = P(\text{success} \mid X_{m,i} = 1) \). Assume the transition probability matrix of the Markov chain \( \{X_n\} \) is \( H_n = \{H_{ij}(n)\} \) which is a function of \( p_i(n) \), \( i = 1, \ldots, K \), i.e., \( E[X_{n+1} \mid X_n] = X_nH \). By using Theorem E instead of the Skorokhod embedding theorem, Zhang (2004) showed that \( N_n \) can be approximated by a multi-dimensional Brownian motion:

\[
N_n - n\mathbf{v} - \mathbf{W}(n)\Sigma = o(n^{1/2-\kappa}) + O\left(\sum_{k=1}^{n} \|H_k - H\|\right) \quad \text{a.s.,}
\]

where \( \kappa > 0 \), \( \mathbf{v} = (v_1, \cdots, v_K) \) is the left eigenvector corresponding to the largest eigenvalue of \( H \) with \( v_1 + \cdots + v_K = 1 \), \( \{\mathbf{W}(t)\} \) is a \( K \)-dimensional standard Brownian motion. In particular, we have asymptotic normality, if

\[
\sum_{k=1}^{n} \|H_k - H\| = o(n^{1/2}). \tag{3.2}
\]

Zhang (2006) studied a kind of non-homogeneous Markov chain designs, in which \( H_n \) is a function of an estimated unknown parameters \( \hat{\theta} \). In this case the condition (3.2) is not satisfied.

4 Randomized play-the-winner rule and urn models

To overcome the drawback that the PW rule is fully deterministic, Wei and Durham (1978) introduced the following randomized play-the-winner (RPW) rule: We start with \((\alpha, \beta)\) balls (type 1 and 2 respectively) in the urn. If a type \( k \) ball is drawn, a patient is assigned to the treatment \( k \), \( k = 1, 2 \). The ball is replaced and the patient’s 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. Let \( Y_{n,1} \) \( Y_{n,2} \) be number of balls of type 1 (2) after \( n \) stage. From the results of Athreya and Karlin (1968), we have

\[
\frac{Y_{n,1}}{Y_{n,1} + Y_{n,2}} \rightarrow \frac{q_2}{q_1 + q_2} \quad \text{a.s.} \quad \text{and} \quad \frac{Y_{n,1}}{n} \rightarrow \frac{q_2}{q_1 + q_2} \quad \text{a.s.}.
\]

The limiting proportion is the same as that of the PW rule. We refer to it as urn proportion. When \( p_1 + p_2 < 1.5 \) (or \( q_1 + q_2 > 0.5 \)), we have the following asymptotic normality:

\[
\sqrt{n}\left(\frac{Y_{n,1}}{Y_{n,1} + Y_{n,2}} - \frac{q_2}{q_1 + q_2}\right) \overset{P}{\rightarrow} N\left(0, \frac{q_1q_2}{(2(q_1 + q_2) - 1)(q_1 + q_2)^2}\right)
\]
and \( \sqrt{n}(N_{n,1}/n - q_2/(q_1 + q_2)) \overset{D}{\rightarrow} N(0, \sigma_{RPW}^2) \), where

\[
\sigma_{RPW}^2 = \frac{q_1 q_2 [5 - 2(q_1 + q_2)]}{[2(q_1 + q_2) - 1][q_1 + q_2]^2}.
\]  (4.1)

The asymptotic normality was first given in Smythe and Rosenberger (1995). When \( q_1 + q_2 < 0.5 \), the limiting distributions of both the urn composition and the allocation proportion are unknown. The RPW rule has the same limiting allocation proportion as the PW rule. But the asymptotic variability is much larger.

As multi-treatment extensions of the RPW rule, one large family of randomized adaptive designs can be developed from the generalized Polya urn (GPU) model. Urn models have also long been recognized as valuable mathematical apparatus in many areas including physical science, biological science, engineering, information science, the study of economic behaviors, etc.

Consider an urn containing balls of \( K \) types. Initially, the urn contains \( Y_0 = (Y_{0,1}, \ldots, Y_{0,K}) \) balls, where \( Y_{0,k} \) denotes the number of balls of type \( k \), \( k = 1, \ldots, K \). A ball is drawn at random. Its type is observed and the ball is then replaced. At the \( m \)th stage, following a type \( k \) drawn, \( D_{kj}(m) \) (\( \geq 0 \)) balls of type \( j \), for \( j = 1, \ldots, K \), are added to the urn. \( D_{kj}(m) \) is a random function of the response \( \xi_{m,k} \) of the \( m \)-th subject on treatment \( k \). The expectation of the total numbers of balls added in each stage is assumed to be the same (say \( \gamma \)), so

\[
\sum_{j=1}^{K} \mathbb{E}\{D_{kj}(m)|\mathcal{F}_{m-1}\} = \gamma, \quad k, j = 1, \ldots, K, m = 1, 2, \ldots,
\]

where \( \mathcal{F}_{m-1} \) is the history sigma field. Without loss generality, we can assume \( \gamma = 1 \).

Let \( H_m \) be the matrix comprising element \( \{h_{ij}(m) = \mathbb{E}[D_{kj}(m)|\mathcal{F}_{m-1}]\} \) and \( D_m = \{D_{kj}(m)\} \). We refer to \( D_m \) as the adding rules and \( H_m \) as the design matrices. If \( D_m \), \( m = 1, 2, \ldots \), are i.i.d., then \( H_m = H \) for all \( n \). In this case the model is said to be homogenous. In general, it is assumed that \( H_m \to H \). Let \( Y_n = (Y_{n,1}, \ldots, Y_{n,K}) \), where \( Y_{n,k} \) represents the number of balls in the urn of type \( k \) after \( n \)th stage. And let \( v = (v_1, \ldots, v_K) \) be the left eigenvector corresponding to the largest eigenvalue of \( H \) with \( v_1 + \ldots + v_K = 1 \). Then \( v_k \) is just the limiting proportion of both the patients assigned to treatment \( k \) and the type \( k \) balls in the urn. Bai, Hu and Zhang (2002), Hu and Zhang (2001) obtained the asymptotic properties via the strong approximation.

**Theorem 4.1** Suppose that \( \{D_m\} \) is sequence of i.i.d. random matrices with \( \sup_m \mathbb{E}\|D_m\|^{2+\delta} < \infty \). Let \( \lambda_1 = \gamma = 1, \lambda_2, \ldots, \lambda_K \) be the eigenvalues of \( H \), and \( \lambda = \max\{\text{Re}(\lambda_2), \ldots, \text{Re}(\lambda_K)\} \).

If \( \lambda < 1 \), then

\[
\frac{N_{n,i}}{n} \to v_i \quad \text{a.s. and} \quad \frac{Y_{n,i}}{\sum_{j=1}^{K} Y_{nj}} \to v_i \quad \text{a.s.} \quad (4.2)
\]

If \( \lambda < 1/2 \), then

\[
\sqrt{n}(\frac{Y_n}{n} - v) \overset{D}{\rightarrow} N(0, \Sigma) \quad \text{and} \quad \sqrt{n}(\frac{N_n}{n} - v) \overset{D}{\rightarrow} N(0, \Sigma^*). \quad (4.3)
\]
Proof. Write $1 = (1, \ldots, 1)$, $|Y_n| = \sum_{k=1}^{K} Y_{nk}$, $\tilde{\mathbf{H}} = \mathbf{H} - 1'v$, $\mathbf{M}_n = \sum_{m=1}^{n} \mathbf{X}_m (\mathbf{D}_m - \mathbf{H})$, $\mathbf{m}_m = \sum_{m=1}^{n} \mathbf{X}_m - \mathbb{E}[\mathbf{X}_m | \mathcal{F}_{m-1}]$. Then $\mathbf{H}1' = 1'$, $\mathbf{m}_m 1' = 0$, and the eigenvalues of $\tilde{\mathbf{H}}$ are $0, \lambda_2, \ldots, \lambda_K$. We have the following lemma on matrices, the proof of which can be founded in Hu and Zhang (2004a).

**Lemma 4.1** If $\Delta \mathbf{Q}_n = \Delta \mathbf{P}_n + \mathbf{Q}_{n-1} \tilde{\mathbf{H}} / (n-1)$, $n \geq 2$, then

$$\|\mathbf{Q}_n\| = O(\|\mathbf{P}_n\|) + \sum_{m=1}^{n} O(\|\mathbf{P}_m\|) (n/m)^{\lambda} \log^{\nu-1}(n/m),$$

where $\nu$ is the degree of the second largest eigenvalue of $\mathbf{H}$.

We prove (4.3) only. Notice

$$\Delta (\mathbf{Y}_n - n \mathbf{v}) = \mathbf{X}_n \mathbf{D}_n - \mathbf{v} = \Delta \mathbf{M}_n + \Delta \mathbf{m}_n \mathbf{H} + \frac{\mathbf{Y}_{n-1}}{|\mathbf{Y}_{n-1}|} \mathbf{H} - \mathbf{v}$$

$$= \frac{\mathbf{Y}_{n-1} - (n-1) \mathbf{v} \mathbf{Y}_{n-1}}{n-1} \tilde{\mathbf{H}} + \Delta \mathbf{M}_n + \Delta \mathbf{m}_n \tilde{\mathbf{H}}$$

$$+ \left( 1 - \frac{\mathbf{Y}_{n-1}}{|\mathbf{Y}_{n-1}|} \right) \left( \frac{\mathbf{Y}_{n-1}}{|\mathbf{Y}_{n-1}|} - \mathbf{v} \right) \tilde{\mathbf{H}}. \quad (4.4)$$

Multiplying $1'$ yields $|\mathbf{Y}_n| - n = \Delta \mathbf{M}_n 1' + |\mathbf{Y}_0| = O(\sqrt{n \log \log n})$ a.s. due to the LIL (Theorem B). It follows that

$$\mathbf{M}_n + \mathbf{m}_n \mathbf{H} + \sum_{m=1}^{n-1} \left( 1 - \frac{\mathbf{Y}_m}{|\mathbf{Y}_m|} \right) \left( \frac{\mathbf{Y}_m}{|\mathbf{Y}_m|} - \mathbf{v} \right) \tilde{\mathbf{H}} = O(\sqrt{n \log \log n}) \ a.s.$$

By applying Lemma 4.1 and noticing $\lambda < 1/2$, we obtain $\mathbf{Y}_n - n \mathbf{v} = O(\sqrt{n \log \log n})$ a.s.

Write $\mathbf{D}_k = (D_{k1}, \ldots, D_{kk})$, $\Sigma_1 = \text{diag}(\mathbf{v}) - \mathbf{v}' \mathbf{v}$ and $\Sigma_2 = \sum_{k=1}^{K} \nu_k \text{Var}(\mathbf{D}_1^{(k)})$. For the martingale $(\mathbf{M}_n, \mathbf{m}_m)$, we have $\sup_n \mathbb{E}[\|\Delta \mathbf{M}_n\|^{2+\delta} < \infty$, $\|\Delta \mathbf{m}_n\| \leq K$, $\mathbb{E}[(\Delta \mathbf{M}_n)' \Delta \mathbf{m}_n | \mathcal{F}_{m-1}] = 0$ and

$$\sum_{m=1}^{n} \mathbb{E}
[(\Delta \mathbf{m}_m)' \Delta \mathbf{m}_m | \mathcal{F}_{m-1}] = \sum_{m=1}^{n} \text{diag}
\left( \frac{\mathbf{Y}_m}{|\mathbf{Y}_m|} \right) - \left( \frac{\mathbf{Y}_m}{|\mathbf{Y}_m|} \right)' \frac{\mathbf{Y}_m}{|\mathbf{Y}_m|}$$

$$= n \Sigma_1 + O(\sqrt{n \log \log n}) \ a.s.,$$

$$\sum_{m=1}^{n} \mathbb{E}
[(\Delta \mathbf{M}_m)' \Delta \mathbf{M}_m | \mathcal{F}_{m-1}] = \sum_{m=1}^{n} \sum_{k=1}^{K} \text{Var}(\mathbf{D}_1^{(k)}) Y_{mk} / |\mathbf{Y}_m|$$

$$= n \Sigma_2 + O(\sqrt{n \log \log n}) \ a.s.$$.

By the strong approximation (Theorem E), there are two independent $d$-dimensional standard Brownian motions $\mathbf{W}_1(t)$ and $\mathbf{W}_2(t)$ such that for some $\kappa > 0$,

$$\mathbf{m}_n = \mathbf{W}_1(n) \Sigma_1^{1/2} + o(n^{1/2-\kappa}) \ a.s., \quad \mathbf{M}_n = \mathbf{W}_2(n) \Sigma_2^{1/2} + o(n^{1/2-\kappa}) \ a.s. \quad (4.5)$$
Without loss generality, we assume $1/2 - \kappa > \lambda$ and $1/2 - \kappa > 1/4$. Let $G_i(t)$ be the solution of the equation

$$G_i(t) = \int_0^t \frac{G_i(x)}{x} \cdot \cdot \cdot + W_i(t) \cdot \Sigma_i^{1/2}, \ G_i(0) = 0, \ (4.6)$$

$i = 1, 2$. Notice $\{[W_i(T(\cdot + s)] - W_i(T(\cdot))] / \sqrt{T}\} \overset{d}{=} \{W_i(\cdot)\}$. It can be checked that $G_i(t)$ is a Gaussian process with stationary increments and $\text{Var}\{G_i(t)\} = t \cdot \text{Var}\{G_i(1)\}$, and

$$\int_0^t \frac{G_i(x)}{x} dx = \sum_{m=1}^{n-1} \frac{G_i(m)}{m} + O((\log n)^{3/2}) \ a.s. \ (4.7)$$

Combing (4.4)–(4.7) yields

$$Y_n - n\nu - G_2(n) - G_1(n) \tilde{H} = \sum_{m=1}^{n-1} \frac{Y_m - m\nu - G_2(m) - G_1(m) \tilde{H}}{m} \tilde{H} + P_n,$$

where

$$P_n = O((\log n)^{3/2}) + o(n^{1/2-\kappa}) + \sum_{m=1}^{n-1} \left(1 - \frac{|Y_m|}{m}\right) \left(\frac{Y_m}{|Y_m|} - \nu\right) \tilde{H} \tilde{H}$$

$$= O((\log n)^{3/2}) + o(n^{1/2-\kappa}) + \sum_{m=1}^{n-1} \left(\sqrt{\log \log m} / m\right)^2 = o(n^{1/2-\kappa}) \ a.s.$$

Now, by applying Lemma 4.1 we conclude that

$$Y_n - n\nu = G_2(n) + G_1(n) \tilde{H} + o(n^{1/2-\kappa}) \ a.s.$$

Finally,

$$N_n - n\nu = m_n + \sum_{m=0}^{n-1} \frac{Y_m}{|Y_m|} - n\nu = m_n + \sum_{m=0}^{n-1} \left(\frac{Y_m}{|Y_m|} - \nu\right) (I - 1'v)$$

$$= m_n + \sum_{m=1}^{n-1} \frac{Y_m - m\nu}{m} (I - 1'v)$$

$$+ \sum_{m=1}^{n-1} \left(1 - \frac{|Y_m|}{m}\right) \left(\frac{Y_m}{|Y_m|} - \nu\right) (I - 1'v) + O(1)$$

$$= W_1(n) + \sum_{m=1}^{n-1} \frac{G_2(m) + G_1(m) \tilde{H}}{m} (I - 1'v) + o(n^{1/2-\kappa})$$

$$= W_1(n) + \int_0^x \frac{G_2(x) + G_1(x) \tilde{H}}{x} dx (I - 1'v) + o(n^{1/2-\kappa})$$

$$= G_1(n) + \int_0^x \frac{G_2(x)}{x} dx (I - 1'v) + o(n^{1/2-\kappa}) \ a.s.$$
This condition can be weakened to
\[ \sum_k \] to treatment the urn is updated in the following way: at the \( m \)th stage, if a subject is assigned to treatment \( k \) and cured, then a type \( k \) ball is added to the urn, otherwise, if treatment \( k \) for a subject fails, then \( \frac{\sqrt{x}}{\sqrt{x}} \) balls are added to the urn for each of the other \( K - 1 \) treatments. In this urn model, \( H = \{h_{kj}, k, j = 1, \ldots, K\} \), where \( h_{kk} = p_k \) and \( h_{kj} = q_k/(K - 1) \) \( (j \neq k) \), and \( p_k \) is the successful probability of treatment \( k \), \( q_k = 1 - p_k \). So \( v_k = (1/q_k)/\sum_{j=1}^{K}(1/q_j) \).

For the non-homogenous case, Bai and Hu (2005) obtained (4.3) under the condition that
\[ \sum_{m=1}^{\infty} \frac{\|H_m - H\|}{\sqrt{m}} < \infty \text{ a.s.} \] (4.8)
This condition can be weakened to \( \sum_{m=1}^{\infty} \|H_m - H\| = o(\sqrt{n}) \) a.s. by use the argument in the above proof. An applicable class of non-homogenous urn models is the sequential estimation-adjusted urn (SEU) model, in which the urn is updated according to the current response and the current estimate of an unknown parameter, and so \( H_m = H(\hat{\theta}_m) \) is a function of the estimator. In this case, the fastest convergence rate of \( H_m \) is \( O_P(\sqrt{m}) \) and the condition (4.8) is not satisfied. Zhang, Hu and Cheung (2006) established the asymptotic properties of SEU models.

Example 4.2 Bai, Hu and Shen (2002) proposed a GUP to allocate subjects, in which the urn is updated in the following way: at the \( m \)th stage, if a subject is assigned to treatment \( k \) and cured, then a type \( k \) ball is added to the urn. If a failure, then \( \frac{\hat{p}_{m-1,j}}{\sum_{i \neq k} \hat{p}_{m-1,i}} \) balls of each type \( j \neq k \) are added. Where \( \hat{p}_{m-1,j} = (S_{m-1,i}+1)/(N_{m-1,j}+1) \), and \( S_{m-1,j} \) is the number of successes of treatment \( j \) in previous \( m-1 \) stages. This model is a SEU model with \( H(x) = \{h_{ij}(x); i, j = 1, \ldots, K\} \), where \( h_{kk}(x) = p_k \) and \( h_{kj}(x) = q_kx_j/\sum_{i \neq k} x_i \) \( (j \neq k) \).
More examples and applications of SEU models can be found in Zhang, Hu and Chueng (2006), in which how to defined a SEU model by using the information of distribution parameters to target a pre-specified limiting allocation proportion is discussed in details.

5 Drop-the-loser rule

The asymptotic normality for the urn models can be obtained only when the condition $\lambda \leq 1/2$ is satisfied. This is a very strict condition. Even in the case of $K = 3$, it is hard to be satisfied and to check it is not an easy work. Also, when $\lambda$ is close or exceeds 1/2, the variability of an urn model is extremely high. Ivanova (2003) proposed a drop-the-loser (DL) rule which has the same limiting proportion as Wei (1979)'s rule (See Example 4.1) but has much smaller variability. Consider an urn containing balls of $K + 1$ types, type 0, 1, ..., $K$, when comparing $K$ treatments. A ball is drawn at random. If it is type $k$, $k = 1, \ldots, K$, the corresponding treatment is assigned and the subject’s response is observed. If the response is a success, the ball is replaced and the urn remains unchanged. If a failure, the ball is not replaced. When a type 0 ball is drawn, no subject is treated, and the ball is returned to the urn together with one ball of each treatment type $k$, $k = 1, \ldots, K$. Ivanova (2003, 2006) established the asymptotic normality after embedding the urn process to a death-and-immigration process. Here we give the strong approximation.

Theorem 5.1 There is a $K$-dimensional standard Brownian motion $W(t)$ such that

$$N_n - n\mathbf{v} = W(n)\text{diag}(\frac{\nu_1p_1}{q_1}, \ldots, \frac{\nu_Kp_K}{q_K})(I - \mathbf{v}') + o(n^{1/2 - \kappa}) \text{ a.s.},$$

for some $\kappa > 0$, where $v_k = (1/q_k)/\sum_{j=1}^{K}(1/q_j)$, $k = 1, \ldots, K$. Hence

$$\sqrt{n}(N_n/n - \mathbf{v}) \xrightarrow{\mathcal{D}} N\left(0, (I - \mathbf{v}')(\text{diag}(\frac{\nu_1p_1}{q_1}, \ldots, \frac{\nu_Kp_K}{q_K})(I - \mathbf{v}'))\right).$$

In particular, in the two-treatment case, $\sqrt{n}(N_n/n - \mathbf{v}) \xrightarrow{\mathcal{D}} N(0, \sigma_{DL}^2)$ with $\sigma_{DL}^2 = q_1q_2(p_1 + p_2)/(q_1 + q_2)^3$, the same as the $\sigma_{PW}^2$. For the generalizations of the DL rule and their applications, one can refer to Zhang, Chan, Cheung and Hu (2007), Sun, Cheung and Zhang (2007).

Proof of the theorem. Let $Z_m = (Z_{m,0}, \ldots, Z_{m,K})$ be the urn compositions after the $m$-the assignment. And let $\mu_m$ be the number of draws of type 0 balls between the $(m - 1)$-th assignment and the $m$-th assignment. Remember that when a type 0 ball is drawn, we add one ball of each treatment type, and when a treatment type ball is drawn, it is replaced only when the response is a success. So

$$Z_{m,k} - Z_{m-1,k} = \mu_m + X_{m,k}(\xi_{m,k} - 1) = \mu_m - X_{m,k}q_k + X_{m,k}(\xi_{m,k} - p_k),$$

where $\xi_{m,k} = 1$ if the response of the $m$-th subject on treatment $k$ is a success, and 0 if failure. Let $M_n = \sum_{m=1}^{n}X_{m,k}(\xi_{m,k} - p_k)$, $M_n = (M_{n,1}, \ldots, M_{n,K})$, and $A_m$ be the
sigma field generated by $\xi_{1,k}, \ldots, \xi_{m,k}$, $k = 1, \ldots, K$, and $X_1, \ldots, X_m, X_{m+1}$. Then $\{M_n, A_m\}$ is a martingale. It follows that $Z_{n,k} - Z_{0,0} = \sum_{m=1}^{n} \mu_m - N_{n,k}q_k + M_{m,k}$. We can prove that $Z_{n,k} = o(n^{1/2-\delta_0})$ a.s. for some $\delta_0 > 0$. For details of the proof, we refer to Zhang, Hu, Chueng and Chan (2006b), Sun, Cheung and Zhang (2007). Hence
\[ N_{n,k} = \sum_{m=1}^{n} \mu_m/q_k + M_{m,k}/q_k + o(n^{1/2-\delta_0}) \quad a.s., \quad k = 1, \ldots, K, \]
which, together with the fact $N_{n,1} + \cdots + N_{n,K} = n$, implies
\[ N_n - nv = M_n diag(1/q_1, \ldots, 1/q_K)(I - v') + o(n^{1/2-\delta_0}) \quad a.s. \]
So, $N_n - nv = O(\sqrt{n \log \log n})$ a.s. by the LIL (Theorem B). On the other hand, for the martingale $\{M_n\}$ we have
\[ \sum_{m=1}^{n} E[(\Delta M_n)' \Delta M_n | F_{m-1}] = diag(N_{n,1}p_1q_1, \ldots, N_{n,K}p_kq_k) \]
\[ = n diag(v_1p_1q_1, \ldots, v_kp_kq_k) + O(\sqrt{n \log \log n}) \quad a.s. \]
By applying the strong approximation (Theorem E), we can define a $K$-dimensional Brownian motion $W(t)$ such that
\[ M_n = W(n) diag(\sqrt{v_1p_1q_1}, \ldots, \sqrt{v_kp_kq_k}) + o(n^{1/2-\kappa}) \quad a.s. \]
The proof is now completed. $\square$

6 Doubly adaptive biased coin designs

The PW rule and urn model designs are a kind of design-driven adaptive designs, which are constructed with intuitive motivation. However, clinical trials are usual complex experiments on humans with multiple, often competing, objectives, including maximizing power to detect clinically relevant differences in treatment outcomes, maximizing the individual patient’s personal experience while treated in the trial, and minimizing the total monetary cost of trial. These and other objectives can be defined in terms of optimization of function of the trial’s parameters, the optimal allocation proportion is often a function of unknown parameters. Take a binary response clinical trial with two treatments 1 and 2 as an example. The well known Neyman proportion is
\[ \rho(p_1, p_2) =: \frac{n_1}{n_1 + n_2} = \frac{\sqrt{p_1q_1}}{\sqrt{p_1q_1} + \sqrt{p_2q_2}}, \]
where $p_k$ ($q_k$) is the probability of success (failure) of a trial treatment $k$, $n_k$ is the number of subjects assigned to treatment $k$, $k = 1, 2$, The Neyman proportion maximizes the power of a test of the simple difference $p_1 - p_2$ for fixed sample size $n$. But if we implement Neyman allocation, when $p_1 + p_2 > 1$, we will assign more subjects to the inferior treatment, which will compromise the ethical objective. Rosenberger, et al
(2001) discussed another important optimization criteria that minimize the expected number of treatment failures, \( n_1q_1 + n_2q_2 \), for fixed the variance, \( p_1q_1/n_1 + p_2q_2/n_2 \), of the statistic \( \hat{p}_1 - \hat{p}_2 \) under an alternative hypothesis \( p_1 \neq p_2 \). This leads the optimal proportion as follows.

\[
\rho(p_1, p_2) = \frac{\sqrt{p_1}}{\sqrt{p_1} + \sqrt{p_2}}.
\]

Many simulation studies have validated that a adaptive design with this proportion as its target performs very satisfactorily for both the consideration of ethic and the test of power. For other optimization criteria one can refer to Jennison and Turnbull (2000) and Rosenberger, et al. (2001). Both Neyman allocation and the allocation of Rosenberger, et al. (2001) discussed another important optimization criteria that minimize the expected number of treatment failures, \( n_1q_1 + n_2q_2 \), for fixed the variance, \( p_1q_1/n_1 + p_2q_2/n_2 \), of the statistic \( \hat{p}_1 - \hat{p}_2 \) under an alternative hypothesis \( p_1 \neq p_2 \). This leads the optimal proportion as follows.

\[
\rho(p_1, p_2) = \frac{\sqrt{p_1}}{\sqrt{p_1} + \sqrt{p_2}}.
\]

Consider a clinical with \( K \) treatments. The outcome of a subject on treatment \( k \) has a distribution \( f_k(\cdot; \theta_k) \). Write \( \theta = (\theta_1, \ldots, \theta_K) \). The pre-specified allocation proportion is \( v = \rho(\theta) = (\rho_1(\theta), \ldots, \rho_m(\theta)) \). Here \( \rho(y) \) is assumed to be continuous function on the parameter space, taking the values on \( (0, 1)^{\otimes k} \) and twice differentiable at the true value of the parameter \( \theta \). A multi-treatment DBCD proposed by Hu and Zhang (2004a) is defined as follows.

To start, allocate \( M \) subjects to each treatment. At stage \( m \), suppose \( m \leq M \) subjects are allocated and the outcomes, \( N_{m-1,k} \) outcomes of treatment \( k \), \( k = 1, \ldots, K \), are observed. Let \( \hat{\theta}_{m-1,k} \) be the MLE of the parameter \( \theta_k \), \( k = 1, \ldots, K \). Write \( \hat{\theta}_{m-1} = (\hat{\theta}_{m-1,1}, \ldots, \hat{\theta}_{m-1,K}) \), and let \( \hat{\rho}_{m-1} = \rho(\hat{\theta}_{m-1}) \) be the current estimate of the target allocation proportion. Now, the \( m \)-th subject is allocated to treatment \( k \) with a probability:

\[
P_{m,k} = \mathbb{P}(X_{m,k} = 1| F_{m-1}) = g_k \left( \frac{N_{m-1,k}}{m-1}, \hat{\rho}_{m-1} \right), \quad (6.1)
\]

\( k = 1, \ldots, K \). Here \( g(x, y) = (g_1(x, y), \ldots, g_K(x, y)) : (0, 1)^{\otimes 2k} \rightarrow (0, 1)^{\otimes k} \) is the allocation function. Write \( P_m = (P_{m,1}, \ldots, P_{m,K}) \).

**Theorem 6.1** Suppose the distributions \( f_1(\cdot; \theta_1), \ldots, f_K(\cdot; \theta_K) \) follow an exponential family. Let \( g(x, y) \) be defined as

\[
g_k(x, y) = \frac{y_k \left( \frac{y_k}{x_k} \right)^\gamma}{\sum_{j=1}^K y_j \left( \frac{y_j}{x_j} \right)^\gamma}, \quad k = 1, \ldots, K; \quad \gamma \geq 0. \quad (6.2)
\]

Then

\[
N_n - nv = O(\sqrt{n \log \log n}) \text{ a.s. and } \sqrt{n}(N_n/n - v) \xrightarrow{D} N(0, \Sigma),
\]

where

\[
\Sigma = \Sigma_{\rho} + \frac{1}{1 + 2\gamma}(\text{diag}(v) - v'v + \Sigma_{\rho}),
\]
\[ \Sigma_{\rho} = \left( \frac{\partial \rho}{\partial \theta} \right)' \text{diag} \left( (v_1 I_1(\theta_1))^{-1}, \ldots, v_K I_1(\theta_K))^{-1} \right) \frac{\partial \rho}{\partial \theta} \]

and \( I_k(\theta_k) \) is the Fisher information function for a single observation on treatment \( k \).

In particular, for the two-treatment case, suppose the targeted allocation proportion of treatment 1 is \( \rho = \rho(\theta_1, \theta_2) \). Then \( \sqrt{n} \left( N_{n,1}/n - \rho \right) \xrightarrow{D} N(0, \sigma^2_{DBCD}) \) where

\[ \sigma^2_{DBCD} = \sigma^2_\rho + \frac{1}{1+2\gamma} \{ \rho(1-\rho) + \sigma^2_\rho \} \]

and \( \sigma^2_\rho = (I_1(\theta_1)\rho)^{-1}(\partial \rho/\partial \theta_1)^2 + (I_2(\theta_2)(1-\rho))^{-1}(\partial \rho/\partial \theta_2)^2 \).

**Example 6.1** Consider the binary response clinical trial with two treatments. For the urn proportion \( \rho = q_2/(q_1 + q_2) \),

\[ \sigma^2_{DBCD} = \frac{q_1 q_2 (p_1 + p_2)}{(q_1 + q_2)^3} + \frac{2q_1 q_2}{(1+2\gamma)(q_1 + q_2)^3} \]

For the Neyman proportion \( \rho = \frac{\sqrt{p_1 q_1}}{\sqrt{p_1 q_1} + \sqrt{p_2 q_2}} \), \( \sigma^2_{DBCD} = \frac{\sqrt{p_1 q_1}}{(1+2\gamma)(\sqrt{p_1 q_1} + \sqrt{p_2 q_2})^2} \) where

\[ \frac{1}{1+2\gamma} \left( \frac{p_2 q_2(q_1-p_1)^2}{\sqrt{p_1 q_1}} + \frac{p_1 q_1(q_2-p_2)^2}{\sqrt{p_2 q_2}} \right) \]

For Rosenberger, et al’s proportion \( \rho = \frac{\sqrt{p_1}}{\sqrt{p_1} + \sqrt{p_2}} \), \( \sigma^2_{DBCD} = \frac{\sqrt{p_1 p_2}}{(1+2\gamma)(\sqrt{p_1} + \sqrt{p_2})^2} + \frac{1+\gamma}{2(1+2\gamma)(\sqrt{p_1} + \sqrt{p_2})^3} \left( \frac{p_2 q_2}{\sqrt{p_1}} + \frac{p_1 q_1}{\sqrt{p_2}} \right) \).

From Theorem 6.1, we find that the asymptotic variability is a decreasing function of parameter \( \gamma \). However, the degree of randomness of the design decreases when \( \gamma \) increases, because, as the value of \( \gamma \) becomes larger, the allocation probabilities shift faster to extreme values 0 and 1 if there is a bias between the current sample allocation and the estimated target. When \( \gamma = \infty \), the variability of the procedure is minimized, but the procedure is completely predictable. The parameter \( \gamma \) can be chosen to reflect the trade-off between the degree of randomness and the variability.

The allocation function defined in (6.2) is very special though it has fine properties. For results for general allocation function \( g(\cdot, \cdot) \), one can refer to Hu and Zhang (2004a).

**Proof the Theorem.** Let \( \xi_{m,k} \), \( m = 1, 2, \ldots \), be i.i.d. random variables, which represent the outcomes on treatment \( k \), \( k = 1, \ldots, K \). In clinical trial, only \( X_{m,k} \xi_{m,k} \)s are observed. Write \( \xi_m = (\xi_{m,1}, \ldots, \xi_{m,K}) \). For simplifying the proof, we assume that \( \theta_k = E \xi_{m,k} \) is the mean of the outcomes, and so we use the sample mean as it estimate:

\[ \hat{\theta}_{m,k} = \frac{\sum_{i=1}^{m} X_{m,k} \xi_{j,k}}{N_{m,k}}, \ k = 1, \ldots, K. \]
In practices, if necessary, we can add $\alpha > 0$ in the numerator and $\beta > 0$ in the denominator to avoid the nonsense case of $0/0$, or to use prior information to estimate the parameters. Assume $\mathbb{E}|\xi_{m,k}|^{2+\delta} < \infty$ and write $\sigma_{k}^{2} = \text{Var}\{\xi_{m,k}\}$. Write $Q_{m,k} = \sum_{i=1}^{m} X_{m,k} (\xi_{m,k} - \theta_{k})$, then $Q_{m,k}$ is a martingale and $\hat{\theta}_{m,k} - \theta_{k} = Q_{m,k}/N_{m,k}$. By the LIL (Theorem B), we have

$$Q_{m,k} = O(\sqrt{n \log \log n}) \text{ a.s.} \quad (6.3)$$

We first show the consistency of $N_{n}/n$. If let $A_{m} = \sigma(X_{1}, \ldots, X_{m+1}, \xi_{1}, \ldots, \xi_{m})$, then $\sum_{i=1}^{m} \mathbb{E}[(X_{i,k}(\xi_{i,k} - \theta_{k}))^2 |A_{i-1}] = \sigma_{k}^{2} N_{m,k}$. By Theorem A (b), it follows that

$$\hat{\theta}_{m,k} \rightarrow \theta_{k} \text{ a.s. on the event } \{N_{m,k} \rightarrow \infty\}. \quad (6.4)$$

On the event $\{N_{m,k} < \infty\}$, $\hat{\theta}_{m,k}$ will fix to a value eventually. In either case, $\hat{\theta}_{m,k}$ has a limit $\bar{\theta}_{k}$ in the parameter space, $k = 1, \ldots, K$. By the continuity of $\rho(\cdot)$, $\hat{\rho}_{m-1} \rightarrow \rho(\bar{\theta}_{1}, \ldots, \bar{\theta}_{K}) := \bar{\rho} \in (0, 1)^{K}$ a.s. Notice that the minimum of $\sum_{j} y_{j}(x_{j}/x_{j})^{\gamma}$ over $\sum_{j} x_{j} = 1$ and $x_{j} \geq 0$ is $\sum_{j} y_{j}$. It is easily seen that $g_{k}(x_{j}, y_{j}) \leq y_{k}(x_{j}/x_{j})^{\gamma} < y_{k}$ if $x_{j} > y_{k}$ and $\sum_{j} x_{j} = \sum_{j} y_{j} = 1$. So, $P_{m,k} \leq \hat{\rho}_{m-1,k}$ if $N_{m-1,k}/(m-1) > \hat{\rho}_{m-1,k}$. Denote $M_{n,k} = \sum_{m=1}^{n} (X_{m,k} - \mathbb{E}[X_{m,k}|\mathcal{F}_{m-1}])$. Let $S_{n} = \max\{m \geq MK + 1 : N_{m-1,k} \leq (m-1)\hat{\rho}_{m-1,k}\}$ and $\bar{S}_{n} = MK$. Then

$$N_{n,k} = N_{S_{n},k} + \sum_{m=S_{n}+1}^{n} (X_{m,k} - \mathbb{E}[X_{m,k}|\mathcal{F}_{m-1}]) + \sum_{m=S_{n}+1}^{n} P_{m,k}$$

$$\leq 1 + N_{S_{n}-1,k} + M_{n,k} - M_{S_{n},k} + \sum_{m=S_{n}}^{n-1} \hat{\rho}_{m,k}$$

$$\leq 1 + N_{MK-1,k} + (M_{n,k} - M_{S_{n},k}) + (S_{n}-1)\hat{\rho}_{S_{n}-1,k} + \sum_{m=S_{n}}^{n-1} \hat{\rho}_{m,k}. \quad (6.5)$$

Notice that $|M_{n,k} - M_{S_{n},k}| \leq \max_{m \leq n} |M_{m,k}| = O(\sqrt{n \log \log n})$ a.s. by the LIL, and $\hat{\rho}_{m,k} \rightarrow \bar{\rho}_{k}$. We conclude that $\limsup_{n \rightarrow \infty} N_{n,k}/n \leq \bar{\rho}_{k}$ a.s., $k = 1, \ldots, K$. From the fact that $\sum_{k=1}^{n} N_{n,k}/n = \sum_{k=1}^{n} \bar{\rho}_{k} = 1$, we conclude that $N_{n,k}/n \rightarrow \bar{\rho}_{k} \in (0, 1)$ a.s., which implies that $N_{n,k} \rightarrow \infty$, $k = 1, \ldots, K$. Hence $\bar{\rho}_{k}$ and $\theta_{k}$ (in the parameter space) must be identical by (6.4). We have proved the consistency of $N_{n}/n$. Further, according to (6.3), we have $\hat{\theta}_{m} - \theta = O(\sqrt{\log \log m}/\sqrt{m})$ a.s., and then $\hat{\rho}_{m} - \bar{\rho} = O(\sqrt{\log \log m}/\sqrt{m})$ a.s., which together with (6.5), yields

$$N_{n,k} - n\bar{\rho}_{k} \leq O(\sqrt{n \log \log n}) + O(\sqrt{S_{n} \log S_{n}})$$

$$+ \sum_{m=S_{n}}^{n-1} O(\sqrt{\log \log m}/\sqrt{m}) = O(\sqrt{n \log \log n}) \text{ a.s.}$$

By the fact that $\sum_{k=1}^{n} N_{n,k}/n = \sum_{k=1}^{n} \bar{\rho}_{k} = 1$ again, we conclude that

$$N_{n} - n\bar{\rho} = O(\sqrt{n \log \log n}) \text{ a.s.} \quad (6.6)$$
Now, we begin the proof of the asymptotic normality. Write $M_n = (M_{n,1}, \ldots, M_{n,K})$ and $Q_n = (Q_{n,1}, \ldots, Q_{n,K})$. Then by (6.3) and (6.6),

$$\hat{\theta}_{m,k} - \theta_k = \frac{Q_{m,k}}{mv_k} + O\left(\frac{\log \log m}{m}\right) \text{ a.s.}$$

It is easily seen that $\partial g/\partial x|_{x=y} = -\gamma(I - 1'v)$ and $\partial g/\partial y|_{x=y} = (\gamma + 1)(I - 1'v)$. By the Taylor formula, we have

$$P_m - v = \rho\left(\frac{N_{m-1}}{m-1}, \hat{\rho}_{m-1}\right) - \rho(v, v)$$

$$= -\gamma\left(\frac{N_{m-1}}{m-1} - v\right)(I - 1'v) + (\gamma + 1)(\hat{\theta}_{m-1} - \theta)\frac{\partial \rho}{\partial \theta}(I - 1'v)$$

$$+ O\left(\left\|\frac{N_{m-1}}{m-1} - v\right\|^2\right) + O\left(\left\|\hat{\theta}_{m-1} - \theta\right\|^2\right)$$

$$= -\gamma\left(\frac{N_{m-1}}{m-1} - v\right) + (\gamma + 1)(\hat{\theta}_{m-1} - \theta)\frac{\partial \rho}{\partial \theta} + O\left(\frac{\log \log m}{m}\right)$$

$$= -\gamma\left(\frac{N_{m-1}}{m-1} - v\right) + (\gamma + 1)\frac{Q_{m-1}}{(m-1)} diag\left(\frac{1}{v}\right)\frac{\partial \rho}{\partial \theta} + O\left(\frac{\log \log m}{m}\right)$$

$$= O\left(\frac{\log \log m}{m}\right).$$

Hence

$$N_n - nv = \sum_{m=1}^{n} (X_m - E[X_m|F_{m-1}]) + \sum_{m=1}^{n} (P_m - v)$$

$$= M_n - \gamma \sum_{m=1}^{n-1} \frac{N_{m-mv}}{m} + (\gamma + 1) \sum_{m=1}^{n-1} \frac{Q_{m}}{m} diag\left(\frac{1}{v}\right)\frac{\partial \rho}{\partial \theta} + o((\log n)^2) \text{ a.s.}$$

On the other hand, it is easily checked that, for the martingale $(M_n, Q_n)$ we have

$$\sum_{m=1}^{n} E[(\Delta M_m)'(\Delta M_m)|F_{m-1}] = \sum_{m=1}^{n} diag(P_m) - P_m'P_m$$

$$= n(diag(v) - v'v) + O(\sqrt{n\log \log n}) \text{ a.s.,}$$

$$\sum_{m=1}^{n} E[(\Delta Q_{m,k})^2|F_{m-1}] = \sum_{m=1}^{n} P_{m,k}\sigma_k^2 = nv_k\sigma_k^2 + O(\sqrt{n\log \log n}) \text{ a.s.,}$$

$E[(\Delta M_m)'(\Delta Q_m)|F_{m-1}] = 0$ and $E[(\Delta Q_{m,k}Q_{m,j})|F_{m-1}] = 0$, $k \neq j$. So, by the strong approximation (Theorem E), there are two independent $K$-dimensional standard Brownian motions $W(t)$ and $B(t)$ such that for some $\kappa > 0$, $M_n = W(n)\Sigma_{1}^{1/2} + o(n^{1/2-\kappa})$ a.s. and $Q_{m,k} = B_k(n)\sigma_k\sqrt{v_k} + o(n^{1/2-\kappa})$ a.s., $k = 1, \ldots, K$, where $\Sigma_{1} = diag(v) - v'v$. It follows that

$$N_n - nv = W(n)\Sigma_{1}^{1/2} - \gamma \sum_{m=1}^{n-1} \frac{N_{m-mv}}{m} + (\gamma + 1) \sum_{m=1}^{n-1} \frac{B(m)}{m}\Sigma_{\rho}^{1/2}$$

$$+ o(n^{1/2-\kappa}) \text{ a.s.}$$
Hence, \( N_n - n\nu = G(n) + o(n^{1/2}) \) a.s., where
\[
G(t) = t^{-\gamma} \int_0^t x^\gamma dW(x) \Sigma_1^{1/2} + (\gamma + 1)t^{-\gamma} \int_0^t x^{\gamma-1} B(x) dx \Sigma_\rho^{1/2}
\]
is the solution of the equation
\[
G(t) = W(t) \Sigma_1^{1/2} - \gamma \int_0^t \frac{G(x)}{x} dx + (\gamma + 1) \int_0^t \frac{B(x)}{x} dx \Sigma_\rho^{1/2}.
\]
It follows that \( \sqrt{n}(N_n/n - \nu) \xrightarrow{d} N(0, \Sigma) \) with
\[
\Sigma = \text{Var}\{G(1)\}
= \Sigma_1 \int_0^1 x^{2\gamma} dx + (\gamma + 1)^2 \Sigma_\rho \int_0^1 \int_0^1 x^{\gamma-1} y^{\gamma-1} (x \wedge y) dxdy
= \frac{1}{2\gamma + 1} \Sigma_1 + \frac{2(\gamma + 1)}{2\gamma + 1} \Sigma_\rho.
\]
The proof is now completed. \( \square \)

7 Delayed responses

In practices, the outcomes in clinical trials are not available immediately prior to the treatment allocation of the next subject. The estimating of the parameters, and the updating of the urn when using urn models, can only be processed according to observed responses. The effect of the delay of treatment results is first studied in theory by Bai, Hu and Rosenberger (2002) for the urn compositions in an urn model design with discrete responses. After that, Hu and Zhang (2004b), Zhang, Chan, Chueng and Hu (2007), Sun, Cheung and Zhang (2007) and Zhang, Hu, Chueng and Chan (2006a) have shown that the delay machine does not effect the asymptotic properties of the sample allocation proportions for many adaptive designs if the delay degree decays with a power rate. The basic reason is that the total delayed responses is a high order of square root of the sample size when the delay degree decays with a power rate.

To describe the delay machine, we let \( t_m \) be the entry time of the \( m \)-th subject, where \( t_m \) is an increasing sequence of random variables. Assume that \( \{t_{m+1} - t_m\} \) is a sequence of independent random variables. The response time of the \( m \)-th subject on treatment \( k \) is denoted by \( r_m(k) \). Suppose \( \{r_m(k); m \geq 1\} \) is sequence of independent random variables, \( k = 1, \ldots, K \). Further, assume that \( \{t_{m+1} - t_m, r_m(k); k = 1, \ldots, K, m \geq n\} \) is independent of the assignments \( X_1, \ldots, X_n \).

**Assumption 7.1** Let \( \delta_k(m, l) = I\{r_m(k) \geq t_{m+1} - t_m\} \) be an indicator function that takes the value 1 if the outcome of the \( m \)-th subject on treatment \( k \) occurs after at least another \( l \) subjects arrive, and 0 otherwise. Suppose for some constants \( C > 0 \) and \( \gamma \geq 2 \),
\[
\mu_k(m, l) = P\{\delta_k(m, n) = 1\} \leq Cl^{-\gamma}, \ m, l = 1, 2, \ldots, k = 1, \ldots, K.
\]
This assumption is easily satisfied. A practical approach is to assume that the entry mechanism generates a Poisson process and the delay time has an exponential distribution in which both \( \{r_m(k)\} \) and \( \{t_{m+1} - t_m\} \) are sequences of i.i.d. exponential random variables with means \( \lambda_k > 0 \) and \( \lambda_0 > 0 \), respectively. This approach is common in clinical studies and the probability \( \mu_k(m, l) \) is \( (\lambda_k/(\lambda_0 + \lambda_k))^l \).

Let \( S^{obs}_{m,k} \) (resp. \( N^{obs}_{m,k} \)) be the sum (resp. the number) of the outcomes on treatment \( k \) observed prior to the \( (m+1) \)-th assignment, and \( S_{m,k} \) (resp. \( N_{m,k} \)) be the sum (resp. the number) of all the outcomes of those being assigned to treatment \( k \) in the first \( m \) subjects, \( k = 1, \ldots, K \).

**Theorem 7.1** Suppose Assumptions 7.1 is satisfied, and the responses on each treatment are i.i.d. random variables having finite \( (2 + \delta) \)-th moments. Then for some \( 0 < \delta_0 < \frac{1}{2} - \frac{1}{2^{1/2}} \), we have

\[
R_{n,k} =: S_{m,k} - S^{obs}_{m,k} = o(n^{1/2 - \delta_0}) \quad \text{a.s.} \quad (7.1)
\]

and \( N_{n,k} - N^{obs}_{n,k} = o(n^{1/2 - \delta_0}) \text{ a.s.}, \ k = 1, \ldots, K \).

**Proof.** Let \( I_k(m, l) \) be the indicator function, which takes value 1 if the outcome \( \xi_{m,k} \) on treatment \( k \) of the \( m \)-th subject occurs after the \( (m + l) \)-th assignment and before the \( (m + l + 1) \)-th assignment, \( k = 1, \ldots, K \). For given \( m \) and \( l \), if \( I_k(m, l) = 1 \), we observe a response \( X_{m,k}\xi_{m,k} \). Hence, between the \( m \)-th assignment and the \( (m + 1) \)-th assignment, the observed outcomes are \( I_k(m, 0)X_{m,k}\xi_{m,k}, I_k(m-1, 1)X_{m-1,k}\xi_{m-1,k}, \ldots, I_k(1,m-1)X_{1,k}\xi_{1,k}, k = 1, \ldots, K \), and the sum of those on treatment \( k \) is \( \sum_{l=0}^{m-1} I_k(m,l)X_{m-l,k}\xi_{m-l,k} = \sum_{l=1}^{m} I_k(l,m-l)X_{l,k}\xi_{l,k} \). Hence,

\[
S^{obs}_{m,k} = \sum_{m=1}^{n} \sum_{l=1}^{m} I_k(l,m-l)X_{l,k}\xi_{l,k} = \sum_{m=1}^{n} \sum_{j=m}^{\infty} X_{m,k}\xi_{m,k}I_k(m,j-m).
\]

On the other hand, it is obvious that \( S_{m,k} = \sum_{m=1}^{n} X_{m,k}\xi_{m,k} = \sum_{m=1}^{n} \sum_{j=m}^{\infty} X_{m,k}\xi_{m,k}I_k(m,j-m) \). It follows that

\[
R_{n,k} = \sum_{m=1}^{n} \sum_{j=n+1}^{\infty} X_{m,k}\xi_{m,k}I_k(m,j-m).
\]

Let \( 0 < \phi < 1/2 \) be a number whose value will be specified later. Write \( l_n = \lceil n^\phi \rceil \). Then

\[
|R_{n,k}| = \left| \left( \sum_{m=n-l_n+1}^{n} + \sum_{m=1}^{n-l_n} \right) \sum_{j=n-m+1}^{\infty} I_k(m,j)X_{m,k}\xi_{m,k} \right|
\]

\[
\leq \sum_{m=n-l_n+1}^{n} X_{m,k}|\xi_{m,k}| + \sum_{m=1}^{n} \delta_k(m,l_n)X_{m,k}|\xi_{m,k}|
\]

\[
\leq Cn^{\phi} + \sum_{m=n-l_n+1}^{n} (|\xi_{m,k}| - E[|\xi_{m,k}|]) + \sum_{m=1}^{n} X_{m,k}E[\delta_k(m,l_n)|\xi_{m,k}|]
\]

\[
+ \sum_{m=1}^{n} X_{m,k}(\delta_k(m,l_n)|\xi_{m,k}| - E[\delta_k(m,l_n)|\xi_{m,k}]) \quad (7.2)
\]
For $\sum_{m=1}^n (|\xi_{m,k}| - E[|\xi_{m,k}|])$, due to Theorems 1.2.1 and 2.6.6 of Csörgő and Révész (1981),

$$\sum_{m=n-l_{n+1}}^n (|\xi_{m,k}| - E[|\xi_{m,k}|]) = O(\sqrt{\frac{1}{n} \log n}) + o(n^{\frac{1}{2+\delta}})$$

$$= o(n^\phi) + o(n^{\frac{1}{2+\delta}}) \text{ a.s.}$$

For the martingale $\sum_{m=1}^n X_{m,k}(\delta_k(m, l_m)|\xi_{m,k} - E[\delta_k(m, l_m)|\xi_{m,k}])$, notice

$$E\left(X_{m,k}(\delta_k(m, l_m)|\xi_{m,k} - E[\delta_k(m, l_m)|\xi_{m,k}])^2\right)$$

$$\leq E(\delta_k(m, l_m)|\xi_{m,k})^2 \leq (E\delta_k(m, l_m))^\frac{\phi}{2+\delta}\left(E|\xi_{m,k}|^{2+\delta}\right)^\frac{1}{2+\delta} \leq m^{-\frac{\phi}{2+\delta}}.$$ 

due to Assumptions [7.1] and the assumption of finite $(2+\delta)$-th moments. So, by the LLN (Theorem A (a)), $\sum_{m=1}^n X_{m,k}(\delta_k(m, l_m)|\xi_{m,k} - E[\delta_k(m, l_m)|\xi_{m,k}]) = o(n^{\frac{1}{2} - \frac{\phi}{2+\delta}} \log n)$ a.s. Also

$$\sum_{m=1}^n X_{m,k}E[\delta_k(m, l_m)|D_{m,k}] \leq \sum_{m=1}^n (E\delta_k(m, l_m))^\frac{\phi}{2+\delta}\left(E|D_{m,k}|^{2+\delta}\right)^\frac{1}{2+\delta}$$

$$\leq C \sum_{m=1}^n m^{-\frac{\phi(1+\delta)}{2+\delta}} \leq Cn^{-\frac{\phi(1+\delta)}{2+\delta}}.$$ 

Combining the above arguments yields

$$R_{n,k} = O(n^\phi) + O(n^{1 - \frac{\phi(1+\delta)}{2+\delta}}) + o(n^{\frac{1}{2+\delta}}) + o(n^{\frac{1}{2} - \frac{\phi}{2+\delta}} \log n) \text{ a.s.}$$

Choosing $\phi = \frac{2+\delta}{1+\frac{1}{(1+\delta)^2}}$ and $0 < \delta_0 < \min\{\frac{1}{2} - \phi, \frac{1}{2} - \frac{1}{2+\delta}, \frac{\phi}{2(2+\delta)}\}$ yields [7.1]. The proof of $N_{n,k} - N_{obest,n,k} = o(n^{1/2-\delta_0})$ a.s. is similar. \(\square\)

### 8 Variability, power and asymptotic best adaptive designs

The variability of the sample proportion $N_{n,k}/n$ is an important quantity, which measures the distance between $N_{n,k}/n$ and its limit $v_k$. The smaller the variability, the smaller is the probability that there is large bias between $N_{n,k}/n$ and $v_k$. When using a adaptive design with high variability, a clinical might result in assigning more subjects to the inferior treatment making the allocation even less ethical than equal allocation. Also, a trial with high variability might result in assigning only a few subjects to one of the the treatments decreasing the efficiency in the test or the estimation of parameters. According to [4.1], the asymptotic variability of the RPW rule is very high unless both treatments have low success rates. It is extremely high when $q_1 + q_2$ is close to $1/2$, and it is showed that $n\text{Var}\{N_{n,1}/n\} \to \infty$ when $q_1 + q_2 < 1/2$. The RPW rule used in ECMO, 1985, trial assigned only one patient to the less successful control therapy (see Royall, 1991, for discussion). The relationship among the
power, the target allocation and the variability of the designs is first revealed by Hu and Rosenberger (2003) in theory, though simulation studies had indicated there is strong relationship among these quantities. Hu and Rosenberger (2003) proved that the average power of a statistical test of the difference of distribution parameters is a decreasing function of the variability of the designs. In Section 6, we have found that the asymptotic variability of DBCD is a decreasing function of the parameter $\gamma$. When $\gamma \to \infty$, the variability tends to its minimums

$$\Sigma_\rho = \left( \frac{\partial \rho}{\partial \theta} \right)' \text{diag} \left( \left( v_1 I_1(\theta_1) \right)^{-1}, \ldots, v_K I_1(\theta_K) \right)^{-1} \frac{\partial \rho}{\partial \theta}.$$

Hu, Rosenberger and Zhang (2006) proved that this limit is the lower bound of the asymptotic variability of adaptive designs among all adaptive designs which have the same limiting proportion.

Assume the following regularity conditions:

1. The parameter space $\Theta_k$ is an open subset in $\mathbb{R}^d$, $j = 1, \ldots, K$;
2. The distributions of outcomes $f_1(\cdot | \theta_1), \ldots, f_K(\cdot | \theta_K)$ follow an exponential family;
3. For the limiting allocation proportion $\rho(\theta) = (\rho_1(\theta), \ldots, \rho_K(\theta)) \in (0, 1)^K$, $N_{n,j}/n \to \rho_j(\theta)$ a.s. $j = 1, \ldots, K$;
4. For a positive definite matrix $V(\theta)$,

$$\sqrt{n} \left( \frac{N_n}{n} - \rho(\theta) \right) \xrightarrow{d} N(0, V(\theta)).$$

**Theorem 8.1** Under regularity conditions 1-4, there exists a $\Theta_0 \subset \Theta = \Theta_1 \otimes \cdots \otimes \Theta_K$ with Lebesgue measure 0 such that for every $\theta \in \Theta - \Theta_0$,

$$V(\theta) \geq \left( \frac{\partial \rho(\theta)}{\partial \theta} \right)' I^{-1}(\theta) \frac{\partial \rho(\theta)}{\partial \theta} := \Sigma_{LB},$$

where $I(\theta) = \text{diag} \left( \rho_1(\theta) I_1(\theta_1), \ldots, \rho_K(\theta) I_K(\theta_K) \right)$ and $I_k(\theta_k)$ is the Fisher information for a single observation on treatment $k = 1, \ldots, K$.

We refer to an adaptive design that attains the lower bound as asymptotic best for that particular allocation $\rho(\theta)$. Table I gives the lower bounds of the asymptotic variabilities ($\sigma_{LB}^2$) for urn proportion (UP), Roenberger, et al’s proportion (RP) and Neyman proportion (NP) in a binary response clinical trial for two-treatments. It is interesting to note that the Zelen (1969)’s deterministic design (PW rule) is asymptotic best among all procedures with limiting allocation proportion $q_2/(q_1 + q_2)$, the urn proportion. The RPW rule has the same limiting proportion, but it is not asymptotic best because $\sigma_{RPW}^2 > \sigma_{LB}^2$. The DL rule proposed by Ivanova (2003) is
a random procedure having the same urn proportion and the asymptotic variability \( \sigma_{DL}^2 = \frac{q_1 q_2 (p_1 + p_2)}{(q_1 + q_2)^3} \). So, the DL rule is asymptotic best. However, both the RPW rule and the DL rule can only target this particular proportion, which is not optimal in any formal sense, and can only be used for binary responses (c.f., Hu and Rosenberger, 2003).

DBCD is also not asymptotic best (except \( \gamma = \infty \)). But, it can target any desired allocation and can be used for general responses, for example, continuous response. Zhang, Hu and Cheung (2006) proposed an urn model, the SEU model, which can target any pre-specified allocation proportion and can be used for general responses. The drop-the-loser rule has also been generalized to GDL model, a kind of urn model with immigration, by Zhang, Chan, Cheung and Hu (2007) and Sun, Chueng and Zhang (2007), by using the estimators of unknown distribution parameters, such that it can target any pre-specified allocation proportion and can be used for general responses. For a general pre-specified allocation proportion \( \rho = \rho(\theta) \) in a \( K \)-treatment trial, the asymptotic variance-covariance matrices of SEU, GDL and DBCD are given in Table 2. Among these models, the DBCD can approach the lower bound for large

| Model | SEU                      | GDL                      | DBCD                      |
|-------|--------------------------|--------------------------|---------------------------|
| Variability | diag(\(\rho\)) − \(\rho' \rho\) + 6\(\Sigma_{LB}\) | 2\(\Sigma_{LB}\) | \(\frac{\text{diag}(\rho'-\rho) \rho}{1+2\gamma} + \frac{2+2\gamma}{1+2\gamma} \Sigma_{LB}\) |

Table 2: The asymptotic variability of SEU, GDL and DBCD for a same limiting allocation

values of \( \gamma \). However, the procedure becomes more deterministic as \( \gamma \) becomes larger, and hence careful tuning of \( \gamma \) must be done to counter the trade-off between the randomness and variability. The use of DBCD with \( \gamma = 2 \) was strongly recommended in Hu and Rosenberer (2003) for binary response trials with two treatments, according to the simulation study.

Very recently, we have found a fully randomized biased coin design (RBCD) for two-treatment clinical trails, a kind of DBCD, which preserves randomization, attains the lower bound, and can target any allocation. Whether or not an urn model can be defined to have these properties is still an open problem. In the RBCD, instead of using a continuous allocation function \( g(x, y) \), we use a discrete function: \( g(x, y) = \alpha y \) if \( x > y \), \( y \) if \( x = y \) and \( 1 - \alpha (1 - y) \) if \( x < y \), where \( 0 < \alpha < 1 \). That is, the \( m \)-th
subject is allocated to treatment 1 with a probability

\[ P(X_{m,1} = 1|\mathcal{F}_{m-1}) = P_{m,1} \]

\[ = \begin{cases} 
\alpha \rho(\hat{\theta}_{m-1}), & \text{if } N_{m-1,1}/(m - 1) > \rho(\hat{\theta}_{m-1}), \\
\rho(\hat{\theta}_{m-1}), & \text{if } N_{m-1,1}/(m - 1) = \rho(\hat{\theta}_{m-1}), \\
1 - \alpha(1 - \rho(\hat{\theta}_{m-1})), & \text{if } N_{m-1,1}/(m - 1) < \rho(\hat{\theta}_{m-1}).
\end{cases} \]

When \( \rho(\theta) \equiv 1/2 \), the RBCD is just the Efron (1971)'s biased coin design. The following theorem gives the asymptotic results for the RBCD, the proof of which will not be presented here.

**Theorem 8.2** Suppose \( \rho(\cdot, \cdot) \) is a continuous function on the parameter space and twice differentiable at the true value of the parameter \( \theta = (\theta_1, \theta_2) \), the distributions \( f_1(\cdot|\theta_1) \) and \( f_2(\cdot|\theta_2) \) of the responses follow an exponential family. Then \( N_{n,1}/n - \rho(\theta) = O(\sqrt{\log \log n/n}) \) a.s. and \( \sqrt{n}(N_{n,1}/n - \rho(\theta)) \xrightarrow{D} N(0, \sigma^2_\rho) \), where

\[ \sigma^2_\rho = (\partial \rho(\theta)/\partial \theta_1)^2 (\rho(\theta)I_1(\theta_1))^{-1} + (\partial \rho(\theta)/\partial \theta_2)^2 ((1 - \rho(\theta))I_2(\theta_2))^{-1}. \]

Further, \( \max_{m \leq n} |N_{m1} - m\rho(\theta) - \sigma_\rho W(m)| = o(\sqrt{n}) \) in probability, where \( W(t) \) is a standard Brownian motion.

**9 Discussion**

In this paper, we have discussed several classes of adaptive designs. The play-the-winner rule is the simplest procedure and has small variability. But it is too deterministic to be used in clinical trials. The randomized play-the-winner rule and urn models are random procedures. But their variabilities are very high. Theoretical results, simulation studies and a real example in ECMO trial all indicate that the statistical test in using a adaptive design with high variability is not powerful. However, besides in adaptive designs, urn models have wide applications in many areas including biological science, random algorithm and sampling, information science, etc. And the urn models have strong relationship with multi-type branching processes. The study of urn models has been of interest in a long history. The DL rule is randomized procedure and has the smallest variability among all the adaptive designs with limiting allocation proportion \( q_2/(q_1 + q_2) \). But it can only target this particular proportion and can only be used for binary responses. When it is generalized to be able to target any pre-specified allocation, the variability is no longer the smallest (c.f. Table 2). Among the adaptive designs mentioned in this paper, the DBCD and RBCD are the only procedures that preserves randomization, attains or can approach the lower bound of the variability, can target any allocation and can be used for general discrete or continuous responses.

The examples considered in this paper are binary response clinical trials. In practices, the responses of clinical trials appear in various types. For more examples and discussion, we refer to a new book of Hu and Rosneberger (2006). In many clinical
trials, covariate information is available that has a strong influence on the responses of patients. For instance, the efficacy of a hypertensive drug is related to a patient’s initial blood pressure and cholesterol level, whereas the effectiveness of a cancer treatment may depend on whether the patient is a smoker or a non-smoker. The theory of an adaptive design in using covariate information is much more complicated than those without covariates. A limit success in deriving the asymptotic properties of covariate-adjusted adaptive designs has been achieved by Zhang, Hu Cheung and Chan (2007). The power study and evaluation of the covariate-adjusted adaptive designs are our future studies. Also, in many clinical trials, the observed responses are usual survival data. Though it has been shown that the delay of treatment results does not effect the asymptotic properties in many adaptive designs, is is assume that the delayed responses are finally observed if the time is long enough. It is an interesting topic of studying the properties of the adaptive designs with missed or censored data.

Finally, in this paper, we only present the asymptotic results. It is important to check the accuracy of the asymptotic approximations when using the theoretical results to evaluate or compare designs. Simulations have indicated that in most cases these designs closely approximate asymptotic results for a moderate sample size of $n = 100$.

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