Theory on Covariate-Adaptive Randomized Clinical Trials: Efficiency, Selection bias and Randomization Methods

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Abstract

The theoretical properties of the power of the conventional testing hypotheses and the selection bias are usually unknown under covariate-adaptive randomized clinical trials. In the literature, most studies are based on simulations. In this article, we provide theoretical foundation of the power of the hypothesis testing and the selection bias under covariate-adaptive randomization based on linear models. We study the asymptotic relative loss of power of hypothesis testing to compare the treatment effects and the asymptotic selection bias. Under the covariate-adaptive randomization, (i) the hypothesis testing usually loses power if the covariates are not balanced enough, the more covariates in testing model are not incorporated in the randomization procedure, the more the power is lost; (ii) the hypothesis testing is usually more powerful than the one under complete randomization; and (iii) comparing to complete randomization, most of the popular covariate-adaptive randomization procedures in the literature, for example, Pocock and Simon’s marginal procedure, stratified permuted block design, etc, produce non-ignorable selection bias. A new family of covariate-adaptive randomization procedures are proposed for considering the power and selection bias simultaneously, under which, the covariate imbalances are small enough so that the power of testing the treatment effects would be asymptotically the largest and at the same time, the selection bias is asymptotically the optimal. The theoretical properties give a full picture how the power of the hypothesis testing, the selection bias of the randomization procedure, and the randomization method affect each other.

Keywords: Balancing covariates; Clinical trial; loss of power; Selection bias; Pocock and Simon’s procedure

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1 Introduction

It is well known that covariates usually play important role in clinical trials. Clinical trialists often concern about unbalanced treatment arms with respect to key covariates of interest. To balance important covariates, covariate-adaptive designs (Rosenberger and Lachin 2002) are usually employed. The most commonly implemented methods are stratified randomization and marginal minimization (McEntegart 2003). Stratified randomization is doing stratification first and then employing separate randomization within each strata; for example, stratified permuted block design, etc. To deal with many covariates, Taves (1974) and Pocock and Simon (1975) introduced the marginal minimization method, attempting to minimize the weighted sum of marginal differences between numbers of patients for all covariates. Hu and Hu (2012) discussed some limitations of these classical designs and proposed a generalized family of covariate-adaptive designs, and obtained their theoretical properties. For more discussion of handling covariates in clinical trials, see McEntegart (2003), Rosenberger and Sverdlow (2008), Zhang et al (2007), Hu and Rosenberger (2006) and reference therein.

It is important to study the statistical inference associated covariate-adaptive designs. In practice, conventional tests are often employed without consideration of covariate-adaptive randomization scheme. It remains a concern if conventional tests are still valid under covariate-adaptive designs, especially when the covariates used in trial design and those incorporated in inference procedures are not the same. Simulation studies on the statistical inference under covariate-adaptive designs are quite a lot, but theoretical work is limited. Birkett (1985) and Forsythe (1987) raised concerns about validity of unadjusted analysis under covariate-adaptive designs, and suggested all covariates used in Taves’s minimization method should be included into analysis to achieve a valid test through simulation studies. Feinstein and Landis (1976) and Green and Byar (1978) studied inference problems for stratified randomization for binary responses. Ciolino et. al. (2011) showed that power loss could be non-ignorable if balancing distributions of important continuous covariates were ignored even if adjustment is made in the analysis for important covariates. More discussions can be found in Simon (1979), Tu, Shalay, and Pater (2000), Aickin (2009), and so on. Recently, Shao, Yu, and Zhong (2010) and Ma, Hu and Zhang (2015) theoretically proved that, when some or all covariates used in trial design are not incorporated in inference procedures, the hypothesis testing to compare treatment effects is usually conservative in terms of small Type I error. It is now generally accepted that covariates used in trial design should also
be incorporated in inference procedures.

In this paper, we consider the opposite that covariates incorporated in inference procedures should be used in trial design. We will study the exact power of the hypothesis testing to compare treatment effects. The expansion of the relative power function is established and it is showed that when some or all covariates used in inference procedures are not incorporated in trial design, the testing usually loses power, the more covariates in the testing model are not incorporated in the randomization procedure, the more the power is lost, but the adaptive-randomization is usually more powerful than complete randomization. When all the covariates incorporated in inference procedures are balanced enough, the power of the testing is asymptotically equivalent to the largest one. A large class of covariate-adaptive designs, which includes most of the covariate-adaptive designs in the literature; for example, Pocock and Simon’s marginal procedure, stratified permuted block design, would achieve the largest power.

In the literature, continuous covariates are typically discretized in order to be included in the randomization scheme (Taves 2010, Ma and Hu 2013). However, as discussed in Scott et. al. (2002), the breakdown of a continuous covariate into subcategories means increased effort and loss of information. Ciolino et. al. (2011) also pointed out that lack of publicity for practical methods for continuous covariate balancing and lack of knowledge on the cost of failing to balance continuous covariates results in a common phenomenon, whereby continuous covariates are excluded from the randomization plan in clinical trials. Our theoretical results on the power gives a picture how the discretization affects the loss of power and give a formula of the cost of failing to balance continuous covariates.

On the other hand, randomization in clinical is fundamental to the design study. Randomization is desirable for a number of reasons including the selection bias which may arise if the person in charge of selecting patients for the trial has advance knowledge of the treatment assignments. Efron (1971) discussed how to measure the lack of randomness and treatment imbalance, and proposed a biased coin design (BCD) to give a tradeoff between the treatment imbalance and lack of randomness. However, the lack of randomness of the covariate-adaptive randomization is seldom considered theoretically. Basing on the measure of selection bias defined by Efron (1971), we will find that, comparing to complete randomization, the selection bias of both Pocock and Simon’s marginal procedure and stratified permuted block design is non-ignorable, though the asymptotic power of these designs would be the largest. A nature question is whether there is a covariate-adaptive
randomization procedure under which both the power and the selection bias are optimal.
We will propose a new family of covariate-adaptive designs which include the Pocock and Simon’s marginal procedure, Hu and Hu (2012)’s design and Wei (1978)’s adaptive biased coin design. Within this family, a new covariate-adaptive randomization procedure is defined by choosing a suitable allocation function, under which the covariate imbalances are small enough so that the power of testing the treatment effects would be asymptotically the largest and, at the same time the selection bias attains the minimum value $1/2$ so that every guessing strategy is asymptotically equally useless against the allocation procedure.

In Section 2, we will study the power of the hypotheses testing to compare the treatment effects. Section 3 will deal with the selection bias. In Section 4, the new family of adaptive-randomization procedures are proposed. The proofs are given in the last section.

2 The power of hypothesis testing under covariate-adaptive designs

In this section, we study the power of hypothesis testing based on a linear model framework for covariate-adaptive designs. Suppose two treatments 1 and 2 are studied under a covariate-adaptive randomized clinical trial, $\mu_1$ and $\mu_2$ are parameters measuring the main effects of treatment 1 and 2, respectively. Let $n$ be the total number of patients enrolled in the study. Let $T_i$ be the assignment of $i$th patient, i.e., $T_i = 1$ for treatment 1 and $T_i = 0$ for treatment 2, $i = 1, 2, ..., n$. Conditional on the treatment assignment $T_i$, the following linear model is assumed for the response of the $i$th patient $Y_i$,

$$Y_i = \mu_1 T_i + \mu_2 (1 - T_i) + \beta_1 X_{i,1} + ... + \beta_I X_{i,I} + \varepsilon_i,$$

where

- $X_{i,k}$s are discrete or continuous covariates which are independent and identically distributed as $X_k$, $k = 1, \ldots, I$;
- partial or all values of $X_{i,k}$s are used in the randomization procedure, $k = 1, \ldots, I$;
- all covariates are independent of each other, and $E X_k = 0$ and $\text{Var}(X_k) > 0$ for all $k$, $k = 1, \ldots, I$;
- $\varepsilon_i$s are independent and identically distributed normal random errors with mean zero and variance $\sigma^2_\varepsilon$ and independent of $X_k$, $k = 1, \ldots, I$. 

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Notice $X_{i,k}$ are assumed to be scalers in model (2.1). If $X_{i,k}$ is a discrete covariate, $X_{i,k}$ is a scaler that can take several values corresponding to different categories. In practice, a vector is usually used to represent a discrete covariate with multiple categories. In this paper, $X_{i,k}$ is assumed to be a scaler for simplicity, but all the results can be extended to the situation where discrete covariates with multiple categories are represented by vectors.

We let $Y = (Y_1, Y_2, ..., Y_n)^T$, $\varepsilon = (\varepsilon_1, \varepsilon_2, ..., \varepsilon_n)^T$, $\beta = (\beta_1, ..., \beta_I)^T$, $\gamma = (\mu_1, \mu_2, \beta_1, ..., \beta_I)^T$, and

$$X = \begin{bmatrix}
  T_1 & 1 - T_1 & X_{1,1} & \cdots & X_{1,I} \\
  T_2 & 1 - T_2 & X_{2,1} & \cdots & X_{2,I} \\
  \vdots & \vdots & \vdots & \ddots & \vdots \\
  T_n & 1 - T_n & X_{n,1} & \cdots & X_{n,I}
\end{bmatrix}.$$

Then model (2.1) can be written as

$$Y = X\gamma + \varepsilon,$$

The ordinary least squares method is used to obtain the estimate of $\gamma$, which has the explicit form

$$\hat{\gamma} = (X^T X)^{-1} X^T Y = \gamma + (X^T X)^{-1} X^T \varepsilon.$$

In the covariate-adaptive randomization, the results of allocations $T_1, \ldots, T_n$ depend only on the covariates $X_1, \ldots, X_n$, and so are independent of $\varepsilon$. Hence, given $X$, $\hat{\gamma}$ follows a multi-dimensional normal distribution with mean $\gamma$ and variance-covariance matrix $\sigma^2(X^T X)^{-1}$.

When model (2.1) is constructed to study data from a covariate-adaptive randomized clinical trial, the primary interest is usually to compare treatment effects between different groups. To compare treatment effects of $\mu_1$ and $\mu_2$, the following right-sided hypothesis testing is usually used

$$H_0 : \mu = 0$$

$$H_A : \mu > 0. \quad (2.2)$$

where $\mu = \mu_1 - \mu_2$ is treatment effect difference. The right-sided t-test statistic for (2.2) is

$$T = \frac{\hat{L} \hat{\beta}}{(\hat{\sigma}^2 L(X^T X)^{-1} L^T)^{1/2}}, \quad (2.3)$$

where $L = (1, -1, 0, \ldots, 0)$, and $\hat{\sigma}^2 = (Y - X \hat{\beta})^T (Y - X \hat{\beta})/(n-I-2)$ is the estimate of $\sigma^2$. If $T > t_{1-\alpha}(\nu)$, where $t_{1-\alpha}(\nu)$ is (1-$\alpha$)th quantile of a t-distribution with degree of freedom $\nu = n-I-2$, we will reject the null hypothesis, otherwise accept the null hypothesis. Given $X$, the conditional power function is

$$\beta_{T,n}(\mu|X) = 1 - F \left( t_{1-\alpha}(\nu); \nu, \frac{\mu}{\sigma^2 L(X^T X)^{-1} L^T}^{1/2} \right),$$

where $F$ is the cumulative distribution function.
where \( F(t; \nu, \delta) \) is the distribution function of a non-central t-distribution with non-central parameter \( \delta \) and degree of freedom \( \nu = n - I - 2 \).

Let \( X_i = (X_{i,1}, \ldots, X_{i,I})^T \),

\[
N_{n,1} = \sum_{i=1}^{n} T_i, \quad N_{n,2} = \sum_{i=1}^{n} (1 - T_i), \quad D_n = N_{n,1} - N_{n,2},
\]

\[
D_n^x = \sum_{i=1}^{n} (2T_i - 1) X_i, \quad D_{n,k} = \sum_{i=1}^{n} (2T_i - 1) X_{i,k}, \quad k = 1, \ldots, I,
\]

\[
\overline{X}_{n,1} = \frac{\sum_{i=1}^{n} T_i X_i}{N_{n,1}}, \quad \overline{X}_{n,2} = \frac{\sum_{i=1}^{n} (1 - T_i) X_i}{N_{n,2}},
\]

\[
\overline{Y}_{n,1} = \frac{\sum_{i=1}^{n} T_i Y_i}{N_{n,1}}, \quad \overline{Y}_{n,2} = \frac{\sum_{i=1}^{n} (1 - T_i) Y_i}{N_{n,2}},
\]

\[
S_{n,xx} = \sum_{i=1}^{n} T_i (X_i - \overline{X}_{n,1})(X_i - \overline{X}_{n,1})^T + \sum_{i=1}^{n} (1 - T_i)(X_i - \overline{X}_{n,2})(X_i - \overline{X}_{n,2})^T.
\]

Here \( D_n \) is the difference between the numbers of patients in treatment group 1 and 2 as total, which can be regarded as a measure of overall treatment imbalance, and, \( D_n^x = \sum_{i=1}^{n} T_i X_i - \sum_{i=1}^{n} (1 - T_i) X_i \) can be regarded as a measure of covariate imbalance. It can been seen that

\[
\overline{X}_{n,1} = \frac{n \overline{X}_n + D_n^x}{n + D_n} \quad \text{and} \quad \overline{X}_{n,2} = \frac{n \overline{X}_n - D_n^x}{n - D_n}
\]

are functions of \( D_n \) and \( D_n^x \), where \( \overline{X}_n = \sum_{i=1}^{n} X_i/n \). Also

\[
L(X^T X)^{-1} L^T = \frac{1}{N_{n,1}} + \frac{1}{N_{n,2}} + (\overline{X}_{n,1} - \overline{X}_{n,2})^T S_{xx}^{-1} (\overline{X}_{n,1} - \overline{X}_{n,2}) = \frac{4}{n(1 - (D_n/n)^2)} + \frac{4Q_n^2}{n(1 - (D_n/n)^2)^2},
\]

where

\[
Q_n^2 = (D_n^x/\sqrt{n} - \overline{X}_n D_n/\sqrt{n})^T \left( \frac{S_{n,xx}}{n} \right)^{-1} (D_n^x/\sqrt{n} - \overline{X}_n D_n/\sqrt{n}).
\]

Hence, the power function can be written as

\[
\beta_{T,n}(\mu|X) = 1 - F \left( t_{1-\alpha}(\nu); \nu, \frac{\mu}{2\sigma \ell_n} \right),
\]

where

\[
\ell_n = \sqrt{\frac{n(1 - (D_n/n)^2)^2}{1 - (D_n/n)^2 + \frac{1}{n} Q_n}} \leq \sqrt{n}.
\]
Because $F(t; \nu, \delta)$ is a non-increasing function of $\delta$, it is obvious that when $D_n = 0$ and $D_{n}^x = 0$, the power function takes its largest value

$$\beta_{T,n}(\mu|0) = 1 - F \left( t_{1-\alpha}(\nu); \nu, \frac{\mu}{2\sigma_\epsilon \sqrt{n}} \right).$$

A clinical trial is only a single realization of a random phenomenon, and it cannot be assumed that the observed imbalances $D_n$ and $D_{n}^x$ will be zero. So, the loss of power is unavoidable. The problem is, comparing to the largest power, how small is the realized power acceptable? The distance between the power functions $\beta_{T,n}(\mu|X)$ and $\beta_{T,n}(\mu|0)$ may reflect the loss of power. However, since the power functions $\beta_{T,n}(\mu|X)$ and $\beta_{T,n}(\mu|0)$ are both convergent to 1, from their difference one can not find how the imbalances $D_n$ and $D_{n}^x$ effect the loss of power clearly. To deal with this problem, we consider the relative loss of power as the ratio:

$$\text{Loss}_{P,T,n}(\mu|X) = \frac{1 - \beta_{T,n}(\mu|0)}{1 - \beta_{T,n}(\mu|X)} = \frac{F \left( t_{1-\alpha}(\nu); \nu, \frac{\mu}{2\sigma_\epsilon \sqrt{n}} \right)}{F \left( t_{1-\alpha}(\nu); \nu, \frac{\mu}{2\sigma_\epsilon \ell_n} \right)},$$

$\nu = n - I - 2$. The smaller is the value of $\text{Loss}_{P,T,n}(\mu|X)$, the more is the power lost.

The following theorem gives the order of the loss of power.

**Theorem 2.1** Write $\sigma_{x,k}^2 = \text{Var}(X_k)$, $k = 1, \ldots, I$,

$$V_n = \left( \frac{D_n}{\sqrt{n}} \right)^2 + \sum_{k=1}^{I} \frac{(D_{n}^x / \sqrt{n})^2}{\sigma_{x,k}^2}.$$

Suppose $\frac{D_n}{n}$ and $\frac{D_{n}^x}{n}$ converge to zero in probability (or almost surely), then

$$\text{Loss}_{P,T,n}(\mu|X) = \exp \left\{ -\frac{\mu^2}{8\sigma_\epsilon^2} V_n (1 + o(1)) \right\}. \quad (2.4)$$

in probability (or almost surely).

In Theorem 2.1, the value of $V_n = \left( \frac{D_n}{\sqrt{n}} \right)^2 + \sum_{i=1}^{p} (D_{n}^x / \sqrt{n})^2 \sigma_{x,k}^{-2}$ gives the order of the loss of power. For the complete randomization in which each patient is allocated to treatment 1 or 2 with the same probability $1/2$,

$$\left( \frac{D_n}{\sqrt{n}}, \frac{D_{n}^x}{\sqrt{n}}, \cdots, \frac{D_{n}^{x,I}}{\sqrt{n}} \right)^T \sim N_{I+1} \left( 0, \text{diag}(1, \sigma_{x,1}^2, \cdots, \sigma_{x,I}^2) \right),$$

where $N_{I+1}$ is a $(I + 1)$-dimensional normal distribution with mean and variance-covariance matrix given between the brackets. So, $V_n \sim \chi^2(I + 1)$, where $\chi^2(I + 1)$ is a $\chi^2$-distributed random variable with $I + 1$ degree of freedom. Hence we have

**Corollary 2.1** If the patients are allocated to treatments by complete randomization, then

$$\text{Loss}_{P,T,n}(\mu|X) \sim \exp \left\{ -\frac{\mu^2}{8\sigma_\epsilon^2} \chi^2(I + 1) \right\} < 1. \quad (2.5)$$
By (2.5), the unconditional relative loss of power is

$$E[\text{Loss}_{P,T,n}(\mu|X)] \approx \left(1 + \frac{\mu^2}{4\sigma^2}\right)^{-\frac{I+1}{4}}.$$

The right hand (2.4) will converge to 1 whenever $V_n \to 0$. Therefore, we conclude

**Corollary 2.2** If

$$\frac{D_n}{\sqrt{n}} \to 0 \quad \text{and} \quad \frac{D^n}{\sqrt{n}} \to 0$$

in probability (or almost surely), then

$$\text{Loss}_{P,T,n}(\mu|X) \to 1$$

in probability (or almost surely).

When the condition (2.6) is satisfied, the power of the hypothesis testing to compare treatment effects under this allocation procedure is equivalent to that under the completely balanced allocation which has the largest power. Such a randomization procedure is called an efficient covariate-adaptive design.

Condition (2.6) means that the covaritates used in the testing model should be balanced enough. In clinical trials, covariate-adaptive designs are usually based on discrete covariates (Taves 2010). If a continuous (or general) covariate is to be used in randomization, a discrete conversion need be performed to breakdown continuous covariate into a discrete variable with several subcategories. In general, the covariate-adaptive design is applied with respect to discrete variables $d_k(X_k)$, where $d_k$s are discrete functions. In such case, define $\delta_k = X_k - E[X_k|d_k(X_k)]$ and $\bar{X}_k = d_k(X_k)$. And so, $\delta_{i,k} = X_{i,k} - E[X_{i,k}|d_k(X_{i,k})]$ and $\bar{X}_{i,k} = d_k(X_{i,k})$ are $i$th observations of covaritates $\delta_k$ and $\bar{X}_k$, $k = 1, \ldots, I$. Suppose $\bar{X}_k$ have $m_k$ levels, resulting in $\prod_{k=1}^I m_k$ strata in total. Let $\bar{X}_i = (\bar{X}_{i,1}, \ldots, \bar{X}_{i,I})$ represent the covariate profile of the $i$th patient used in randomization, i.e., $\bar{X}_i = (\bar{x}^t_1, \bar{x}^t_2, \ldots, \bar{x}^t_I)$ if $\bar{X}_{i,k}$ is at level $\bar{x}^t_k$. For convenience, we use $(t_1, \ldots, t_I)$ to denote the stratum formed by patients who have the same covariate profile $(\bar{x}^t_1, \ldots, \bar{x}^t_I)$, and use $(j; t_j)$ to denote the margin formed by patients with $\bar{X}_j = \bar{x}^t_j$. Then let

- $D_n = N_{n,1} - N_{n,2}$ be the difference between the numbers of patients in treatment group 1 and 2 as total;
- $D_n(j; t_j)$ be the differences between the numbers of patients in the two treatment groups on the margin $(j; t_j)$, respectively.
These differences play important roles in properties of statistical inference for covariate-adaptive designs.

**Theorem 2.2** Let \( \sigma_{\delta,k}^2 = E[\text{Var}(\delta_k|d_k(X_k))] = E[\delta_k^2] \), \( k = 1, \ldots, p \). Assume that each assignment \( T_m \) depends only on \( T_1, \ldots, T_{m-1} \) and \( \tilde{X}_1, \ldots, \tilde{X}_m \), i.e., the probability of \( T_m = 1 \) is a function of \( T_1, \ldots, T_{m-1} \) and \( \tilde{X}_1, \ldots, \tilde{X}_m \). Suppose

\[
\frac{D_n}{\sqrt{n}} \rightarrow 0 \quad \text{and} \quad \frac{D_n(j,t_j)}{\sqrt{n}} \rightarrow 0 \tag{2.7}
\]

in probability (or almost surely), \( t_j = 1, \ldots, m_j, j = 1, \ldots, I \). Then

\[
\text{Loss}_{P_{T,n}}(\mu|X) \xrightarrow{d} \exp \left\{ -\frac{\mu^2}{8\sigma^2} \sum_{k=1}^{I} \frac{\sigma_{\delta,k}^2}{\sigma_{x,k}^2} \chi_k^2(1) \right\}, \tag{2.8}
\]

where \( \chi_k^2(1), \ldots, \chi_I^2(1) \) are independent \( \chi^2 \)-distributed random variables with 1 degree of freedom. The unconditional relative loss of power is

\[
E[\text{Loss}_{P_{T,n}}(\mu|X)] \cong \prod_{i=1}^{I} \left( 1 + \frac{\mu^2 \sigma_{\delta,k}^2}{4\sigma^2 \sigma_{x,k}^2} \right)^{-1/2}.
\]

Condition (2.7) is satisfied under various covariate-adaptive designs for balancing covariates. For example, under stratified permuted block designs, the class of covariate-adaptive designs proposed by Hu and Hu (2012), and Pocock and Simon’s marginal procedure,

\[
D_n \quad \text{and} \quad D_n(j,t_j), \quad \text{are bounded in probability,} \tag{2.9}
\]

\( t_j = 1, \ldots, m_j, j = 1, \ldots, I \) (c.f. Ma, Hu and Zhang 2015), and so (2.7) is satisfied. Further, if \( X_k = d_k(X_k) \), \( k = 1, \ldots, I \), then \( D_n \) and \( D_n^k \) are bounded in probability, resulting in \( V_n = O(n^{-1}) \) and

\[
V_n = O(n^{-1}) \quad \text{and} \quad \text{Loss}_{P_{T,n}}(\mu|Z) = 1 + O(n^{-1}) \quad \text{in probability.}
\]

Note that \( O(n^{-1}) \) is the fastest convergence rate unless the treatments are completely balanced so that \( D_n = 0 \) and \( D_n(j,t_j) = 0 \) for all \( t_j \) and \( j \), which indicates that Efron’s biased coin design, as well as its generalizations such as Pocock and Simon’s marginal procedure and Hu and Hu’s design, is usually efficient in terms of power with respect to the problem it considered. Similar evidence had also been found in Hu, Zhang and He (2009) for response-adaptive designs.

Simulation studies showed that Taves (1974)’s minimization method also reduces marginal imbalances as well as the overall imbalance. However, theoretical evidence has not found in
literature to our best knowledge. Whether (2.9) holds or not is still an open problem. We will show that (2.7) is true under Taves’s minimization method (c.f., Theorem 4.1 and Corollary 4.1), so it is an an efficient covariate-adaptive design in sense that \( \text{LossP}_{T,n}(\mu|X) \xrightarrow{P} 1 \) if \( X_k = d_k(X_k) \), \( k = 1, \ldots, I \).

In Theorem 2.2, the ratio \( \sigma^2_{\delta,k}/\sigma^2_{x,k} \) describers the cost to loss of power of failing to balance the \( k \)th covariate completely. It is obvious that \( 0 \leq \sigma^2_{\delta,k}/\sigma^2_{x,k} \leq 1 \). The larger \( \sigma^2_{\delta,k} \) is, the larger the cost is. If \( E[X_k|d_k(X_k)] = X_k \), i.e., the \( k \)-covariate is not considered in the randomization, then \( \sigma^2_{\delta,k}/\sigma^2_{x,k} = 1 \) and accordingly, the \( k \)-covariate contributes its all to the loss of power and so the cost is the largest. If \( E[X_k|d_k(X_k)] = d_k(X_k) \), i.e., the \( k \)th covariate is discrete and is balanced enough with respect to all of its values, then \( \sigma^2_{\delta,k} = 0 \) and accordingly, the contribution of the \( k \)-covariate to the loss of power can be neglected. So, the less of the covariates and their values are balanced, the more the power is lost. Comparing the results in Corollary 2.1 and Theorem 2.2, we find that the hypothesis testing to compare treatment effects under a covariate-adaptive randomization procedure is usually more powerful than the one under complete randomization.

In the literature, covariate-adaptive randomization schemes are usually based on discrete covariates. When the covariates are continuous, the covariates are usually discretized. However, as discussed in Scott et. al. (2002), the discretization means increased effort and loss of information. Ciolino et. al. (2011) also pointed out that uncontrolled imbalances in continuous covariates may affect the statistical analysis of the trial outcome. In the formula (2.8), \( \sigma^2_{\delta,k} \) is the variances of the uncontrolled part of the \( k \)th covariate. The ratio \( \sigma^2_{\delta,k}/\sigma^2_{x,k} \) just gives the cost of failing to balance the covariate \( X_k \) completely. It is easily seen that the cost can be decreased by refining the discretization.

The inconsistency of the covariates considered in the randomization and the covariates used in the hypothesis testing for treatment effects may affect the hypothesis testing. The evidences have been found in many simulation studies (c.f, Birkett 1985, Forsythe 1987, Tu, Shalay, and Pater 2000, Aickin 2009, Ciolino et al 2011 etc.). Ma, Hu and Zhang (2015) derived the theory for the case that the covariates considered in the testing are less than those considered in the randomization under a large class of covariate-adaptive randomization procedures satisfying (2.9) (c.f, their conditions (A) and (B)). Here we consider the converse case. Following the lines of Ma, Hu and Zhang’s proofs, one can find that their Theorems 3.1 and 3.2 remains true when (2.9) is replaced by (2.7). Combing the results in Theorem 2.2 and those of Ma, Hu and Zhang (2015), we conclude that, under a large class of covariate-
adaptive designs for balancing covariates, (i) if the covariates considered in the testing are less than those considered in the randomization, then the hypothesis testing is usually conservative in terms of small Type I error, and, the more of the values of covariates are not consistent, the more the testing is conservative; (ii) if the covariates considered in the testing are more than those considered in the randomization, then the hypothesis testing usually losses power, and, the more of the values of covariates are not consistent, the more the power is lost; (iii) in any case, the hypothesis testing is usually more powerful than the one under complete randomization.

**Remark 2.1** The conclusions of Theorems 2.1 and 2.2 remain true when the statistic $|T|$ is used to test the following two-sided hypothesis testing

$$H_0 : \mu = 0 \text{ versus } H_A : \mu \neq 0. \quad (2.10)$$

When $\sigma_\epsilon^2$ is known. Theorems 2.1 and 2.2 are also valid for one-sided or two-sided $z$-test.

The formula (2.4) reamains true under the alternative hypothesis with $0 < \mu = \mu_n \to 0$ and $\mu_n \sqrt{n} \to \infty$. But it no longer holds when a sequence of local alternative hypotheses of the type $H_A : \mu = \eta/\sqrt{n} > 0$ are considered. In such case, one can show that $\frac{d}{d\delta} F(t; \nu, \delta)$ converges to a continuous function $f_\infty(t; \delta) < 0$ as $\nu \to \infty$ uniformly in $t$ and $\delta$ on bounded intervals. It follows that

$$F \left( t_{1-\alpha}(\nu); \nu, \frac{\eta}{2\sigma_\epsilon} \frac{\mu_n}{\sqrt{n}} \right) - F \left( t_{1-\alpha}(\nu); \nu, \frac{\eta}{2\sigma_\epsilon} \right) = - \frac{\eta}{4\sigma_\epsilon} f_\infty \left( z_{1-\alpha}; \frac{\eta}{2\sigma_\epsilon} \right) \frac{n - \mu_n^2}{n} (1 + o(1)) = C_{\alpha, \eta} \frac{V_n}{n} (1 + o(1)).$$

Hence

$$\beta_{T,n}(u|0) - \beta_{T,n}(u|X) = O(1) \frac{V_n}{n}. \quad (2.11)$$

The value of $V_n$ also reflects the order of losing power. When the distribution of model error $\epsilon_i$ is not normal, though it is difficult to derive the exact power function, (2.11) is expected to be true especially when the errors follows a continuous distribution. An approximation method is usually applied to approximate the true distribution of the statistic $T$ for hypothesis testing, when the distribution of error $\epsilon_i$ is not normal or unknown. It is well known that if normal approximation is used, the approximation precision of the distribution as well as the power function is $O(1/\sqrt{n})$. If the Bootstrap method is used, the approximation precision would be improved to $O(1/n)$. Hence, comparing to the approximation precise, the loss of power $O(1) \frac{V_n}{n}$ can be ignored whenever $V_n \to 0$. Again, the condition (2.6) is needed.
3 Selection bias

As advocated in Efron (1971), selection bias (lack of randomness) of the design shows in the possibility for the experimenter to guess partially the sequence of treatment allocations; thus it can be measured, say, by the expected percentage of correct guesses when an optimal guessing strategy is used. Let $J_m = 1$ if the $m$th assignment is guessed correctly, and $J_m = 0$ otherwise. The expected proportion of correct guesses is

$$SB_n(\Delta) = \mathbb{E} \left[ \frac{1}{n} \sum_{m=1}^{n} J_m \right] = \frac{1}{n} \sum_{m=1}^{n} \mathbb{P}(J_m = 1).$$

Here ‘$\Delta$’ stands for selection bias of the allocation procedure $\Delta$. Every guessing strategy is equally useless against complete randomization, yielding the expected percentage of correct guesses $\frac{1}{2}$ for any $n$; this is then the optimal value of $SB_n$. Clearly $1/2 \leq SB_n(\Delta) \leq 1$ for any allocation procedure design $\Delta$. An equivalent way is to consider Smith’s (1984) index, namely the difference between the mean percentage of correct guesses and that of incorrect guesses:

$$U_n(\Delta) = 2SB_n(\Delta) - 1,$$

which has the advantage of going from 0 to 1.

For all the adaptive randomization, the optimal strategy consists, at each step, of picking the under-represented treatment, which is always the treatment with the higher probability of being allocated, with no preference in case of a tie. Let $p_m$ be the conditional probability of assigning the $m$-patient to treatment 1 given the history $\sigma$-field including the information of historical allocations, historical covariates and current covariate observed. The probability that the $m$th assignment is guessed correctly is

$$E[p_m \lor (1 - p_m)].$$

So,

$$SB_n(\Delta) = \frac{1}{n} \sum_{m=1}^{n} E[p_m \lor (1 - p_m)] = \frac{1}{2} + \frac{1}{n} \sum_{m=1}^{n} E[p_m - \frac{1}{2}].$$

It is easily seen that $SB_n(\Delta) > 1/2$ unless $p_m \equiv 1/2$ for $m$, i.e., the procedure is complete randomization. In general, we consider the asymptotic selection bias $SB(\Delta) = \lim_{n \to \infty} SB_n(\Delta)$.

Under stratified permuted block designs, or Taves (1974)’s minimization method, a positive percentage of patients are assigned deterministically, and so are guessed correctly, resulting in

$$\liminf_{n \to \infty} SB_n > 1/2.$$

For the class of biased coin designs, when the design does not include the covariate, Efron (1971) gives the formula of the asymptotic selection bias $SB$ of his original biased coin design which indicates that $SB(BCD) > 1/2.$
For the Pocock and Simon (1975)’s procedure, no close form of the asymptotic selection bias $SB$ has been found in literature. Pocock and Simon’s procedure is a generalization of biased coin design for balancing covariates. Under this procedure, after $m - 1$ ($m > 1$) assignments and suppose the covariate value of the $m$th patient is observed and falls within stratum $(t_1, \ldots, t_I)$, the $m$th patient is then randomized by tossing a biased coin according to the value of weighted sum of marginal imbalances $\Lambda_{m-1}(t_1, \ldots, t_I) = \sum_{j=1}^{I} w_j D_{m-1}(j, t_j)$.

When this value is negative, the probability $p_m$ of assigning the patient to treatment 1 is $p (1/2 < p < 1)$, when it is positive, the probability is $q (= 1 - p)$, and when it is zero, the probability is $1/2$. Due to Theorem 3.3 of Ma, Hu and Zhang (2015) and its proof, $\{\Lambda_n(t); t_j = 1, \cdots, m_j, j = 1, \cdots, I\}$ is an irreducible positive recurrent multi-dimensional Markov Chain with an invariant distribution $\pi$, where $t = (t_1, \ldots, t_I)$, and so

$SB(PS) - \frac{1}{2} = \lim_{n \to \infty} \frac{1}{n} \sum_{m=1}^{n} E[|p_m - \frac{1}{2}|] = (p - \frac{1}{2}) \lim_{n \to \infty} \frac{1}{n} \sum_{m=1}^{n} \sum_{t} P(\Lambda_{m-1}(t) \neq 0) p(t) = (p - \frac{1}{2}) \sum_{t} \pi(\Lambda(t) \neq 0) p(t) > 0,$

by the ergodic theorem, where $p(t) = P(\tilde{X} = (\tilde{x}_1, \ldots, \tilde{x}_I)) > 0$. Here the last inequality is due to the fact that the Markov chain is irreducible and so each possible state has a positive probability mass under the invariant distribution. For the Hu and Hu’s (2012) procedure, the stratified biased coin design, we have a similar result. In general, Pocock and Simon (1975)’s procedure can be generalized by defining the allocation probability $p_m = g(\Lambda_{m-1}(t))$ as a non-increasing function of the weighted imbalances $\Lambda_{m-1}(t)$ with $0 < g(x) < 1$, $g(0) = 1/2$ and $g(x) \neq 1/2$ (c.f. Antognini and Giovagnoli 2004). With a similar argument, we also have

$SB(GPS) - \frac{1}{2} = \sum_{t} E_\pi\left[|g(\Lambda(t)) - \frac{1}{2}|\right] p(t) > 0.$

Here, GPS stands for the generalized Pocock and Simon procedure.

So, for all the covariate-adaptive randomization that have been introduced so far, when the condition (2.7) is satisfied so that the loss of power would be neglectable, the asymptotic selection bias $SB$ is larger than $1/2$ so that the lack of randomness is non-ignorable.

When the clinical trials have many covariates, one may think that it is hard for the experimenter to know all the information so that he or she can use an optimal guessing strategy, and so the selection bias can be ignored. We can show that this is not the true
at least for the Pocock and Simon (1975)’s procedure. Write the allocation probability
\[ p_m = g(\Lambda_{m-1}(\bar{X}_m)) \]
as a function of \( \Lambda_{m-1}(\bar{X}_m) \). The guessing strategy is to guess treatment
1 when \( G_m > 0 \), treatment 2 when \( G_m < 0 \), and guess treatment 1 or 2 with probability 1/2
when \( G_m = 0 \), where \( G_m \) is the guessing factor. Then the expected proportion of correct
guesses is
\[ SB_n(g, G) = \frac{1}{2} + \frac{1}{n} \sum_{m=1}^{n} E \left[ \left( p_m - \frac{1}{2} \right) \text{sgn}(G_m) \right], \]
where ”g” stands for the allocation \( g(x) \), ”G” stands for the guessing strategy \( G_m \). Because
the experimenter uses part or all information of \( \Lambda_{m-1}(\bar{X}_m) \), so \( G_m = G(\Lambda_{m-1}(\bar{X}_m)) \)
is a function of \( \Lambda_{m-1}(\bar{X}_m) \), where \( G(\cdot) \) is a random function. We assume that under the
guessing strategy, the allocation is guessed in a correct direction, i.e., for any point \( x, y, \)
\[ \text{Pr}\{g(x) - G(x) \cdot g(y) \geq 0\} = P(x, y) \geq 1/2, \] and there is at least a pair of points
\( x_0 \) and \( y_0 \) such that \( \text{Pr}(G(x_0) > 0 > G(y_0), g(x_0) > g(y_0)) > 1/2. \)

**Theorem 3.1** For the Pocock and Simon’s procedure, Hu and Hu’s procedure or more gen-
eral procedures as in Remark 4.1, we have
\[ \lim_{n \to \infty} SB_n(g, G) > \frac{1}{2}. \]

**Proof.** Let \( \Lambda^*_{n-1}(t), \bar{X}^*_n \) be independent copies of \( \Lambda_{n-1}(t), \bar{X}_n \) and define \( p^*_m \) and \( G^*_m \)
similarly. Write \( \eta_m = \Lambda_{n-1}(\bar{X}_n), \eta^*_m = \Lambda^*_{n-1}(\bar{X}^*_n), \eta = \Lambda(\bar{X}), \eta^* = \Lambda^*(\bar{X}^*) \). Then
\[
SB_n(g, G) - \frac{1}{2} = \frac{1}{n} \sum_{m=1}^{n} E \left[ p_m - \frac{1}{2} \right] E \left[ \text{sgn}(G_m) \right]
+ \frac{1}{2} \frac{1}{n} \sum_{m=1}^{n} E \left[ (p_m - p^*_m) \left( \text{sgn}(G_m) - \text{sgn}(G^*_m) \right) \right]
= \frac{1}{n} \sum_{m=1}^{n} E \left[ p_m - \frac{1}{2} \right] E \left[ \text{sgn}(G_m) \right]
+ \frac{1}{2} \frac{1}{n} \sum_{m=1}^{n} E \left[ (p_m - p^*_m) \left( \text{sgn}(G_m) - \text{sgn}(G^*_m) \right) \right] (2P(\eta_m, \eta^*_m) - 1)
\to E_{\pi} \left[ g(\eta) - \frac{1}{2} \right] E \left[ \text{sgn}(G(\eta)) \right] +
\frac{1}{2} E_{\pi} \left[ (g(\eta) - g(\eta^*)) \left( \text{sgn}(G(\eta)) - \text{sgn}(G(\eta^*)) \right) \right] (2P(\eta, \eta^*) - 1),
\]
by the ergodic theorem. For the value of the limit, the second term is positive due to the
assumption for guessing in a correct direction. The first term is zero because \( E_{\pi} g(\eta) = 1/2 \)
under the invariant distribution \( \pi \), which can be verified by
\[
E_{\pi} [D_n] = \frac{1}{n} \sum_{j=1}^{n} E_{\pi} [2T_j - 1] = \frac{1}{n} \sum_{j=1}^{n} 2(E_{\pi} p_j - 1) = 2E_{\pi} g(\eta) - 1.
\]
The proof is completed. □

It is obvious that, if
\[ p_m \to \frac{1}{2} \text{ in probability}, \tag{3.1} \]
then \( SB \) attains the minimum value \( 1/2 \) of the selections biases, and every guessing strategy is asymptotically equally useless against the design. When the trials do not include the covariate, Wei (1978) defines the adaptive BCD satisfying (3.1) such that \( SB = 1/2 \). But Wei’s design does not satisfy (2.7). The problem is that, can we find a randomization procedure such that \( SB = 1/2 \) and the condition (2.7) is also satisfied? The next section will deal with this problem.

4 A New family of Covariate-Adaptive Randomization methods

In this section, we consider the randomization methods. We first give a general framework of the covariate-adaptive randomization. We consider the same setting as that of Pocock and Simon (1975) and only focus on two treatment groups 1 and 2 here. As before, let \( T_j \) be the assignment of the \( j \)th patient, \( j = 1, \ldots, n \), i.e., \( T_j = 1 \) for treatment 1 and \( T_j = 0 \) for treatment 2. Recall that \( \tilde{X}_j = (d_1(X_{j,1}, \ldots, d_I(X_{j,I})) \) indicates the discrete part of the covariate profile of that patient considered in adaptive randomization, i.e., \( \tilde{X}_j = (\tilde{x}^{t_1}, \ldots, \tilde{x}^{t_I}) \) if his or her \( i \)th covariate is at level \( \tilde{x}^{t_i} \), \( 1 \leq i \leq I \) and \( 1 \leq t_i \leq m_i \). For convenience, we use \( (t_1, \ldots, t_I) \) to denote the stratum formed by patients who possess the same covariate profile \( (\tilde{x}^{t_1}, \ldots, \tilde{x}^{t_I}) \), resulting in \( M = \prod_{i=1}^I m_i \) strata, and use \( (i; t_i) \) to denote the margin formed by patients whose \( i \)th covariate is at level \( \tilde{x}^{t_i} \).

4.1 The randomization procedure

The procedure is defined as follows:

1) The first patient is assigned to treatment 1 with probability 1/2.

2) Suppose \( (n-1) \) patients have been assigned to treatments \( (n > 1) \) and the covariate value \( X_n = x_n^* \) of the \( n \)th patient is observed and falls within stratum \( (t^{t}_1, \ldots, t^{t}_I) \).

3) For the first \( (n-1) \) patients,
- let $D_{n-1} = N_{n-1,1} - N_{n-1,2}$ be the difference between the numbers of patients in treatment group 1 and 2;
- similarly, let $D_{n-1}(i; t^*_i)$ and $D_{n-1}(t^*_1, \ldots, t^*_I)$ be the differences between the numbers of patients in the two treatment groups on the margin $(i; t^*_i)$, and within the stratum $(t^*_1, \ldots, t^*_I)$, respectively;
- each one of these differences is used to measure the imbalance at the corresponding level (overall, marginal, or within-stratum).

4) If the $n$th patient were assigned to treatment 1, then $D^{(1)}_n = D_{n-1} + 1$ would be the “potential” overall difference in the two groups; similarly,
$$D^{(1)}_n(i; t^*_i) = D_{n-1}(i; t^*_i) + 1$$
and
$$D^{(1)}_n(t^*_1, \ldots, t^*_I) = D_{n-1}(t^*_1, \ldots, t^*_I) + 1$$
would be the potential differences on margin $(i; t^*_i)$ and within stratum $(t^*_1, \ldots, t^*_I)$, respectively.

5) Define an imbalance measure $Imb^{(1)}_n$ by
$$Imb^{(1)}_n = w_o[D^{(1)}_n]^2 + \sum_{i=1}^{I} w_{m,i}[D^{(1)}_n(i; t^*_i)]^2 + w_s[D^{(1)}_n(t^*_1, \ldots, t^*_I)]^2,$$
which is the weighted imbalance that would be caused if the $n$th patient were assigned to treatment 1. $w_o$, $w_{m,i}$ ($i = 1, \ldots, I$) and $w_s$ are nonnegative weights placed on overall, within a covariate margin and within a stratum cell, respectively. Without loss of generality we can assume
$$w_o + w_s + \sum_{i=1}^{I} w_{m,i} = 1.$$

6) In the same manner we can define $Imb^{(2)}_n$, the weighted imbalance that would be caused if the $n$th patient were assigned to treatment 2. In this case, the three types of potential differences are the existing ones minus 1, instead of plus 1.

7) Conditional on the assignments of the first $(n-1)$ patients as well as the covariates’ profiles of the first $n$ patients, assign the $n$th patient to treatment 1 with probability
$$P(T_n = 1|Z_{n-1}, \tilde{X}_n = (\tilde{x}^t_1, \ldots, \tilde{x}^t_I), T_{n-1}) = g_n(Imb^{(1)}_n - Imb^{(2)}_n)$$
(4.1)
where \( n > 1 \), \( Z_{n-1} = (\bar{X}_1, \ldots, \bar{X}_{n-1}) \), \( T_{n-1} = (T_1, \ldots, T_{n-1}) \). Here \( g_n(x) \) is a real function with \( 0 \leq g_n(x) \leq 1 \). It is called an allocation function.

Using the basic equation \((x + 1)^2 - (x - 1)^2 = 4x\), the critical quantity \( Imb_n^{(1)} - Imb_n^{(2)} \) in Step 7) can be simplified as

\[
Imb_n^{(1)} - Imb_n^{(2)} = 4 \left\{ w_o D_{n-1} + \sum_{i=1}^{I} w_{m,i} D_{n-1}(i; t_i^*) + w_s D_{n-1}(t_1^*, \ldots, t_I^*) \right\}
\]

\[
:= 4 \cdot \Lambda_{n-1}(t_1^*, \ldots, t_I^*) \tag{4.2}
\]

Therefore, the allocation probability \( g_n(Imb_n^{(1)} - Imb_n^{(2)}) \) is determined by the value of \( \Lambda_{n-1}(t_1^*, \ldots, t_I^*) \), which is a weighted average of current imbalances at different levels.

This framework includes various kinds of covariate-adaptive randomization procedures. If stratified randomization is considered, one just need to let \( w_s = 1 \) and other weights to be zero. If \( w_o = w_s = 0 \), the design is a marginal randomization procedure. Hu and Hu (2012)'s design is a special case with the weights satisfying some specified conditions.

### 4.2 The choice of the allocation function

In the literature different views have been given as to the selection of the allocation probability function \( g_n(\cdot) \). Efron (1971), Pocock and Simon (1975), Hu and Hu (2012) suggested

\[
g_n(x) = \begin{cases} 
q, & \text{if } x > 0, \\
\frac{1}{2}, & \text{if } x = 0, \\
p, & \text{if } x < 0,
\end{cases} \tag{4.3}
\]

where \( 1 > p > 1/2 \) and \( q + p = 1 \). If the allocation function is chosen in this way, and \( w_s = w_o = 0 \), then the design is the Pocock and Simon (1975)'s marginal procedure. Ma, Hu and Zhang (2015) had theoretically proved that under Pocock and Simon’s procedure, the marginal imbalances and overall imbalance are bounded in probability. But the selection bias is not optimal as we have seen in Section 3.

When the design does not include the covariate, Wei (1978) defines the adaptive BCD with allocation function being defined as

\[
g_n(x) = g \left( \frac{x}{n-1} \right), \tag{4.4}
\]

where \( g(x) \) is a non-increasing function with \( 0 \leq g(x) \leq 1 \), \( g(x) = 1 - g(-x) \), \( g(0) = 0.5 \) and \( g'(0) < 0 \). It has been showed that \( SB(WeiBCD) = 1/2 \), which attains the minimum
value as complete randomization does. However, Wei’s BCD does not satisfy the condition (2.7) and so power loss could be nontrivial (c.f. Antognini and Giovagnoli 2004, Antognini 2008).

Next, we show that a covariate-adaptive design can be defined by choosing suitable allocation function $g_n(x)$ so that the selection bias is asymptotically the minimum and the covariate imbalances considered are of the order of $o(n^{1/2})$ in probability for which the loss of power would be negligible.

In general, we assume the allocation function $g_n(x)$ (0 ≤ $g_n(x)$ ≤ 1) satisfying the following conditions

$$g_n(x) \leq \frac{1}{2} \leq g_n(-x) \text{ when } x \geq 0,$$

$$\frac{|1/2 - g_n(x_n)|}{|x_n|/n} \rightarrow +\infty \text{ whenever } 0 < \frac{|x_n|}{n} \rightarrow 0$$

and

$$g_n(x_n) \rightarrow \frac{1}{2} \text{ whenever } \frac{x_n}{n} \rightarrow 0.$$  

We will show that if the allocation function satisfy the conditions (4.5) and (4.6), then covariate imbalances are of the order of $o(n^{1/2})$ in probability and, if the conditions (4.5) and (4.7) are satisfied, then the asymptotically selection bias is 1/2. The allocation function $g_n(x)$ of BCD given in (4.3) satisfies (4.5) and (4.6), but it does not satisfy condition (4.7). Wei’s allocation function $g_n(x)$ given in (4.4) satisfies (4.5) and (4.7), but it does not satisfy condition (4.6).

It is easily seen that $g_n(x) = 1 - \Phi \left( \text{sgn}(x) \sqrt{|x|/n} \right)$ satisfy all the condition (4.5)-(4.7), where $\Phi(x)$ is the standard normal distribution function. It can be chosen as an allocation function to define a design as desired.

In the following we will give a specified allocation function. For this allocation function, the design has much fine properties. Let 0 ≤ $g(x)$ ≤ 1 be a non-increasing function with $g(0) = 0.5$, $g'(0) < 0$. Define

$$g_n(x) = g \left( \frac{x}{(n - 1)\gamma} \right), \quad 0 \leq \gamma \leq 1.$$  

When $\gamma = 1$, the allocation function $g_n(x)$ is Wei’s function given in (4.4). When $\gamma = 0$, the design is a generalization of the Pocock and Simon (1975)’s procedure as well as Hu and Hu (2012)’s design. In this paper, we mainly consider the case 0 < $\gamma$ < 1. When 0 ≤ $\gamma$ < 1, the allocation function given in (4.8) satisfied the condition (4.5) and (4.6), but may not satisfy (4.7). However, we will show that the design defined by this allocation function satisfy (3.1) when 0 < $\gamma$ ≤ 1.
4.3 Theoretical Properties

For consider the asymptotic properties of the design, we need some more notations. For the first $n$ patients, we know that $D_n(t_1, \ldots, t_I)$ is the true difference between the two treatment arms within stratum $(t_1, \ldots, t_I)$. Let
\[
D_n = [D_n(t_1, \ldots, t_I)]_{1 \leq t_1 \leq m_1, \ldots, 1 \leq t_I \leq m_I}
\]
be an array of dimension $m_1 \times \ldots \times m_I$ which stores the current assignment differences in all strata and so stores the current imbalances. Also, the covariates $\tilde{X}_1, \tilde{X}_2, \ldots$ are independently and identically distributed. Since $\tilde{X}_n = (\tilde{x}_1^{t_1}, \ldots, \tilde{x}_I^{t_I})$ can take $M = \prod_{i=1}^I m_i$ different values, it in fact follows an $M$-dimension multinomial distribution with parameter $p = (p(t_1, \ldots, t_I))$, each element being the probability that a patient falls within the corresponding stratum. Without loss of generality, we assume $p(t_1, \ldots, t_I) > 0$ for all $(t_1, \ldots, t_I)$.

Write $t = (t_1, \ldots, t_I)$. Define
\[
M_n = \sum_t w_s D_n^2(t) + \sum_{i=1}^I \sum_{t_i=1}^{m_i} w_{m,i} D_n^2(i; t_i) + w_o D_n^2.
\]

Now we give our main results.

**Theorem 4.1** Suppose the allocation function $g_n(x)$ satisfying the conditions (4.5) and (4.6). Then
\[
E \left( \frac{M_n}{n} \right)^r \to 0 \quad \forall r > 0,
\]
\[
(4.9)
\]
i.e., $M_n = o(n)$ in $L_r$ for all $r > 0$. In particular,

(i) If $w_s > 0$, then $D_n = o(n^{1/2})$ in $L_r$ for any $r > 0$;

(ii) If $w_s + w_{m,i} > 0$, then $D_n(i; t_i) = o(n^{1/2})$ in $L_r$ for any $r > 0$, $t_i = 1, \ldots, m_i$;

(iii) For any case $D_n = o(n^{1/2})$ in $L_r$ for any $r > 0$.

Further, if the condition (4.7) is satisfied, then
\[
SB_n \to \frac{1}{2}.
\]

**Theorem 4.2** Let the allocation function $g_n(x)$ be defined as (4.8) with $0 < \gamma \leq 1$, and $0 \leq g(x) \leq 1$ be a non-increasing function with $g(0) = 1/2$, $g'(0) < 0$. Then
\[
M_n = O(n^\gamma) \quad \text{in } L_r \quad \text{for all } r > 0,
\]
\[
(4.10)
\]
\[
M_n = o(n^{\gamma+\epsilon}) \quad \text{a.s. for any } \epsilon > 0
\]
\[
(4.11)
\]
and

\[ SB_n = \frac{1}{2} + O(n^{-\gamma/2}). \]  (4.12)

In particular,

(i) If \( w_s > 0 \), then \( D_n = O(n^{\gamma/2}) \) in \( L_r \) for any \( r > 0 \), and \( D_n = o(n^{\gamma/2+\epsilon}) \) a.s. for any \( \epsilon > 0 \);

(ii) If \( w_s + w_{m,i} > 0 \), then \( D_n(i; t_i) = O(n^{\gamma/2}) \) in \( L_r \) for any \( r > 0 \), and \( D_n(i; t_i) = o(n^{\gamma/2+\epsilon}) \) a.s. for any \( \epsilon > 0 \), \( t_i = 1, \ldots, m_i \);

(iii) For any case \( D_n = O(n^{\gamma/2}) \) in \( L_r \) for any \( r > 0 \), and \( D_n = o(n^{\gamma/2+\epsilon}) \) a.s. for any \( \epsilon > 0 \);

(iv) Suppose \( w_s + w_{m,i} > 0 \), \( X_i = d_i(X_i) \) (the covariates in the test and in the randomization procedure are the same), \( i = 1, \ldots, I \). Then

\[ \text{LoP}_{T,n}(\mu|X) = 1 + O(n^{\gamma-1}) \text{ in probability.} \]

Further, in (4.12), \( O(n^{-\gamma/2}) \) can be written as \( a_n n^{-\gamma/2} \) with

\[ c_0 < \lim \inf_{n \to \infty} a_n \leq \lim \sup_{n \to \infty} a_n \leq \frac{2 \sqrt{|g'(0)|}}{2 - \gamma}, \]

where \( c_0 > 0 \) is a constant which does not depend on \( \gamma \).

The value of \( \gamma \) gives the order of the allocation bias as well as the order of selection bias, which gives a picture how the efficiency and selection bias conflict each other. The smaller \( \gamma \) is, the smaller the allocation bias is, but the larger the selection bias is. In practice, one may choose \( \gamma = 1/2 \) to give a tradeoff between two kinds of bias, both of which are medium.

**Remark 4.1** Theorem 4.2 does not include the case of \( \gamma = 0 \). When \( \gamma = 0 \), suppose \( 0 < g(x) \leq 1/2 \leq g(-x) < 1 \) for all \( x \geq 0 \), and \( \lim \inf_{x \to \infty} |g(x) - 1/2| > 0 \). It can be showed that \( \Lambda_n(t_1, \ldots, t_I) \) is a positive recurrent Markov chain with an invariant distribution \( \pi \) and \( \sup_n \mathbb{E}[M_r^n] < \infty \) for all \( r > 0 \). Further,

\[ \lim_{n \to \infty} SB_n = \frac{1}{2} + \sum_t \mathbb{E}_\pi \left[ \left| g(\Lambda(t)) - \frac{1}{2} \right| p(t) \right] > 1/2. \]

So, Theorem 4.2 is still valid for \( \gamma = 0 \). For details, one can refer to Hu and Zhang (2013).
It shall be note that Taves (1974)’s minimization method is not included in Remark 4.1, because the related allocation function is $g_n(x) = 1/2$ if $x = 0$, $g_n(x) = 0$ if $x > 0$ and $g_n(x) = 1$ if $x < 0$. This allocation function $g_n(x)$ satisfying the conditions (4.5) and (4.6). So (4.9) and (i)-(iii) of Theorem 4.1 remain true. We have more precise results as in the following corollary.

**Corollary 4.1** Suppose the allocation function $g_n(x)$ satisfying the conditions (4.5) and there exist constants $x_0 > 0$ and $p_0 > 0$ such that

$$|g_n(x) - \frac{1}{2}| \geq p_0 \text{ for all } |x| \geq x_0 \text{ and } n \geq 1. \quad (4.13)$$

Then

$$M_n = O(n^\epsilon) \text{ a.s. and in } L_r \text{ for all } r > 0, \epsilon > 0. \quad (4.14)$$

In particular,

(i) If $w_s > 0$, then $D_n = O(n^\epsilon) \text{ a.s. and in } L_r \text{ for any } r > 0 \text{ and } \epsilon > 0$;

(ii) If $w_s + w_{m,i} > 0$, then $D_n(i; t_i) = O(n^\epsilon) \text{ a.s. and in } L_r \text{ for any } r > 0 \text{ and } \epsilon > 0$,

\[ t_i = 1, \ldots, m_i; \]

(iii) For any case $D_n = O(n^\epsilon) \text{ a.s. and in } L_r \text{ for any } r > 0 \text{ and } \epsilon > 0$.

5 Concluding Remarks

In this paper, we studied the theoretical properties of hypothesis testing, selection bias and randomization methods under covariate-adaptive designs. Basing on a linear normal model framework, we derived the corresponding asymptotic power of the hypothesis testing to compare treatment effects. To apply Theorem 2.2 to a specific covariate-adaptive randomized clinical trial and find efficient randomization, one just need to check the condition (2.7) or (2.6). The conclusion can be applied to a broad range of designs, including stratified permuted block design and Pocock and Simon’s procedure. The asymptotic selection bias is also studied. To check or find a most random covariate-adaptive randomization procedure, one just need to check a simple condition (3.1). A new family of covariate-adaptive randomization procedures are showed to satisfy the condition (2.7) and (3.1) simultaneously. The results in this paper provide new insights about balance, selection bias, efficiency, randomization method of clinical trials, and the framework can be used to study properties
of other statistical methods under covariate-adaptive randomization procedures and define new covariate-adaptive randomization procedures.

The condition (2.6) is important for ensuring that the asymptotic loss of power can be ignored so that the randomization procedure is efficient. When the covariates are discrete, it is satisfied for a large family of covariate-adaptive designs, including many popular designs in literature, and the new family proposed in this paper. But, all covariate-adaptive designs considered in this article are based on discrete covariates. When the covariates are continuous, covariates are typically discretized in order to be included in the randomization scheme. Formula (2.8) gives the cost to the loss of power of failing to balance the $k$th covariate completely when a randomization scheme is included by breakdown continuous covariate into a discrete variable with several subcategories. One may consider covariate-adaptive designs (Lin and Su 2012; Ma and Hu 2013) that directly use continuous covariates without discretization. However, related theoretical work is limited in the literature. The loss of power is seldom considered. We leave this as a future research project. There are some other kinds of covariate-adaptive randomization procedures in the literature, including Zelen (1974), Begg and Iglewicz (1980), and Atkinson (1982). Theorems 2.1 and 2.2 may not apply to these designs, because it is unknown whether the condition (2.6) or (2.7) remains true for these designs.

The proposed properties for covariate-adaptive designs can be generalized in several ways. First, the proposed properties and adaptive-randomization procedures are based on clinical trials with two treatments, which can be generalized to multiple treatments (Hu and Zhang 2004, Tymofyeyev, Rosenberger, and Hu 2007). Second, one assumption to derive theoretical results on the power is the independence between covariates. We may apply the similar idea to dependent covariates by incorporating correlation structure. Third, to derive the relative loss of power, one important assumption is the normality of the regression errors. It is an open problem whether the conclusions in Theorems 2.1 and 2.1 are still valid for a general distribution of errors, especially when an approximation distribution is applied. Maybe, this is a difficult problem and, the precise self-normalized Cramér-type large deviation is helpful for solving it (c.f. Jing, Shao and Wang 2003). Fourth, the randomization procedures considered in this paper only depend on the covariates, the response of patients to treatments are not incorporated. It is possible to generalize the results to efficient randomized response-adaptive designs (Hu, Zhang and He 2009) and covariate-adjusted adaptive designs (Zhang et al 2007). Those topics are left for future
Finally, from Corollary 2.2 it can be seen that balancing the continuous covariates is very important. Recently, Ma, Li and Hu (2021) proposed a procedure which can balance the continuous covariates \( X_i \)s directly. Let \( D_n = \sum_{i=1}^{n} (2T_i - 1) \) and \( D_n^x = \sum_{i=1}^{n} (2T_i - 1)X_i \) be defined as in Section 2. Denote the measure of imbalance by \( M_n = (D_n)^2 + \|D_n^x\|^2, \text{Imb}^{(1)}_n = M_n\bigg|_{T_n=1} \) and \( \text{Imb}^{(2)}_n = M_n\bigg|_{T_n=0} \). Ma, Li and Hu’s procedure assigns the \( n \)th patient to treatment 1 with probability \( q > 1/2 \) when \( \text{Imb}^{(1)}_n < \text{Imb}^{(2)}_n \), 1/2 when \( \text{Imb}^{(1)}_n = \text{Imb}^{(2)}_n \), and \( 1-q \) when \( \text{Imb}^{(1)}_n > \text{Imb}^{(2)}_n \). This procedure can be generalized by defining the allocation probability as \( g_n(\text{Imb}^{(1)}_n - \text{Imb}^{(2)}_n) \). We may have similar results as in Theorems 4.1-4.2 and Corollary 4.1. In particular, if \( g_n(x) \) satisfies the conditions (4.5)-(4.7) in Theorem 4.1, we will have

\[
\text{LossP}_{T,n}(\mu|X) \rightarrow 1 \text{ in probability and } \lim_{n \rightarrow \infty} SB_n = \frac{1}{2}.
\]

6 Appendix: Proofs

We first prove the results on the power of the hypothesis testing to compare treatment effects.

6.1 Proofs of the results in Section 2

Proof of Theorem 2.1. Write \( W_n = (D_n/\sqrt{n})^2 + Q_n^2 \). Then

\[
n - \ell^2_n = W_n + O(1)\frac{W_n^4}{n} = W_n(1 + o(1)).
\]

Let \( H(x) = \ln F(t_{1-\alpha}(\nu); \nu, \sqrt{x}) \). Then

\[
H'(x) = \frac{1}{2} \left. \frac{d}{d\delta} F(t_{1-\alpha}(\nu); \nu, \delta) \right|_{\delta=\sqrt{x}}.
\]

We first show that

\[
\frac{d}{d\delta} F(t; \nu, \delta) \rightarrow -1 \quad \text{as } \delta \rightarrow \infty \text{ and } \nu \rightarrow \infty
\]  \hspace{1cm} (6.1)

uniformly in \( t \) on a bounded interval. Note

\[
F(t; \nu, \delta) = \mathbb{E} \left[ \Phi(t\sqrt{\chi^2(\nu)/\nu - \delta}) \right],
\]

\[
\frac{d}{d\delta} F(t; \nu, \delta) = -\mathbb{E} \left[ \varphi(t\sqrt{\chi^2(\nu)/\nu - \delta}) \right].
\]
where $\chi^2(\nu)$ is a random variable which has a $\chi^2$ distribution with degree of freedom $\nu$.

Choose a sequence $\epsilon_\nu$ such that $0 < \epsilon_\nu \to 0$, $\epsilon_\nu \delta^2 \to \infty$ and $\epsilon_\nu \nu \to \infty$. Let $E = \{\chi^2(\nu)/\nu \leq \epsilon_\nu \delta^2\}$. Note
\[
\varphi(\delta) \frac{\delta}{1 + \delta^2} \leq 1 - \Phi(\delta) = \Phi(-\delta) \leq \varphi(\delta^2), \quad \varphi(-\delta) = \varphi(\delta).
\]

On the event $E$,
\[
\varphi(t \sqrt{\chi^2(\nu)/\nu - \delta}) \leq \frac{\delta}{1 + \delta^2} \Phi(t \sqrt{\chi^2(\nu)/\nu - \delta}) \to 1
\]
uniformly in $t$ on a bounded interval and $\omega$. Hence
\[
E \left[ \varphi(t \sqrt{\chi^2(\nu)/\nu - \delta}) I_E \right] = (1 + o(1)) \delta E \left[ \Phi(t \sqrt{\chi^2(\nu)/\nu - \delta}) I_E \right]
\]
uniformly in $t$ on a bounded interval. On the other hand,
\[
P(E^c) \leq e^{-\nu \epsilon_\nu \delta^2/4} E \left[ e^{\chi^2(\nu)/4} \right] \leq e^{-\nu (\epsilon_\nu \delta^2/4 - 1)} \leq e^{-2\delta^2}
\]
\[
\leq e^{-\delta^2} \delta \Phi(-\delta) \leq e^{-\delta^2} \delta F(t; \nu, \delta)
\]
when $\delta$ and $\nu$ large enough. Hence
\[
E \left[ \varphi(t \sqrt{\chi^2(\nu)/\nu - \delta}) \right] = (1 + o(1)) \delta E \left[ \Phi(t \sqrt{\chi^2(\nu)/\nu - \delta}) \right]
\]
uniformly in $t$ on a bounded interval. (6.1) is proved, which implies
\[
H'(x) = \left. \frac{\partial}{\partial \delta} F(t_{1-\alpha}(\nu); \nu, \delta) \right|_{\delta = \sqrt{x}} = -\frac{1}{2} (1 + o(1))
\]
as $\nu, x \to \infty$. So, for $0 \leq y_n \leq x_n \to \infty$ with $y_n/x_n \to 0$, we have
\[
H(x_n^2) - H(x_n^2 - y_n^2) = y_n^2 H'(z_n) = -\frac{y_n^2}{2} (1 + o(1)),
\]
where $z_n \in (x_n^2 - y_n^2, x_n^2)$. Hence
\[
\frac{F(t_{1-\alpha}(\nu); \nu, x_n)}{F(t_{1-\alpha}(\nu); \nu, \sqrt{x_n^2 - y_n^2})} = \exp \left\{ -\frac{y_n^2}{2} (1 + o(1)) \right\}.
\]

(6.2)

Now, let $x_n^2 = \frac{\mu^2}{4\sigma^2}$, $y_n^2 = \frac{\mu^2}{4\sigma^2} (n - t_n^2)$. Then $y_n^2 = \frac{\mu^2}{4\sigma^2} W_n^2 (1 + o(1))$. It follows that
\[
LossP_{T,n}(\mu|X) = \exp \left\{ -\frac{u_n^2}{8\sigma^2} W_n (1 + o(1)) \right\}
\]
(6.3)

Finally, note $X_n \to 0$ a.s. and
\[
\frac{S_{n,xx}}{n} = \frac{1}{n} \left\{ \sum_{i=1}^{n} (X_i - \overline{X}_n)^T (X_i - \overline{X}_n) \right\}
\]
\[
- N_{n,1}(\overline{X}_{n,1}^T \overline{X}_{n,1} - \overline{X}_n^T \overline{X}_n) - N_{n,2}(\overline{X}_{n,2}^T \overline{X}_{n,2} - \overline{X}_n^T \overline{X}_n)
\]
\[
\to \text{Var}(X) = \text{diag}(\sigma^2_{x,1}, \ldots, \sigma^2_{x,1}) \quad \text{a.s.}
\]
We have

\[ W_n = \left( \frac{D_n}{\sqrt{n}} \right)^2 + \left( \frac{D_n^x}{\sqrt{n}} \right)^T \left[ \text{Var}(X) \right]^{-1} \left( \frac{D_n}{\sqrt{n}} \right) + o(1) \left( \left( \frac{D_n}{\sqrt{n}} \right)^2 + \left\| D_n^x / \sqrt{n} \right\|^2 \right) \]

\[ = V_n (1 + o(1)). \]

(2.4) are proved. □

**Proof of Theorem 2.2.** Note that \( E[X_k | d_k(X_k)] \) is a function of \( \tilde{X}_k = d_k(X_k) \). We write it as \( f_k(\tilde{X}_k) \). Then \( X_{i,k} = \delta_{i,k} + f_k(\tilde{X}_{i,k}) \). Under the conditions of \( \frac{D_n(t_k)}{\sqrt{n}} \to 0, t_k = 1, \ldots, m_k, k = 1, \ldots, p \), we have

\[ \sum_{i=1}^{n} \left( 2T_i - 1 \right) f_k(\tilde{X}_{i,k}) = \sum_{t_k=1}^{m_k} D_n(k; t_k)f_k(\tilde{x}_{t_k}^k) \to 0. \]

Because the probability of \( T_i = 1 \) is a function of \( \tilde{X}_i \), the sequence \( (2T_i - 1)(\delta_{i,1}, \ldots, \delta_{i,I}) \), \( i = 1, 2, \ldots, \) is a sequence of martingale vector differences with

\[ \text{Var} \left( (2T_i - 1)(\delta_{i,1}, \ldots, \delta_{i,I}) | \mathcal{F}_{i-1} \right) = \text{diag} \left( \sigma^2_{\delta,1}, \ldots, \sigma^2_{\delta,I} \right), \]

where \( \mathcal{F}_i \) is the history \( \sigma \)-field generated by \( T_1, \ldots, T_{i-1}, \tilde{X}_1, \ldots, \tilde{X}_{i-1} \). By the central limit theorem of martingales, we have

\[ \sum_{i=1}^{n} \left( 2T_i - 1 \right) (\delta_{i,1}, \ldots, \delta_{i,I})^T \to N_I \left( 0, \text{diag} \left( \sigma^2_{\delta,1}, \ldots, \sigma^2_{\delta,I} \right) \right). \]

Hence

\[ V_n \to \sum_{k=1}^{I} \frac{\sigma^2_{\delta,k}}{\sigma^2_{x,k}} \chi^2_k(1). \]

The results follow. □

**Proof of Remark 2.1.** We first consider the two-sided t-test. Note that the distribution function of \( T^2 \) is a F-distribution function \( F(t; m, \nu, \delta) \) with degree of freedom \( m = 1 \) and \( \nu = n - p - 2 \), and the non-central parameter \( \delta = \frac{\mu^2}{\sigma_x^2} \). It is sufficient to show that

\[ \frac{d}{d\delta} \frac{F(t; m, \nu, \delta)}{F(t; m, \nu, 0)} = -\frac{1}{2} \left( 1 + o(1) \right) \]

(6.4)

uniformly in \( t \in [0, t_0] \) as \( \nu \to \infty \) and \( \delta \to \infty \). The non-central F-distribution has the following expansion

\[ F(t; m, \nu, \delta) = \sum_{j=0}^{\infty} e^{-\delta/2} \frac{(\delta/2)^j}{j!} F \left( \frac{m}{m+2j} t; m+2j, \nu, 0 \right) \]

\[ = \sum_{j=0}^{\infty} e^{-\delta/2} \frac{(\delta/2)^j}{j!} \int_0^t f(x; m, \nu, j)dx, \]

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where
\[ f(x; m, \nu, j) = \frac{\Gamma((m + \nu)/2 + j) \nu^{\nu/2} m^{m/2+j} x^{m/2-1+j}}{\Gamma(m/2 + j) \Gamma(\nu) (\nu + mx)^{(\nu+m)/2+j}}. \]

So,
\[
\begin{align*}
\frac{dF(t; m, \nu, \delta)}{d\delta} + \frac{1}{2} F(t; m, \nu, \delta) \\
= \frac{1}{2} \sum_{j=0}^{\infty} e^{-\delta/2 (\delta/2)^j} \frac{1}{j!} \int_0^t f(x; m, \nu, j + 1) dx \\
= \frac{1}{2} \sum_{j=0}^{\infty} e^{-\delta/2 (\delta/2)^j} \frac{1}{j!} F \left( \frac{m}{m+2(j+1)} t; m+2(j+1), \nu, 0 \right). 
\end{align*}
\]

It is obvious that
\[
\begin{align*}
&\quad \frac{1}{2} \sum_{j=0}^{\infty} e^{-\delta/2 (\delta/2)^j} \frac{1}{j!} F \left( \frac{m}{m+2(j+1)} t; m+2(j+1), \nu, 0 \right) \\
&= \frac{2(j+1)}{\delta} e^{-\delta/2 (\delta/2)^j+1} \frac{1}{(j+1)!} F \left( \frac{m}{m+2(j+1)} t; m+2(j+1), \nu, 0 \right) \\
&\leq \frac{2(j+1)}{\delta} F(t; m, \nu, \delta) \\
&\text{and} \\
\int_0^t f(x; m, \nu, j + 1) dx \leq \frac{\nu + m + 2j}{m+2j} \frac{mt}{\nu + mt} \int_0^t f(x; m, \nu, j) dx.
\end{align*}
\]

It follows that
\[
0 \leq \frac{dF(t; m, \nu, \delta)}{d\delta} + \frac{1}{2} F(t; m, \nu, \delta) \\
\leq \frac{1}{2} \sum_{j=0}^{K_m} \frac{2(j+1)}{\delta} F(t; m, \nu, \delta) \\
+ \frac{1}{2} \int_{K_m}^{\infty} e^{-\delta/2 (\delta/2)^j} \frac{1}{j!} \left( \frac{mt}{\nu} + \frac{mt}{m+2j} \right) \int_0^t f(x; m, \nu, j) dx \\
\leq \left( \frac{2(K_m+1)^2}{\delta} + \frac{mt}{\nu} + \frac{t}{2K+1} \right) F(t; m, \nu, \delta).
\]

(6.4) is proved.

For the one-side z-test for (2.2), the test statistic is
\[ U = \frac{L\beta}{\sigma^2 L(X^T X)^{-1} L^T}^{1/2}. \]

The power function is
\[ \beta_{U,n}(\mu|X) = 1 - \Phi(z_{1-\alpha} - \sqrt{\delta}) \text{ with } \delta = \frac{u^2}{4\sigma^2 e_n}. \]

It is obvious that
\[
\frac{d}{d\delta} \Phi(z_{1-\alpha} - \sqrt{\delta}) \Phi(z_{1-\alpha} - \sqrt{\delta}) \to \frac{1}{2} \text{ as } \delta \to \infty.
\]
We have a similar result as (6.4).

For the two-side z-test for (2.10), the test statistic is \( U \) and the power function is

\[
\beta_{U|n}(\mu |X) = 1 - \Phi(z_{1-\alpha/2} - \sqrt{\delta}) + \Phi(-z_{1-\alpha/2} - \sqrt{\delta}) \quad \text{with} \quad \delta = \frac{u^2}{4\sigma_n^2}.
\]

It is easily seen that

\[
\frac{d}{d\delta}\Phi(z_{1-\alpha/2} - \sqrt{\delta}) - \Phi(-z_{1-\alpha/2} - \sqrt{\delta})
= -\frac{1}{2\sqrt{\delta}} \left( \varphi(z_{1-\alpha/2} - \sqrt{\delta}) - \varphi(-z_{1-\alpha/2} - \sqrt{\delta}) \right)
\sim -\frac{1}{2\sqrt{\delta}} \varphi(z_{1-\alpha/2} - \sqrt{\delta}) \rightarrow -\frac{1}{2} \quad \text{as} \quad \delta \rightarrow \infty.
\]

We have a similar result as (6.4). The proof is completed. \( \square \)

### 6.2 Proofs of the results in Section 4

We now prove the results on covariate adaptive randomization procedures.

Recall that \( t = (t_1, \ldots, t_I) \), \( t_i = 1, \ldots, m_i, i = 1, \ldots, I \), has \( M = \prod_{k=1}^I m_k \) values. Our purpose is to study the properties of \( D_n = [D_n(t)] \). Besides \( D_n \), we will also consider the weighted average of the imbalances \( \Lambda_{n-1}(t) \) as in (2.1). Let

\[
\Lambda_n(t) = w_n D_n + \sum_{i=1}^I w_{mi} D_n(i; t_i) + w_s D_n(t),
\]

\[
\Lambda_n = [\Lambda_n(t)]_{1 \leq t_1 \leq m_1, \ldots, 1 \leq t_I \leq m_I}.
\]

Also let \( \mathcal{F}_{n-1} \) be the history \( \sigma \)-field generated by the covariates \( \tilde{X}_1, \ldots, \tilde{X}_{n-1} \) and results of allocation \( T_1, \ldots, T_{n-1} \). Then the allocation probability in (4.1) of the \( n \)th patient as

\[
P \left( T_n = 1 | \mathcal{F}_{n-1}, \tilde{X}_n = (\tilde{x}_1^{t_1}, \ldots, \tilde{x}_I^{t_I}) \right) = g_n (4\Lambda_{n-1}(t)).
\]

is a function of \( \Lambda_{n-1} \). It is obvious that \( \Lambda_n = L(D_n) : D_n \rightarrow \Lambda_n \) is a linear transform of \( D_n \). The following proposition gives the relation between \( D_n \) and \( \Lambda_n \) and tells us that both \( (D_n)_{n \geq 1} \) and \( (\Lambda_n)_{n \geq 1} \) are Markov chains.

**Proposition 6.1** (i) If \( w_s > 0 \), then \( \Lambda_n = L(D_n) \) is a one to one linear map; If \( w_s + w_{mi} > 0 \), then each \( D_n(i; t_i) = D_{i; t_i}(\Lambda_n) \) is a linear transform of \( \Lambda_n \); For any case, \( D_n = D(\Lambda_n) \) is a linear transform of \( \Lambda_n \).

(ii) \( (D_n)_{n \geq 1} \) is a non-homogeneous Markov chain on the space \( \mathbb{Z}^m \) with period 2;

(iii) \( (\Lambda_n)_{n \geq 1} \) is a non-homogeneous Markov chain on the space \( L(\mathbb{Z}^m) \) with period 2.
Proof. For (i), taking the summation of $\Lambda_n(t)$ over all $t$ yields

$$\sum_t \Lambda_n(t) = (w_s + \sum_{i=1}^l w_{m,i} \prod_{j \neq i} m_j + w_o M) D_n.$$ 

So $D_n$ is a linear transform of $\Lambda_n$. Taking the summation of $\Lambda_n(t)$ over all $t_1, \ldots, t_I$ except $t_i$ yields

$$\sum_{t_1, \ldots, t_{I-1}, t_{I+1}, \ldots, t_I} \Lambda_n(t_1, \ldots, t_I) = (w_s + w_{m,i} \prod_{j \neq i} m_j) D_n(i; t_i) + (\sum_{l \neq i} w_{m,l} \prod_{j \neq l} m_j + w_o \prod_{j \neq 1} m_j) D_n.$$ 

Hence, when $w_s + w_{m,i} > 0$, each $D_n(i; t_i)$ is a linear transform of $\Lambda_n$ and $D_n$, and so it is a linear transform of $\Lambda_n$. Finally, when $w_s > 0$, it is obvious that each $D_n(t)$ is a linear transform of $\Lambda_n(t)$, $D_n(1; t_1), \ldots, D_n(I; t_I)$ and $D_n$, and so it is a linear transform of $\Lambda_n$. Hence, when $w_s > 0$, $\Lambda_n = L(D_n)$ is a one to one linear map.

For (ii) and (iii), notice

$$D_n(t) = D_{n-1}(t) + 2(T_n - \frac{1}{2}) \mathbb{I}\{X_n = (\tilde{x}_{t_1}, \ldots, \tilde{x}_{t_I})\}.$$ 

Then

$$P(\Delta D_n(t) = 1|\mathcal{F}_{n-1}) = g_n(4\Lambda_{n-1}(t)) p(t),$$

$$P(\Delta D_n(t) = -1|\mathcal{F}_{n-1}) = [1 - g_n(4\Lambda_{n-1}(t))] p(t),$$

$$P(\Delta D_n(t) = 0|\mathcal{F}_{n-1}) = 1 - p(t).$$

Let $\Delta \mathcal{D}$ be the state space of $\Delta D_n = D_n - D_{n-1}$, i.e., each $d \in \Delta \mathcal{D}$ has only one non-zero element which is 1 or $-1$. For two vectors $x$ and $y$ on $\mathbb{Z}^{m_1 \times \ldots \times m_I}$, we write $x \cdot y = \sum_t x(t) y(t)$, $|x| = (|x(t)|)$. The conditional probability above can be write in the following form,

$$P(\Delta D_n = d|\mathcal{F}_{n-1}) = \left( g_n(4|d| \cdot \Lambda_{n-1}) - \frac{1}{2} \right) d \cdot p + \frac{1}{2} |d \cdot p|$$

$$= \left( g_n(4|d| \cdot L(D_{n-1})) - \frac{1}{2} \right) d \cdot p + \frac{1}{2} |d \cdot p|,$$

$$d \in \Delta \mathcal{D},$$

which depends only on $\Lambda_{n-1} = L(D_{n-1})$. So, conditional on $D_{n-1}$, $D_n$ is conditionally independent of $(D_1, \ldots, D_{n-2})$. It follows that $(D_n)_{n \geq 1}$ is a Markov chain on $\mathbb{Z}^m$. 

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For (iii), note for any point \( e \) in the state space \( \{ \mathbf{L}(\mathbf{d}) : \mathbf{d} \in \Delta \} \) of \( \Delta \Lambda_n \),
\[
P(\Delta \Lambda_n = e | \mathcal{F}_{n-1}) = \sum_{d : \mathbf{L}(d) = e, d \in \Delta} \left\{ \left( g_n(4|\mathbf{d}| \cdot \Lambda_{n-1}) - \frac{1}{2} \right) \mathbf{d} \cdot \mathbf{p} + \frac{1}{2} |\mathbf{d} \cdot \mathbf{p}| \right\},
\]
which depends only on \( \Lambda_{n-1} \). So, given \( \Lambda_{n-1}, \Lambda_n \) is conditionally independent of \( (\Lambda_1, \ldots, \Lambda_{n-2}) \).
It follows that \( \Lambda_n \) is a Markov chain. The proof of Proposition 6.1 is completed. □

**Proof of Theorem 4.1.** Recall
\[
M_n = \sum_{t} w_s D_n^2(t) + \sum_{i=1}^{I} \sum_{t_i=1}^{m_i} w_{m,i} D_n^2(i; t_i) + w_o D_n^2.
\]
By Proposition 6.1 (i), \( M_n = M^{*}(\Lambda_n) \) is a function of \( \Lambda_n \), and \( M_n \leq C\|\Lambda_n\|^2 \). On the other hand,
\[
\|\Lambda_n(t)\|^2 \leq (w_o|D_n| + \sum_{i=1}^{I} w_{m,i}|D_n(i; t_i)| + w_s|D_n(t)|)^2
\]
\[
\leq (w_o|D_n|^2 + \sum_{i=1}^{I} w_{m,i}|D_n(i; t_i)|^2 + w_s|D_n(t)|^2) (w_o + \sum_{i=1}^{I} w_{m,i} + w_s),
\]
\[
= w_o|D_n|^2 + \sum_{i=1}^{I} w_{m,i}|D_n(i; t_i)|^2 + w_s|D_n(t)|^2,
\]
which implies that \( \|\Lambda_n\|^2 \leq M \cdot M_n \). We will prove the theorem via two steps. First, we will show that under condition (4.5),
\[
M_n = O(n) \text{ in } L_r \quad \forall r > 0. \quad (6.8)
\]
In the second step, we will show that under conditions (4.5) and (4.6),
\[
M_n = o(n) \quad \text{in probability}, \quad (6.9)
\]
which, together with (6.8), implies that \( M_n = o(n) \) in \( L_r \) for any \( r > 0 \). (i)-(iii) follows from immediately. Finally,
\[
\mathbb{E} [p_n \lor (1 - p_n)] = \frac{1}{2} + \sum_{t} p(t) \mathbb{E} \left[ \frac{1}{2} - g_n(4\Lambda_{n-1}(t)) \right] \to \frac{1}{2}
\]
due to the condition (4.7) and the fact that \( \frac{\|\Lambda_n\|}{n} \leq C \frac{M_n^{1/2}}{n} \to 0 \) in probability. Hence
\[
SB_n = \frac{1}{n} \sum_{m=1}^{n} \mathbb{E} [p_m \lor (1 - p_m)] \to \frac{1}{2}.
\]
Now, we begin the proofs of (6.8) and (6.9). Given $\bar{X}_n = (\bar{x}_1^t, \ldots, \bar{x}_T^t)$, if $T_n = 1$, then

$$M_n - M_{n-1} = w_s \left\{ (D_{n-1}(t) + 1)^2 - D_{n-1}^2(t) \right\}$$

$$+ \sum_{i=1}^{I} w_{m,i} \left\{ (D_{n-1}(i; t_i) + 1)^2 - D_{n-1}^2(i; t_i) \right\}$$

$$+ w_o \left\{ (D_{n-1} + 1)^2 - D_{n-1}^2 \right\}$$

$$= -2\Lambda_{n-1}(t) + 1,$$

while, if $T_n = 0$, then $M_n - M_{n-1} = -2\Lambda_{n-1}(t) + 1$. So,

$$M_n - M_{n-1} = 2\Lambda_{n-1}(t) (2T_n - 1) \mathbb{I}\{\bar{X}_n = (\bar{x}_1^t, \ldots, \bar{x}_T^t)\} + 1. \quad (6.10)$$

Hence

$$\mathbb{E} \left[ M_n - M_{n-1} | \bar{X}_n = (x_1^t, \ldots, x_T^t), \mathcal{F}_{n-1} \right]$$

$$= 2\Lambda_{n-1}(t) [2g_n(4\Lambda_{n-1}(t)) - 1] + 1$$

$$= -4 \Lambda_{n-1}(t) \cdot \frac{1}{2} - g_n(4\Lambda_{n-1}(t)) + 1,$$

due the condition that $g_n(-x) \leq 1/2 \leq g_n(x)$ when $x \geq 0$. It follows that

$$\mathbb{E} \left[ M_n | \mathcal{F}_{n-1} \right] - M_{n-1} = -4S_n(\Lambda_{n-1}) + 1, \quad (6.11)$$

where

$$S_n(\Lambda_{n-1}) = \sum_t \left| \Lambda_{n-1}(t) \cdot \frac{1}{2} - g_n(4\Lambda_{n-1}(t)) \right| p(t) \quad (6.12)$$

is a nonnegative function of $\Lambda_{n-1}$.

From (6.11) and by noting $M_0 = 0$, it follows that

$$\mathbb{E} [M_n] \leq n. \quad (6.13)$$

Further, by (6.10) we have

$$M_n = M_{n-1} + 1 + 2\Lambda_{n-1}(t)(2T_n - 1) \mathbb{I}\{\bar{X}_n = (\bar{x}_1^t, \ldots, \bar{x}_T^t)\}$$

$$= M_{n-1} + 1 + \xi.$$

It is obvious that

$$|\xi| = 2|\Lambda_{n-1}(t)| \leq 2\sqrt{M_{n-1}}, \quad \mathbb{E}[\xi | \mathcal{F}_{n-1}] = -4S_n(\Lambda_{n-1}).$$
It follows that for positive integer \( r \),

\[
M_n^{r+1} - M_n^{r+1} = (r + 1)(M_{n-1} + 1)^r \xi \\
+ \left\{ (M_{n-1} + 1)^{r+1} - M_n^{r+1} + \sum_{k=2}^{r+1} \binom{r+1}{k} \xi^k(M_{n-1} + 1)^{r+1-k} \right\} \\
\leq (r + 1)(M_{n-1} + 1)^r \xi + C_r(M_{n-1} + 1)^r,
\]

where \( C_r \) is a constant which depends on \( r \). It follows that

\[
\mathbb{E}[M_n^{r+1} | \mathcal{F}_{n-1}] - M_n^{r+1} \\
\leq -4(r + 1)(M_{n-1} + 1)^r S_n(A_{n-1}) + C_r(M_{n-1} + 1)^r \\
\leq C_r(M_{n-1} + 1)^r.
\] (6.14)

By (6.13) and the induction we conclude (6.8). Obviously, (6.8) implies

\[
\frac{\|A_n\|}{n} \to 0 \text{ in probability.}
\]

Next, we consider (6.9). By (6.11),

\[
\mathbb{E}[M_n] - \mathbb{E}[M_{n-1}] = -4\mathbb{E}[S_n(A_{n-1})] + 1.
\] (6.15)

Let \( m := m_n \in \{0, 1, \ldots, n\} \) be the last one for which \( 1 - 4\mathbb{E}[S_{m+1}(A_m)] \geq 0 \). Then

\[
\mathbb{E}[M_n] \leq \mathbb{E}[M_{m+1}] \leq \mathbb{E}[M_m] + 1
\]

and

\[
4\mathbb{E}[S_{m+1}(A_m)] \leq 1.
\]

If \( m = m_n \) is bounded, the proof is completed. Assume \( m \to \infty \). Recall (6.12). Note the condition (4.6) implies

\[
\frac{S_{m+1}(A_m)}{m} \sum_t |A_m(t)|^2 p(t) \to +\infty \text{ as } \frac{\|A_m\|}{m} \to 0.
\]

On the other hand,

\[
M_m \geq \sum_t |A_m(t)|^2 p(t) \geq c_0 M_m.
\]

So for any \( 0 < \epsilon < 1 \), there is a \( \delta > 0 \) such that

\[
S_{m+1}(A_m) \mathbb{I}\{\frac{\|A_m\|}{m} \leq \delta\} \geq \frac{1}{\epsilon} \frac{M_m}{m} \mathbb{I}\{\frac{\|A_m\|}{m} \leq \delta\}.
\]

So

\[
\mathbb{E}[M_m \mathbb{I}\{\frac{\|A_m\|}{m} \leq \delta\}] \leq \epsilon m \mathbb{E}[S_{m+1}(A_m)] \leq \frac{\epsilon m}{4}.
\]

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By a way,
\[
E\left[M_m I\left\{ \frac{\|\Lambda_m\|}{m} > \delta \right\} \right] \leq \left\{ E\left[M_m^2\right]\right\}^{1/2} \left\{ P\left( \frac{\|\Lambda_m\|}{m} > \delta \right) \right\}^{1/2} \\
\leq c m P^{1/2}\left( \frac{\|\Lambda_m\|}{m} > \delta \right).
\]

It follows that
\[
E\left[M_n\right] \leq n\left\{ \frac{\epsilon}{4} + c P^{1/2}\left( \frac{\|\Lambda_m\|}{m} > \delta \right) \right\} + 1.
\]

By the fact \( P\left( \frac{\|\Lambda_m\|}{m} > \delta \right) \to 0 \), we conclude that \( \frac{E[M_n]}{n} \to 0 \). (6.9) is proved. The proof of Theorem 4.1 is completed. □

**Proof of Theorem 4.2.** Note by (6.14),
\[
E[M_n^{r+1}] - E[M_n^{r+1}] \leq - 4(r + 1)E\left[ (M_{n-1} + 1)^r S_n(A_{n-1}) \right] + C_r E \left[ (M_{n-1} + 1)^r \right].
\]

Let \( m := m_n \in \{0, 1, \ldots, n\} \) be the last one for which
\[
- 4(r + 1)E\left[ (M_{m+1} + 1)^r S_{m+1}(A_m) \right] + C_r E \left[ (M_{m+1} + 1)^r \right] \geq 0. \tag{6.16}
\]

Then
\[
E[M_n^{r+1}] \leq E[M_{m+1}^{r+1}] \leq E[M_m^{r+1}] + C_r E \left[ (M_{m+1} + 1)^r \right]. \tag{6.17}
\]

Recall (6.12). Note for \( \delta > 0 \) small enough, on the event \( E = E(t) = \left\{ \frac{|\Lambda_m(t)|}{m} \leq \delta \right\}, \)
\[
S_{m+1}(A_m) \geq \frac{-g'(0)}{2} \frac{1}{m^\gamma} |\Lambda_m(t)| |p(t) \geq c_0 \frac{1}{m^\gamma} |\Lambda_m(t)|^2,
\]
and on the event \( E^c, \)
\[
S_{m+1}(A_m) \geq \left( \frac{1}{2} - g(c\delta) \right) \vee \left( \frac{1}{2} - g(-c\delta) \right) |\Lambda_m(t)| |p(t) \geq c_0 |\Lambda_m(t)|.
\]

\( C^{-1} M_n \leq \|\Lambda_n\|^2 \leq C \cdot M_n. \) Then by (6.16),
\[
E[|\Lambda_m(t)|^{2r+2} E] \leq C m^\gamma E \left[ (M_{m+1} + 1)^r S_{m+1}(A_m) \right] \leq C_r m^\gamma E \left[ (M_{m+1} + 1)^r \right],
\]
and
\[
E[|\Lambda_m(t)|^{2r+1} E^c] \leq CE \left[ (M_{m+1} + 1)^r S_{m+1}(A_m) \right] \leq C_r E \left[ (M_{m+1} + 1)^r \right].
\]

By the Hölder inequality,
\[
E[|\Lambda_m(t)|^{2r+2} E] = E \left[ |\Lambda_m(t)|^{\frac{2r+2}{p}} |\Lambda_m(t)|^{\frac{2r+2}{q}} E \right] \\
\leq (E \left[ |\Lambda_m(t)|^{2r+1} E^c \right])^{1/p} \left( E \left[ |\Lambda_m(t)|^{2r+1+q} E^c \right] \right)^{1/q} \\
\leq C_r \left( E \left[ (M_{m+1} + 1)^r \right] \right)^{1/p} \left( E \left[ M_m^{r+\frac{1}{2}+\frac{1}{2}q} \right] \right)^{1/q} \\
\leq C_r \left( E \left[ (M_{m+1} + 1)^r \right] \right)^{1/p} \left( E \left[ M_m^{2r+1+q} \right] \right)^{1/2q},
\]

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where \( p, q > 1 \), \( 1/p + 1/q = 1 \). It follows that
\[
\mathbb{E}[M_n^{r+1}] \leq \mathbb{E}[M_m^{r+1}] + C_r \mathbb{E}[(M_m+1)^r] \leq C_r \sum_t \mathbb{E}[\Lambda_m(t)^{2r+2}] + C_r \mathbb{E}[(M_m+1)^r]
\]
\[
\leq C_r m^{\gamma} \mathbb{E}[(M_m+1)^r] + C_r \left( \mathbb{E}[(M_m+1)^r] \right)^{1/p} \left( \mathbb{E}[M_m^{2r+1+q}] \right)^{1/2q}.
\] (6.18)

We will use the induction method to obtain the moment estimates of \( \mathbb{E}[M_n^r] \) by inducting both in \( n \) and \( r \). We assume
\[
\mathbb{E}[M_n^s] \leq C_s n^{\beta s} \text{ for all integers } n, s \geq 0,
\] (6.19)
and
\[
\mathbb{E}[M_n^r] \leq C_r n^{\alpha r} \text{ for all } n,
\] (6.20)
where \( 0 < \beta/2 < \alpha \leq \beta \leq 2 \).

Let \( q \) be an integer large enough such that
\[
\frac{\alpha r}{p} + \frac{\beta}{2q} + \frac{1}{2} = \alpha r + \frac{r(\beta - \alpha) + \beta/2}{q} + \frac{1}{2} \leq (r+1)\alpha.
\]
Then
\[
\mathbb{E}[M_m^{r+1}] \leq C_r m^{\gamma} m^{\alpha r} + C_r (m^{\alpha r})^{1/p} \left( m^{\beta(2r+1+q)} \right)^{1/2q}
\]
\[
\leq C_r \left( m^{\gamma} m^{\alpha r} + m^{\alpha(r+1)} \right).
\]
By (6.17),
\[
\mathbb{E}[M_n^{r+1}] \leq C_r \left( n^{\gamma} n^{\alpha r} + n^{\alpha(r+1)} \right) \leq C_{r+1} n^{\alpha(r+1)} \text{ for all } n,
\] (6.21)
whenever \( \alpha \geq \gamma \).

Obviously, (6.19) holds for \( \beta = 2 \) since \( M_n \leq n^2 \), and (6.20) is true for \( r = 0 \). So, by (6.21) and the induction, (6.20) holds for all integer \( r \) whenever \( \alpha > 1 \), which implies that (6.19) holds for any \( \beta \) with \( \beta \geq \gamma \) and \( \beta > 1 \). Repeating the above procedure \( i \) times concludes that (6.19) holds for any \( \beta \) with \( \beta \geq \gamma \) and \( \beta > 1/2^{i-1} \). Stooping the procedure when \( 1/2^{i-1} < \gamma \), we conclude that
\[
EM_n^r \leq C_r n^{\gamma r} \text{ for all integers } n \text{ and } r.
\]

(4.10) is proved. By (4.10), for any \( \epsilon, \delta > 0 \),
\[
\sum_n P(M_n \geq \delta n^{\gamma r+\epsilon}) \leq \sum_n \frac{EM_n^Q}{\delta^Q n^{\gamma r+Q}} \leq C \leq \sum n^{-Q} \epsilon \epsilon \leq \infty
\]
when \( Q > 1/\epsilon \). By the Borel-Cantelli lemma, (4.11) is proved. And so, (i)-(iii) follows by Proposition 6.1.
Finally, we consider the selection bias. Note
\[
\left| \frac{1}{2} - g_{m+1}(4\Lambda_m(t)) \right| = -4g'(0)\frac{\Lambda_m(t)}{m^\gamma} + 4\theta_m(t)\frac{\Lambda_m(t)}{m^\gamma}, \tag{6.22}
\]
where
\[
\theta_m(t) = \left| \frac{1}{2} - g\left( \frac{4\Lambda_m(t)}{m^\gamma} \right) \right| + 4g'(0)
\]
is bounded and converges to 0 in probability due to the fact that \(0 \leq g(x) \leq 1\), \(g'(0)\) is finite and \(\frac{\Lambda_m(t)}{m^\gamma} \to 0\) in probability. So, \(E\theta_m(t)^2 = o(1)\) as \(m \to \infty\). By the Cauchy-Schwartz inequality,
\[
E \left| \theta_m(t) \frac{\Lambda_m(t)}{m^\gamma} \right| = o(1) \cdot \left( E \left| \frac{\Lambda_m(t)}{m^\gamma} \right|^2 \right)^{1/2}.
\]
It follows that
\[
E[p_m \vee (1 - p_m)] = \frac{1}{2} + \sum_t p(t)E\left( \frac{1}{2} - g_m(\Lambda_{m-1}(t)) \right)
\]
\[
= \frac{1}{2} + \sum_t p(t)E\left(-4g'(0)\frac{\Lambda_{m-1}(t)}{(m-1)^\gamma}\right) + \sum_t p(t)o(1) \left( E \left| \frac{\Lambda_{m-1}(t)}{(m-1)^\gamma} \right|^2 \right)^{1/2}
\]
\[
= \frac{1}{2} - 4g'(0)\sum_t p(t)\frac{E[\Lambda_{m-1}(t)]}{(m-1)^\gamma} + o\left( \frac{1}{(m-1)^{\gamma/2}} \right), \tag{6.23}
\]
where, the last equality are due to the fact that \(\|\Lambda_m\| \leq CM_m^{1/2} = O(m^{\gamma/2})\) in any \(L_r\).
Hence
\[
SB_n = \frac{1}{n} \sum_{m=1}^n E[p_m \vee (1 - p_m)]
\]
\[
= \frac{1}{2} - 4g'(0)\frac{1}{n} \sum_{m=1}^n \sum_t p(t)\frac{E[\Lambda_m(t)]}{m^\gamma} + o\left( \frac{1}{n^{\gamma/2}} \right)
\]
\[
= \frac{1}{2} + a_n n^{-\gamma/2} + o\left( n^{-\gamma/2} \right).
\]

Next, we show \(a_n\) is bounded from zero and infinity. From (6.15), we conclude that
\[
0 = \lim_{n \to \infty} \frac{E[M_{n+1}]}{n} = -4 \lim_{n \to \infty} \frac{1}{n} \sum_{m=1}^n E[S_{m+1}(\Lambda_m)] + 1.
\]
By noting (6.22), similar to (6.23) we have
\[
E[S_{m+1}(\Lambda_m)] = -g'(0)\sum_t p(t)\frac{E[\Lambda_m(t)]^2}{m^\gamma} + o(1) \sum_t p(t)\frac{E[\Lambda_m(t)]^2}{m^\gamma}
\]
\[
= -g'(0)\sum_t p(t)\frac{E[\Lambda_m(t)]^2}{m^\gamma} + o(1).
\]
It follows that
\[
\lim_{n \to \infty} \frac{1}{n} \sum_{m=1}^{n} \sum_{t} p(t) \frac{E|\Lambda_m(t)|^2}{m^{\gamma/2}} = \frac{1}{16g'(0)}.
\]

Regarding the summation of the right hand above as \(E|Z_n|^2\) of a random variable \(Z_n = \frac{\Lambda_{\tau}}{\tau^{\gamma/2}}\), where \(P(\tau = m) = \frac{1}{n}\), \(P(\kappa = t) = p(t)\), then
\[
\frac{1}{n} \sum_{m=1}^{n} \sum_{t} p(t) \frac{E|\Lambda_m(t)|}{m^{\gamma/2}} = E|Z_n| \leq (E|Z_n|^2)^{1/2} \sim \frac{1}{4\sqrt{-g'(0)}}.
\]

Hence
\[
a_n n^{-\gamma/2} = -4g'(0) \frac{1}{n} \sum_{m=1}^{n} mE|Z_m| - (m-1)E|Z_{m-1}| \leq -4g'(0) \frac{1}{n} \left[ nE|Z_n| \sum_{m=1}^{n-1} mE|Z_m| \left( \frac{1}{m^{\gamma}} - \frac{1}{(m+1)^{\gamma/2}} \right) \right] \sim 2\sqrt{|g'(0)|} n^{-\gamma/2}.
\]

Hence \(\limsup_{n \to \infty} a_n \leq 2\sqrt{|g'(0)|}/(2 - \gamma)\).

On the other hand,
\[
E|Z_n|^3 = \frac{1}{n} \sum_{m=1}^{n} \sum_{t} p(t) \frac{E|\Lambda_m(t)|^3}{m^{3\gamma/2}} = O(1)
\]
and \(EZ_n^2 \leq (E|Z_n|)^{1/2}(E|Z_n|^3)^{1/2}\). It follows that
\[
\liminf_{n \to \infty} a_n = \liminf_{n \to \infty} \left[ -4g'(0) \right] \liminf_{n \to \infty} E|Z_n| \geq \liminf_{n \to \infty} \left[ -4g'(0) \right] \left( \frac{EZ_n^2}{EZ_n^3} \right)^2 \geq c_0 > 0
\]
by (6.24). (4.12) is proved. To show the constant \(c_0\) does not depend on \(\gamma\). It is sufficient to show that for any integer \(r \geq 0\), there is a constant \(A_r\) which does not depend on \(\gamma\) such that
\[
\limsup_{n \to \infty} \frac{EM_n^r}{n^{r/\gamma}} \leq A_r.
\]
We use the induction, assume (6.25) holds for \(r\). We now consider \(r + 1\). Let \(m = m_n\) such
that (6.16) and (6.17) hold. Similar to (6.23), we have

\[
\frac{c_r}{4(r + 1)} E(M_m + 1)^r \geq E[(M_m + 1)^r S_{m+1}(A_m)] \\
= - 4g'(0)E \left[(M_m + 1)^r \sum_t \Lambda^2_m(t)p(t) \right] \\
+ o(1) \left[ E \left( (M_m + 1)^r \sum_t \Lambda^2_m(t)p(t) \right)^2 \right]^{1/2} \geq cm^{-\gamma}E \left[ (M_m + 1)^r M_m \right] + o(1)m^{-\gamma} \left[ EM_m^{2(r+1)} \right]^{1/2} \\
= cm^{-\gamma}E \left[ M_m^{r+1} \right] + o(1)m^{-\gamma}m^{\gamma(r+1)}. 
\]

Hence, by (6.16),

\[
E[M_n^{r+1}] \leq m^\gamma \left( \frac{C_r}{4(r + 1)c} + C_r \right) E(M_m + 1)^r + o(1)m^{\gamma(r+1)}. 
\]

It follows that

\[
\limsup_{n \to \infty} \frac{E[M_n^{r+1}]}{n^{\gamma(r+1)}} \leq \left( \frac{C_r}{4(r + 1)c} + C_r \right) A_r, 
\]

by the induction. The proof is completed. □

**Proof of the Remark 4.1.** The proof can be found in Hu and Zhang (2013). For the consistency of this paper, we give a skeleton of the proof here. The allocation function probability \( g(4\Lambda_{n-1}(t)) \) is now only a function of \( \Lambda_{n-1} \), so the Markov chain \( \Lambda_n \) is homogeneous. Note \( 0 < g(x) < 1 \) for all \( x \). The transient probability in (6.7) is always positive. So the Markov chain is irreducible. It can be verified that \( S_n(\Lambda_{n-1}) \to +\infty \) as \( M_{n-1} \to \infty \). By (6.14), it follows that there is positive constants \( b_r \) and \( c_r \) such that

\[
E[M_n^{r+1} | \mathcal{F}_{n-1}] - M_{n-1}^{r+1} \leq -(M_{n-1} + 1)^r + b_r \mathbb{I} \{M_{n-1} \leq c_r\}. 
\]

Note \( M_n = M^\ast(\Lambda_n) \) is a function of \( \Lambda_n \). The above inequality just is

\[
P_\lambda(M^\ast)^{r+1} - (M^\ast)^{r+1} \leq -(M^\ast + 1)^r + b_r \mathbb{I} \{M^\ast \leq c_r\}, 
\]

where \( (P_\lambda f) (\Lambda) = \sum_{\Lambda' \in L(\mathbb{Z}^m)} P_\lambda(\Lambda, \Lambda') f(\Lambda') \) is the transient expectation of the function \( f \), \( P_\lambda(\Lambda, \Lambda') \) is the transient probability from \( \Lambda \) to \( \Lambda' \). Then (6.26) implies that the irreducible Markov chain \( \Lambda_n \) with period 2 is positive recurrent with an invariant distribution \( \pi \) and \( \sup_n E[(M_n + 1)^r] < \infty \). In fact, write

\[
\mathbb{P}^{(n)}_\lambda(\Lambda, \Lambda') = \frac{1}{n} \sum_{m=0}^{n-1} P_\lambda^{(m)}(\Lambda, \Lambda'), 
\]
where $P^{(m)}_{\lambda}(\Lambda, \Lambda')$ is the m-step transient probability from $\Lambda$ to $\Lambda'$. (6.26) implies that for any initial distribution $\pi_0$,

$$\limsup_{n \to \infty} \pi_0 P^{(n)}_{\lambda} (M^* + 1)^r \leq b_r \limsup_{n \to \infty} \pi_0 P^{(n)}_{\lambda} I\{M^* \leq c_r\} + \limsup_{n \to \infty} \frac{\pi_0 (M^*)^{r+1}}{n}$$

$$\leq b_r \limsup_{n \to \infty} \pi_0 P^{(n)}_{\lambda} I\{M^* \leq c_r\}, \forall r > 0. \quad (6.27)$$

If the Markov-Chain is not positive recurrent, then for any $\Lambda$ and $\Lambda'$, $P^{(n)}_{\lambda}(\Lambda, \Lambda') \to 0$. So, for any $C > 0$, $\pi_0 P^{(n)}_{\lambda} I\{M^* \leq C\} \to 0$. It follows that the limit in (6.27) is zero, which is obvious a contradict. Hence $\Lambda_n$ is a positive recurrent Markov Chain with an invariant distribution $\pi$. Now, (6.27) implies

$$E_\pi [(M^* + 1)^r] = \pi P^{(n)}_{\lambda} (M^* + 1)^r \leq b_r, \forall r > 0,$$

which implies $\sup_n E[M^n_r] < \infty$ since $\frac{1}{2}(E[M_{2n}^r] + E[M_{2n+1}^r]) \to E_\pi [(M^*)^r]$. The proof is completed. □.

**Proof of Corollary 4.1.** Note $C^{-1}M_n \leq \|\Lambda_n\|^2 \leq CM_n$. By the condition (4.13), when $4|\Lambda_n(t)| \geq x_0$,

$$|g_n(4\Lambda_n(t)) - \frac{1}{2}| \geq p_0 > 0.$$

Let $E = \{4|\Lambda_m(t)| < x_0\}$. Then on $E^c$,

$$S_{m+1}(\Lambda_m) \geq c_0|\Lambda_m(t)|.$$

It follows that

$$E[|\Lambda_m(t)|^{2r+2}E] \leq C,$$

and

$$E[|\Lambda_m(t)|^{2r+1}E^c] \leq CE \left[|\Lambda_m(t)|^{2r}S_{m+1}(\Lambda_m)\right] \leq CE \left[(M_m + 1)^r S_{m+1}(\Lambda_m)\right].$$

Let $m \in \{0,1,\ldots,n\}$ satisfy (6.16) and (6.17). Then (6.18) remains true with $\gamma = 0$. The remainder proof is similar to that of (4.10) and (4.11) by repeating the induction procedure (6.19)-(6.21) $i$ times until $1/2^{i-1} < \epsilon/2$. □

**REFERENCES**

[1] Aickin, M. (2009). A Simulation study of the validity and efficiency of design-adaptive allocation to two groups in the regression situation. The International Journal of Biostatistics 5, 14.

[2] Baldi Antognini, A. (2008). A theoretical analysis of the power of biased coin designs. Journal of Statistical Planning and Inference 138, 1792-1798.
[3] Atkinson, A. C. (1982). Optimum biased coin designs for sequential clinical trials with prognostic factors. Biometrika 69, 61-67.

[4] Baldi Antognini, A. and Giovagnoli, A. (2004). A new 'biased coin design' for the sequential allocation of two treatments. Journal of the Royal Statistical Society. Series C (Applied Statistics) 53, 651-664.

[5] Begg, C. B. and Iglewicz, B. (1980). A treatment allocation procedure for sequential clinical trials. Biometrics 36, 81-90.

[6] Birkett, N. J. (1985). Adaptive allocation in randomized controlled trials. Controlled Clinical Trials 6, 146-155.

[7] Ciolino, J., Zhao, W., Martin, R., & Palesch, Y (2011). Quantifying the cost in power of ignoring continuous covariate imbalances in clinical trial randomization. Contemporary Clinical Trials 32, 250-259.

[8] Efron, B. (1971). Forcing a sequential experiment to be balanced. Biometrika 58, 403-417.

[9] Feinstein, A. R., and Landis, J. R. (1976). The role of prognostic stratification in preventing the bias permitted by random allocation of treatment. Journal of Chronic Diseases 29, 277-284.

[10] Forsythe, A. B. (1987). Validity and power of tests when groups have been balanced for prognostic factors. Computational Statistics and Data Analysis 5, 193-200.

[11] Green, S. B., and Byar, D. P. (1978). The effect of stratified randomization on size and power of statistical tests in clinical trials. Journal of Chronic Diseases 31, 445-454.

[12] Hu, Y. and Hu, F. (2012). Asymptotic properties of covariate-adaptive randomization. Annals of Statistics 40, 1794-1815.

[13] Hu, F. and Rosenberger, W. F. (2006). The Theory of Response-Adaptive Randomization in Clinical Trials. John Wiley and Sons. Wiley Series in Probability and Statistics.

[14] Hu, F. and Zhang L.-X. (2004). Asymptotic properties of doubly adaptive biased coin designs for multitreatment clinical trials. The Annals of Statistics 32, 268-301.

[15] Hu, F. and Zhang, L.-X. (2013). On the theory of covariate-adaptive designs. Manuscript. ArXiv:2004.02994

[16] Hu, F., Zhang, L.-X. and He, X. (2009), Efficient randomized adaptive designs. The Annals of Statistics 37, 2543-2560.

[17] Jing, B. Y., Shao, Q. M. and Wang, Q.Y. (2003). Self-normalized Cramér-type large deviations for independent random variables. Annals of Probability 31, 2167-2215.

[18] Ma, W. Hu, F. and Zhang, L.-X. (2015) Testing hypotheses of covariate-adaptive randomized clinical trials. Journal of the American Statistical Association 110, 669-680.

[19] Ma, W., Li, P. and Hu, F. (2021) Kernel Based Covariate Adaptive Randomization Procedures and Their Properties. Manuscript.

[20] McEntegart, D. J. (2003). The pursuit of balance using stratified and dynamic randomization techniques: An overview. Drug Information Journal 37, 293-308.

[21] Meyn, S. P. and Tweedie, R. L. (1993). Markov chains and stochastic stability. Springer-Verlag, London.
[22] Pocock, S. J. and Simon, R. (1975). Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* **31**, 103-115.

[23] Rosenberger, W. F. and Lachin, J. M. (2002). *Randomization in Clinical Trials: Theory and Practice*. John Wiley and Sons. Wiley Series in Probability and Statistics.

[24] Rosenberger, W. F. and Sverdlov, O. (2008). Handling covariates in the design of clinical trials. *Statistical Science* **23**, 404-419.

[25] Scott, N. W., McPherson, G. C., Ramsay, C. R. and Campbell, M. K. (2002). The method of minimization for allocation to clinical trials: A review. *Control Clinical Trials* **23**, 662-674.

[26] Shao, J., Yu, X. and Zhong, B. (2010). A theory for testing hypotheses under covariate-adaptive randomization. *Biometrika* **97**, 347-360.

[27] Simon, R. (1979). Restricted randomization designs in clinical trials. *Biometrics* **35**, 503-512.

[28] Smith, R. L. (1984). Properties of biased coin designs in sequential clinical trials. *Annals of Statistics* **12**, 1018-1034.

[29] Taves, D. R. (1974). Minimization: A new method of assigning patients to treatment and control groups. *Clinical Pharmacology and Therapeutics* **15**, 443-453.

[30] Taves, D. R. (2010). The use of minimization in clinical trials. *Contemporary Clinical Trials* **31**, 180-184.

[31] Toorawa, R., Adena, M., Donovan, M., Jones, S. and Conlon, J. (2009). Use of simulation to compare the performance of minimization with stratified blocked randomization. *Pharmaceutical Statistics* **8**, 264-278.

[32] Tu, D., Shalay, K. and Pater, J. (2000) Adjustment of treatment effect for covariates in clinical trials: statistical and regulatory issues. *Drug Information Journal* **31**, 180-184.

[33] Tymofyeyev, Y., Rosenberger, W.F. and Hu, F. (2007). Implementing optimal allocation in sequential binary response experiments. *Journal of the American Statistical Association* **102**, 224-234.

[34] Wei, L. J. (1978). The adaptive biased coin design for sequential experiments. *Annals of Statistics*, 6, 92-100

[35] Zelen, M. (1974). The randomization and stratification of patients to clinical trials. *Journal of Chronic Diseases* **27**, 365-375.

[36] Zhang, L.X., Hu, F., Cheung. S.H. and Chan, W.S. (2007). Asymptotic properties of covariate-adjusted adaptive designs. *Annals of Statistics* **35**, 1166-1182.

[37] Zelen, M. (1974). The randomization and stratification of patients to clinical trials. *Journal of Chronic Diseases* **27**, 365-375.