Pairwise Sequential Randomization and Its Properties

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SUMMARY: In comparative studies, such as in causal inference and clinical trials, balancing important covariates is often one of the most important concerns for both efficient and credible comparison. However, chance imbalance still exists in many randomized experiments. This phenomenon of covariate imbalance becomes much more serious as the number of covariates \( p \) increases. To address this issue, we introduce a new randomization procedure, called pairwise sequential randomization (PSR). The proposed method allocates the units sequentially and adaptively, using information on the current level of imbalance and the incoming unit’s covariate. With a large number of covariates or a large number of units, the proposed method shows substantial advantages over the traditional methods in terms of the covariate balance, estimation accuracy, and computational time, making it an ideal technique in the era of big data. The proposed method attains the optimal covariate balance, in the sense that the estimated treatment effect under the proposed method attains its minimum variance asymptotically. Also the proposed method is widely applicable in both causal inference and clinical trials. Numerical studies and real data analysis provide further evidence of the advantages of the proposed method.

KEYWORDS: Asymptotic variance; Big Data; Causal Inference; Clinical trial; Experiment design; Treatment effect.
1 Introduction

Randomization is the foundation for the treatment effect evaluation. However, traditional randomization methods often generate unsatisfactory configurations with unbalanced prognostic covariates; this issue has been extensively discussed ever since Fisher (1926) noted: “Most of experimenters on carrying out a random assignment of plots will be shocked to find out how far from equally the plots distribute themselves.” The advantages of balanced covariates are at least threefold (Hu et al., 2014). First, covariate balance improves the efficiency of estimation for the treatment effect. Second, it increases the interpretability of the estimated treatment effect by making the units in the treatment groups more comparable, thereby enhancing the credibility of the analysis. Third, it makes the analysis more robust against model misspecification. Consequently, covariate imbalance can significantly undermine the validity of subsequent analysis. In the absence of covariate balance, various problems must be addressed before a valid conclusion can be drawn.

In causal inference and clinical studies, if a significant imbalance exists, any inferences regarding the treatment effect will be inaccurate, and any claims about the treatment effect will need to rely on unverifiable assumptions (Lock, 2011). Researchers must assess the balance in the covariate distribution before estimating the causal effect. Although some ex-post adjustments, such as regression (Freedman, 2008) and subsample selection using matching or trimming based on propensity scores (Imbens and Rubin, 2015), can cope with such an imbalance, they are much less efficient than achieving an ex-ante balance from the start (Bruhn and McKenzie, 2008). In addition, these adjustments often rely on at least a nearly correct model, which can be difficult to test (Cochran, 1965; Cochran and Rubin, 1973). Rubin (2008) explained why the greatest possible efforts should be made during the design phase of an experiment rather than during the analysis stage, at which point the researcher has the potential...
to bias the results (Lock, 2011; Imbens and Rubin, 2015).

More recently, covariate balance has attracted growing interest in the field of crowdsourced-internet experimentation (Horton et al., 2011; Chandler and Kapelner, 2013; Kapelner and Krieger, 2014). Researchers increasingly recruit workers from online labor markets into their experiments, such as by asking them to label tumor cells in images. Because of the nature of the recruiting process, a large number of workers with many covariates (e.g., 2500 workers in Chandler and Kapelner (2013)), typically are enrolled in such studies, which consequently pose challenges for traditional randomization methods.

Furthermore, the phenomenon of covariate imbalance is exacerbated as the number of covariates \( p \) and the sample size \( n \) increase, which is nearly ubiquitous in the era of big data. For example, suppose that the probability of one particular covariate being unbalanced is 5%. For a study with 10 independent covariates, the chance of at least one covariate exhibiting imbalance is \( 1 - (1 - 5\%)^{10} = 40\% \). Meanwhile, some may argue that imbalance tends to be milder as the sample size increases. However, as the sample size increases, even though the difference in covariate means between groups becomes smaller, however, at the same rate, confidence intervals and hypothesis testing are becoming more sensitive to small differences in outcome variables which can be affected by the small imbalance in covariates (Morgan and Rubin, 2012).

In the framework of causal inference, Morgan and Rubin (2012) have proposed rerandomization (RR). They propose to repeatedly randomize the units into treatment groups using complete randomization (CR), until certain the balance criterion is satisfied, e.g., \( M < a \), where \( M \) is the Mahalanobis distance between the sample means across different treatment groups and \( a > 0 \) is a threshold.

\[
M = (\bar{x}_1 - \bar{x}_2)^T[\text{cov}(\bar{x}_1 - \bar{x}_2)]^{-1}(\bar{x}_1 - \bar{x}_2)
\]

\[
\propto (\bar{x}_1 - \bar{x}_2)^T\text{cov}(x)^{-1}(\bar{x}_1 - \bar{x}_2),
\]
where \( \bar{x}_1 \in \mathbb{R}^p \) and \( \bar{x}_2 \in \mathbb{R}^p \) are the sample means for two treatment groups, \( \text{cov}(x) \in \mathbb{R}^{p \times p} \) is the covariance matrix of the covariate. They have also assumed fixed equal numbers of units in two treatment groups and demonstrated various desirable properties under rerandomization.

Although rerandomization works well in the case of a few covariates, it is incapable of scaling up to address massive amounts of data. For example, as the number of covariates increases, the probability of acceptance, \( p_a = P(M < a) \), of each complete randomization decreases drastically, causing the rerandomization procedure to remain in loop for a long time. To compromise the computational burden, one can increase \( a \), which unavoidably leads poorer covariate imbalance.

In clinical trials, to balance important covariates, most existing methods such as stratified permuted block design, minimization methods (Taves, 1974; Pocock and Simon, 1975; Hu and Hu, 2012) and CA-BCD (Antognini and Zagoraiou, 2011) are only for discrete covariates. Discretizing continuous covariates is often less efficient and changes the nature of the covariates. A variety of methods for balancing continuous covariates have been proposed in the literature: the methods based on ranks (Ciolino et al., 2011; Hoehler, 1987; Stigsby and Taves, 2010); based on p-value (Frane, 1998); based on Kullback-Leibler divergence (KLD); based on empirical cumulative distribution (Lin and Su, 2012); based on kernel density (Ma and Hu, 2013), etc. However, the performance of those procedures was usually evaluated by simulation studies, their theoretical properties are not well investigated in literature. Also these methods are usually applicable for only a few covariates.

In this article, we propose a new approach — pairwise sequential randomization (PSR) — to generate a more balanced treatment allocation and thus to improve the subsequent analysis for both causal inference and clinical trials settings. Unlike rerandomization or complete randomization, in which all units are allocated independently,
we allocate units adaptively and sequentially by assigning one randomly chosen pair of units at a time. For each pair of units, using their covariate information and the existing level of imbalance of the previously allocated units, we adjust the probability with which the pair is allocated to treatment groups to avoid incidental covariate imbalance. In this way, we are able to produce a much more balanced allocation of units. The properties of the PSR procedure are illustrated both theoretically and numerically.

The advantages of the proposed method are: (i) For cases with a large number of covariates or a large number of units, the proposed method exhibits superior performance, with more balanced randomization and less computational time; (ii) The PSR procedure attains the optimal covariate balance, in the sense that the estimated treatment effect under the proposed method attains its minimum variance asymptotically; and (iii) The proposed procedure is designed for directly randomizing units with both continuous and discrete covariates. Therefore the PSR procedure is widely applicable for balancing many important covariates in comparative studies.

This article is organized as follows. We introduce the proposed method and investigate its theoretical properties in Section 2. We demonstrate its advantages in the treatment effect estimation and present theoretical properties in Section 3. Numerical studies to verify the finite sample properties of the proposed method are shown in Section 4. We further present an real data example to demonstrate the superior performance of our method in Section 5. Finally, we conclude with a discussion in Section 6 and relegate the outlining of proofs to Section 7.
2 Pairwise Sequential Randomization

2.1 Proposed Method and Its Properties

Suppose that $n$ units (patients) are to be assigned to two treatment groups. Let $T_i$ be the assignment of the $i$-th unit, i.e., $T_i = 1$ for treatment 1 and $T_i = 0$ for treatment 2. Consider $p$ continuous covariates for each unit. Let $\mathbf{x}_i = (x_{i1}, \ldots, x_{ip})^T \in \mathbb{R}^p$ represent the covariates of the $i$-th unit. Suppose all units are available for assignment at the beginning of the randomization. We choose the Mahalanobis distance as the covariate imbalance measure, $M(n) = (\bar{x}_1 - \bar{x}_2)^T \text{cov}(\bar{x}_1 - \bar{x}_2)^{-1}(\bar{x}_1 - \bar{x}_2) \propto (\bar{x}_1 - \bar{x}_2)^T \text{cov}(\bar{x})^{-1}(\bar{x}_1 - \bar{x}_2)$. This Mahalanobis distance functions as a measure of the covariate balance throughout this article. A smaller value of $M(n)$ indicates a better covariate balance. To assign units to treatment groups, we propose the following procedure, pairwise sequential randomization (PSR).

1. Arrange all $n$ units randomly into a sequence $\mathbf{x}_1, \ldots, \mathbf{x}_n$.
2. Assign the first two units with $T_1 = 1$ and $T_2 = 0$.
3. Suppose that $2i$ units have been assigned to treatment groups, for the $(2i + 1)$-th and $(2i + 2)$-th units:
   - (3a) If the $(2i + 1)$-th unit is assigned to treatment 1 and the $(2i + 2)$-th unit to treatment 2, then we can calculate the “potential” Mahalanobis distance, $M_1(2i + 2)$, between the updated treatment groups with $2i + 2$ units.
   - (3b) Similarly, if the $(2i + 1)$-th unit is assigned to treatment 2 and the $(2i + 2)$-th unit to treatment 1, then we can calculate the other “potential” Mahalanobis distance, $M_2(2i + 2)$.
4. Assign the $(2i + 1)$-th unit to treatment groups according to the following prob-
abilities:

\[
P(T_{2i+1} = 1|x_{2i}, ..., x_1, T_{2i}, ..., T_1) = \begin{cases} 
q & \text{if } M_1(2i + 2) < M_2(2i + 2), \\
1 - q & \text{if } M_1(2i + 2) > M_2(2i + 2), \\
0.5 & \text{if } M_1(2i + 2) = M_2(2i + 2), 
\end{cases}
\]

where 0.5 < q < 1, and assign \( T_{2i+2} = 1 - T_{2i+1} \) to maintain the equal proportions.

(5) Repeat the last two steps until all units are assigned. If \( n \) is odd, assign the last unit to two treatments with equal probabilities.

There are several advantages for adopting Mahalanobis distance as the imbalance measure. First, it is an affinely invariant imbalance measure, which is appealing especially for multivariate data. It is an overall imbalance measure which standardizes and aggregates each covariate imbalance information. A low Mahalanobis distance guarantees low imbalance levels in all covariates. Note that when the covariance matrix is identity matrix, the Mahalanobis distance essentially becomes the L2 norm of the imbalance vector, which is a traditional measure of covariate imbalance in clinical trials. In addition, using Mahalanobis distance as imbalance measure, various desirable statistical properties can be obtained, such as the reduction in variance of the estimated treatment effect and optimal asymptotic variance for treatment effect estimation. In practice, the covariance matrix is replaced with the sample covariance matrix.

The value of \( q \) is set to 0.75 throughout this article. Different values of \( q \) will not affect the theoretical results presented in this article. For a further discussion of \( q \), please see Hu and Hu (2012). Note that the sequence in which the units are allocated is not unique. Rather, there are \( n! \) different possible sequences, but their performances are similar, especially when \( n \) is large.

We now study the asymptotic properties of the Mahalanobis distance, \( M(n) \), obtained using the proposed method.
Theorem 2.1. Under the pairwise sequential randomization (PSR), suppose that the covariate $x_i$, $i = 1, ..., n$, is independent and identically distributed as a multivariate normal distribution with zero mean; then we have $M(n) = O_p(n^{-1})$.

Note that the Mahalanobis distance that is obtained through the complete randomization, $M_{CR}(n)$, has a stationary distribution of a Chi-square distribution with $p$ degrees of freedom (regardless of $n$), i.e., $M_{CR}(n) \sim \chi^2_{df=p}$. Therefore, the Mahalanobis distance obtained through rerandomization, $M_{RR}(n)$, has a conditional Chi-square distribution, i.e., $M_{RR}(n) \sim \chi^2_{df=p} | \chi^2_{df=p} < a$. Hence, as the sample size $n$ increases, the proposed method reveals a greater advantage over both rerandomization and complete randomization, because $M(n)$ converges to 0 at the rate of $1/n$. That is, the more units included, the better the covariate balance becomes.

Moreover, as the number of covariates $p$ increases, the distribution of $M_{CR}(n)$ becomes flatter, which implies poorer allocation in terms of covariate balance. As a consequence, rerandomization has a lower probability of acceptance, $p_a = P(M_{CR}(n) < a)$. Therefore, the advantage of the proposed method also becomes more significant as $p$ increases, because the $M(n)$ obtained using the proposed method converges to 0 regardless of the magnitude of $p$.

In Figure 1, we conduct a simple simulation by plotting the sequences of Mahalanobis distance as more units are assigned using the proposed method. As we can see, the trajectories converges to zero approximately at the speed of $1/n$. Extensive simulation studies can be found in Section 4.

2.2 Clinical Trial Settings

The proposed algorithm can be easily adopted in clinical trial studies where patients are sequentially enrolled and the treatment is conducted after the individual enrollment. Since the units come in a natural order, we do not need Step 1 anymore. In order to
Figure 1: Convergence of $M(n)$ using the proposed method. Solid curves are fitted trends $M = c/n$ with $c > 0$.

have a valid covariance matrix estimate, we also need to increase the burn in number in Step 2 to be larger than $p$. For example, we can implement the first $m$ pairs ($2m > p$) by simple randomization (in each pair, the assignment is (1, 0) or (0, 1) with half probability). For the $(i + 1)$th pair (here $i > m$), $2i$ units have already been enrolled in study. In Step 3, one calculate calculate the potential Mahalanobis distance, we only need to use the sample covariance matrix of $2i$ units, $\hat{\Sigma}_{2i}$. Other steps are the same.

In literature, continuous covariates are usually discretized in order to be included in the above balancing procedures. However, breakdown of a continuous covariate into subcategories means increased effort and loss of information as pointed in Scott et al. (2002). Ciolino et al. (2011) further 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.” It is important to note that the proposed method is designed for directly randomizing units with continuous covariates. Also the PSR procedure works well for large $p$ and $n$, while the
other methods only work for small $p$.

Through simulation studies (Section 4), we can show that the above scenarios yield similar results in terms of covariate balance especially when sample size is large.

## 3 Treatment Effect Estimation

### 3.1 Framework

After allocating the units to treatment groups, we are interested in estimating the treatment effect from the outcome variable $y_i$ obtained under the treatment $T_i$ for $i = 1, ..., n$. A natural choice is

$$\hat{\tau} = \frac{\sum_{i=1}^{n} T_i y_i}{\sum_{i=1}^{n} T_i} - \frac{\sum_{i=1}^{n} (1 - T_i) y_i}{\sum_{i=1}^{n} (1 - T_i)},$$

which is simply the difference in the sample means of $y_i$ for the different groups. One problem with $\hat{\tau}$ is that if there is an imbalance in the covariates, it will affect the accuracy of $\hat{\tau}$. For example, if we estimate the effect of a drug when the treatment 1 group contains mostly males and the treatment 2 group contains mostly females, then the estimated treatment effect $\hat{\tau}$ will not be able to exclude the effect of gender.

To adjust for such an imbalance, we can use linear regression to estimate the treatment effect. That is, conditional on the treatment assignment $T_i$, each outcome variable is assumed to follow the model below:

$$y_i = \mu_1 T_i + \mu_2 (1 - T_i) + \beta_1 x_{i1} + ... + \beta_p x_{ip} + \epsilon_i,$$

where $\mu_1$ and $\mu_2$ are the main effects of treatments 1 and 2, respectively, and $\mu_1 - \mu_2 = \tau$ is the treatment effect. Furthermore, $\beta_j$ represents the covariate effect, and $\epsilon_i$ is an independent and identically distributed random error with zero mean and constant variance $\sigma^2_{\epsilon}$, and is independent of $x_i = (x_{i1}, ..., x_{ip})^T$. All covariates $x_i, i = 1, ..., n$, are independent and identically distributed.
Let us define

\[
Y = \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix}, \quad X = \begin{bmatrix} x^T_1 \\ x^T_2 \\ \vdots \\ x^T_n \end{bmatrix} = \begin{bmatrix} x_{11} & \cdots & x_{1p} \\ x_{21} & \cdots & x_{2p} \\ \vdots & \ddots & \vdots \\ x_{n1} & \cdots & x_{np} \end{bmatrix}, \quad T = \begin{bmatrix} T_1 \\ T_2 \\ \vdots \\ T_n \end{bmatrix}, \quad \tilde{T} = \begin{bmatrix} T_1 & 1 - T_1 \\ T_2 & 1 - T_2 \\ \vdots & \vdots \\ T_n & 1 - T_n \end{bmatrix},
\]

\[
\tilde{X} = [\tilde{T}; X], \quad \beta = (\beta_1, \ldots, \beta_p)^T, \quad \beta^* = (\mu_1, \mu_2, \beta_1, \ldots, \beta_p)^T.
\]

Then, we can obtain the ordinary least squares estimate of \(\beta^*\):

\[
\hat{\beta}^* = (\tilde{X}^T \tilde{X})^{-1} \tilde{X}^T Y.
\]

Let us consider \(L = (1, -1, 0, \ldots, 0)^T\), a \((p + 2)\)-dimensional vector. We define

\[
\tilde{\tau} = L^T \hat{\beta}^*,
\]

which is another estimate of the treatment effect that is adjusted for the imbalance in the covariates. Note that if \(\tilde{X}\) does not include any covariates, i.e., \(\tilde{X} = \tilde{T}\), then the regression model is \(y_i = \mu_1 T_i + \mu_2 (1 - T_i) + \epsilon_i\), and \(\tilde{\tau}\) becomes \(\hat{\tau}\) in Equation (1), which is the estimated treatment effect without adjusting for the imbalance in the covariates.

In the next section, we study the properties of \(\hat{\tau}\) and \(\tilde{\tau}\) under our proposed method (i.e., \(\hat{\tau}_{PSR}\) and \(\tilde{\tau}_{PSR}\)) and under complete other randomization methods such as CR and RR.

### 3.2 Theoretical Properties

Under complete randomization and rerandomization, \(\hat{\tau}_{CR}\) and \(\hat{\tau}_{RR}\) are unbiased. We can similarly show the consistency and asymptotic normality of \(\hat{\tau}_{PSR}\) and \(\tilde{\tau}_{PSR}\) for the proposed method. Before introducing our key properties, we first show the following properties:
Theorem 3.1. Under the pairwise sequential randomization (PSR), suppose that the covariate \( x_i \), \( i = 1, \ldots, n \), is independent and identically distributed as a multivariate normal distribution with zero mean; then we have

\[
\operatorname{cov}[\bar{x}_1 - \bar{x}_2 | X, \text{PSR}] = u_n \operatorname{cov}[\bar{x}_1 - \bar{x}_2 | X, \text{CR}],
\]

where \( u_n = \mathbb{E}[M(n)/p | X, \text{PSR}] \) and \( u_n = O(n^{-1}) \).

In randomized experiments, the emphasis typically is placed on the percent reduction in variance (PRIV) defined by Morgan and Rubin (2012). This quantity represents the percentage by which the randomization method reduces the variance of the differences in the means calculated for the different treatment groups. A higher value of the PRIV indicates that the means are closer to each other. Consider the PRIV for the \( j \)-th covariate,

\[
100 \left( \frac{\operatorname{Var}[\bar{x}_{j,1} - \bar{x}_{j,2} | X, \text{CR}] - \operatorname{Var}[\bar{x}_{j,1} - \bar{x}_{j,2} | X, \text{PSR}]}{\operatorname{Var}[\bar{x}_{j,1} - \bar{x}_{j,2} | X, \text{CR}] \right),
\]

where \( \bar{x}_{j,1} \) and \( \bar{x}_{j,2} \) are the \( j \)-th elements of \( \bar{x}_1 \) and \( \bar{x}_2 \). According to Theorem 3.1, the PRIV of each covariate is 100(1 – \( u_n \))% under the proposed method. Recall that the PRIV of rerandomization for each covariate is 100(1 – \( v_a \))% where \( v_a > 0 \) is a function of \( a \). In contrast, for the proposed method, \( \text{PRIV}_{PSR} \to 100\% \) as \( n \to \infty \), which implies that, as the sample size increases, the covariate imbalance reaches the minimum level. This is particularly useful when the covariates and outcome are correlated, because in this case, the proposed method will in turn improve the precision of the estimation of the treatment effect, as detailed in the following theorem.

Theorem 3.2. Under the pairwise sequential randomization (PSR), suppose that the outcome variable \( y_i \) and the covariate \( x_i \) are normally distributed and that the treatment effect is additive; then, the percent reduction in variance (PRIV) of \( \hat{\tau}_{PSR} \) is

\[
100(1 – u_n)R^2,
\]

where \( R^2 \) is the squared multiple correlation between \( y_i \) and \( x_i \) within the treatment groups, and \( u_n = O(n^{-1}) \).
Figure 2: The percent reductions in variance of the estimated treatment effect under the proposed method, $\hat{\tau}_{PSR}$, and under rerandomization, $\hat{\tau}_{RR}$, for various sample sizes and numbers of covariates. Panel (a): proposed method. Panel (b): rerandomization.

Recall that the PRIV of $\hat{\tau}_{RR}$ is $100(1 - v_a)R^2$ (Morgan and Rubin, 2012), which is a constant and does not depend on the sample size. In contrast, the PRIV of $\hat{\tau}_{PSR}$ is $100(1 - u_n)R^2$ and converges to $100R^2$ as the sample size $n \to \infty$. In fact, the PRIV of $\hat{\tau}_{PSR}$ is simply the PRIV of the covariates scaled by $R^2$. We further plot the PRIVs of $\hat{\tau}_{PSR}$ and of $\hat{\tau}_{RR}$ (with a fixed acceptance probability of $p_a = 0.05$) in Figure 2. Note that we let $R^2 = 1$ in both figures only for illustrative purposes (as in Morgan and Rubin (2012)). It is evident that as $n$ increases, at each value of $p$, the PRIV of $\hat{\tau}_{PSR}$ increases to 100%. However, the PRIV of $\hat{\tau}_{RR}$ at a given $p$ does not vary with different $n$. The advantage of the proposed method over rerandomization is clear, especially for large $n$ and large $p$.

Meanwhile, the percent reduction in variance due to the adjustment via linear regression in complete randomization is $100[(1 + M_{CR}(n)/n)R^2 - M_{CR}(n)/n]$ (Cox, 1982), which converges to $100R^2$ as $n \to \infty$. Therefore, we conclude that the proposed
method can reduce the asymptotic variance to the minimum level.

In addition, if we further assume that the outcome variable \( y_i \) truly follows a linear regression model, we can show that \( \hat{\tau}_{PSR} \) achieves the optimal precision even without adjusting for the imbalance in the covariates using linear regression. That is,

**Theorem 3.3 (Optimal precision).** Suppose that the outcome variable \( y_i \) follows the linear regression model in Equation (2) and that we estimate the treatment effect under the proposed method and under complete randomization; then, we have

\[
\sqrt{n}(\hat{\tau}_{PSR} - (\mu_1 - \mu_2)) \overset{D}{\to} N(0, V_1),
\]

\[
\sqrt{n}(\tilde{\tau}_{PSR} - (\mu_1 - \mu_2)) \overset{D}{\to} N(0, V_2),
\]

\[
\sqrt{n}(\tilde{\tau}_{CR} - (\mu_1 - \mu_2)) \overset{D}{\to} N(0, V_3),
\]

\[
\sqrt{n}(\hat{\tau}_{CR} - (\mu_1 - \mu_2)) \overset{D}{\to} N(0, V_4),
\]

where \( 4\sigma^2 = V_1 = V_2 = V_3 < V_4 \).

This theorem implies that under the proposed method, the precision of the estimated treatment effect obtained using a simple sample mean difference, \( \hat{\tau}_{PSR} \), is the same as the precision of the estimate obtained through a linear regression which adjusts for the covariate imbalance, \( \tilde{\tau}_{PSR} \). This suggests that the regression adjustment would not be necessary under the proposed method. In other words, the proposed method can balance the covariates so well that, asymptotically, the simple sample mean difference \( \hat{\tau}_{PSR} \) is just as good as the linear-regression-adjusted estimate \( \tilde{\tau}_{PSR} \).

Furthermore, the theorem also implies that the precision of \( \hat{\tau}_{PSR} \) is the same as the precision of the estimated treatment effect obtained from a linear regression under complete randomization, \( \tilde{\tau}_{CR} \), which is considered optimal. Therefore, we conclude that the \( \hat{\tau}_{PSR} \) attains optimal precision. Although \( \tilde{\tau}_{CR} \) and \( \hat{\tau}_{PSR} \) have the same precision, it is worth noting that to calculate \( \tilde{\tau}_{CR} \), it is necessary to estimate all regression
coefficients $\beta^*$, whereas $\hat{\tau}_{PSR}$ is simply the sample mean difference and does not require the estimation of any additional coefficients.

Similarly, we present the properties of $\hat{\tau}_{RR}$ and $\tilde{\tau}_{RR}$ for comparison. Note that all properties are derived under the proposed framework which is different from the framework in Morgan and Rubin (2012).

**Corollary 3.4.** Under the same assumptions in Theorem 3.3, suppose that we estimate the treatment effect under the rerandomization; then, we have

$$\sqrt{n}(\tilde{\tau}_{RR} - (\mu_1 - \mu_2)) \overset{D}{\to} N(0, V_5),$$

$$\sqrt{n}(\hat{\tau}_{RR} - (\mu_1 - \mu_2)) \overset{D}{\to} N(0, V_6),$$

where $4\sigma^2 = V_1 = V_2 = V_3 = V_5 < V_6 < V_4$.

From the theorem above, we conclude that rerandomization cannot achieve the optimal precision in contrast to the proposed method. It cannot completely remove the covariate imbalance either. In Table 1, we summarize the relationships of the asymptotic variances of the different estimates presented by this article.

### 3.3 Computational Advantage

The previous section clearly demonstrates the advantages of the proposed method. A natural question is whether we can also let $v_a \to 0$ in the rerandomization to improve its performance to match that of the proposed method (because rerandomization allows researchers to increase the power of the analysis at the expense of computational time (Morgan and Rubin, 2012)). However, this option is extremely computationally expensive in many cases, as illustrated below.

**Theorem 3.5.** For rerandomization, to achieve the same level of covariate balance of the pairwise sequential randomization (PSR) (i.e., the average Mahalanobis distance
Randomized Covariates | Randomization Method | Working model for estimating $\mu_1 - \mu_2$
---|---|---
CR | $\text{lm}(Y \sim \tilde{T})$ | $\text{lm}(Y \sim \tilde{T} + X)$
RR | $\text{Asym. Var.}$ | $\text{Asym. Var.}$
X | $\text{Asym. Var.}$ | $\text{Asym. Var.}$
Proposed | $\text{Asym. Var.}$ | $\text{Asym. Var.}$

Table 1: Demonstration of the relationship of asymptotic variances of different estimates. All results are derived under the proposed framework.

**under the PSR**, the acceptance probability $p_a$ of rerandomization is $\chi^2_{df=p}(a^*)$, where $\chi^2_{df=p}(\cdot)$ is the cumulative distribution function of a Chi-square distribution with $p$ degrees of freedom, and $a^*$ is the root of $\gamma(p/2, a^*/2)Dp^2 = 2\gamma(p/2 + 1, a^*/2)n$ where $D > 0$ is a constant and $\gamma(w, t) = \int_0^t x^{w-1} \exp\{-x\}dx$ is the incomplete gamma function.

We report the acceptance probabilities for several scenarios as quantitative values in Table 2. As we can see, for a small sample size and low-dimensional covariates, the acceptance probability are reasonable. However, as either $p$ and $n$ increase, the acceptance probability approaches 0 very fast.

Suppose that the time to allocate one additional unit by the proposed method is $C(p)$ and that the time to allocate one additional unit by complete randomization is $R > 0$. Note that complete randomization is not covariate-adaptive, therefore $R$ does not depend on $p$. Suppose that the time to evaluate the Mahalanobis distance is $E(p)$. Then, we have the following corollary.

**Corollary 3.6.** *To achieve the same level of covariate balance, the ratio of the average...*
computational time of the proposed method to the average computational time of the rerandomization method is proportional to $\chi^2_{df=p(a^*)C(p)}/[E(p)R]$. 

Because of the unknown properties of $C(p)$ and $E(p)$, we are unable to demonstrate the ratio of computational times as we did in Table 2 for acceptance probability. However, we have conducted extensive simulation studies in the next section to demonstrate the computational advantages of the proposed method.

### 4 Numerical Studies

In this section, we perform simulation studies to verify the theoretical results and demonstrate the advantages of the proposed method.

#### 4.1 Convergence Rate

First, we perform a simple experiment to verify the rate of convergence stated in Theorem 2.1. We simulate the unit’s covariate $\mathbf{x}$ according to multivariate normal distribution $\mathbf{x} \sim \text{MN}(0, \mathbf{I})$. Using different numbers of covariates $p$, we simulate sequences of units, assign them to treatment groups and record the corresponding sequences of Mahalanobis distances. We repeat the procedure for 5000 times and plot the average

| $n$  | $p = 2$      | $p = 5$      | $p = 10$     | $p = 20$     | $p = 30$     |
|------|--------------|--------------|--------------|--------------|--------------|
| 1000 | 0.019360138  | 5.889118e-04 | 1.366763e-05 | 2.041414e-07 | 2.886993e-08 |
| 2000 | 0.009504544  | 1.058795e-04 | 4.742458e-07 | 3.091250e-10 | 2.424319e-12 |
| 3000 | 0.006528596  | 3.886533e-05 | 6.451756e-08 | 6.184287e-12 | 7.804135e-15 |

Table 2: Acceptance probabilities of rerandomization to match the covariate balance produced by the proposed method for different levels of $n$ and $p$. 

| table2 |
Figure 3: Verification of the rate of convergence of $M(n)$ using the proposed method.

Mahalanobis distance against the reciprocal of the sample size ($1/n$) in Figure 3. It is clear that the expected Mahalanobis distance converges to 0 at the rate of $1/n$, as evidenced by the straight lines.

4.2 Pairwise sequential randomization under Different Settings

We also demonstrate the performance of the PSR under two different scenarios: (1) all units are available for assignment before the randomization starts, such as causal inference studies, (2) units come to the study sequentially and are assigned to treatment sequentially, such as clinical trial studies. In both cases, we can adopt the proposed method, the only difference is the number of burn in and the calculation of the sample covariance matrix as explained in Section 2.2.

We simulate the unit’s covariate $\mathbf{x}$ according to multivariate normal distribution $\mathbf{x} \sim \text{MN}(0, \mathbf{I})$. Using different $p$s and $n$s, we simulate these units, assign them to treatment groups and record the final Mahalanobis distances. We plot the distributions of the Mahalanobis distance in Figure 4. As the figure shows, the distributions of the
Figure 4: Comparison of the distributions of the Mahalanobis distances obtained via the proposed method, $M(n)$, under three scenarios. Red curves are for true covariance is known. Blue curves are for causal inference. Green curves are for clinical trial.

Mahalanobis distance under these two scenarios are almost identical, especially when the sample sizes are large. This is because as more and more units are assigned, the sample covariance matrix converges and the behaviors of Mahalanobis distance are the same for these two scenarios. This simulation study verifies the applicability of the proposed method in both two scenarios, i.e., causal inference and clinical trial studies.

4.3 Covariate Balance and Computational Advantage

In this section, we compare the proposed method with other methods, especially rerandomization, in terms of covariate balance and computational feasibility.

We first compare the proposed method with rerandomization (with $p_a = 0.05$) by simulating the covariates with $\mathbf{x} \sim \text{MN}(0, I)$; the results are presented in Figure 5.
Figure 5: Comparison of the distributions of the Mahalanobis distances obtained via the proposed method, $M(n)$, and rerandomization, $M_{RR}(n)$, for different sample sizes $n$ and different numbers of covariates $p$.

For different $n$s and $p$s, we plot the histograms of $M(n)$ of the proposed method and $M_{RR}(n)$ of rerandomization. As the figure shows, as $n$ increases, the distribution of $M_{RR}(n)$ remains unchanged, whereas the distribution of $M(n)$ rapidly converges to 0. Moreover, as $p$ increases, the distributions obtained through rerandomization and the proposed method become wider, but the inflation of distribution is much less severe for the proposed method (i.e., the overlap between the two distributions becomes smaller as $p$ increases).

Next, we compare the proposed method with rerandomization in terms of computational times. Note that the proposed method only requires one iteration, whereas rerandomization requires multiple iterations of complete randomization to achieve an acceptable balance level. Therefore, we compared the number of iterations required
Figure 6: Comparison of the numbers of iterations, the computational times, and the ratios of computational times for rerandomization and the proposed method. Panel (a): numbers of iterations of rerandomization required to achieve the same performance as the proposed method. Panel (b): the corresponding computational times used in Panel (a). Panel (c): the ratios of computational times shown in Panel (b).

for rerandomization to achieve the same performance (same Mahalanobis distance) as the proposed method. In addition, we also compared the corresponding computational times. The results are shown in Figure 6. As seen in Figures 6a and 6b, when $n$ and $p$ are small, the computational advantage of the proposed method is not obvious. As $n$ and $p$ increase, however, the proposed method gradually shows a significant advantage over rerandomization, because more iterations and more time are required for rerandomization in order to achieve the same level of performance as the proposed method. As $p$ continues to increase, rerandomization will eventually become very computationally expensive. In other words, it is nearly impossible for rerandomization to achieve the same performance as the proposed method. Note that the computational time of the proposed method grows only linearly with $n$ and remains the same for different $p$s, whereas the computational time of rerandomization grows exponentially as either $n$ or $p$ increases.
4.4 Treatment Effect Estimation

Finally, we compare the proposed method with other randomization methods in terms of estimating the treatment effect. We simulate ten continuous covariates \( \mathbf{x}_i = (x_{i1}, ..., x_{i10})^T \) according to \( \mathbf{x}_i \sim \text{MN}(0, I_{10 \times 10}) \) with sample size of 5000. We applied the proposed method, rerandomization and complete randomization to these simulated units and obtained the simulated treatment assignments \( T_i \). We further simulate the outcome variable according to \( y_i = \mu_1 T_i + \mu_2 (1 - T_i) + \sum_{j=1}^{10} \beta_j x_{ij} + \epsilon_i \), where \( \mu_1 = 0, \mu_2 = 1, \beta_j = 1 \) for \( j = 1, ..., 10 \) and \( \epsilon_i \sim N(0, 2^2) \).

Using the simulated data, we estimate the treatment effect using four different working models and obtain the standard error for each method under different randomization methods.

W1: \( y_i = \mu_1 T_i + \mu_2 (1 - T_i) + \epsilon_i \)

W2: \( y_i = \mu_1 T_i + \mu_2 (1 - T_i) + \sum_{j=1}^{3} \beta_j x_{ij} + \epsilon_i \)

W3: \( y_i = \mu_1 T_i + \mu_2 (1 - T_i) + \sum_{j=4}^{10} \beta_j x_{ij} + \epsilon_i \)

W4: \( y_i = \mu_1 T_i + \mu_2 (1 - T_i) + \sum_{j=1}^{10} \beta_j x_{ij} + \epsilon_i \)

Note that W1 is equivalent to the sample mean difference \( \hat{\tau} \). The results are presented in Table 3, which is consistent with Table 1. As we can see, proposed method obtain the smallest standard errors among all methods. Rerandomization performs well, but its standard errors are significantly larger than these of the proposed method. Finally, not surprisingly, complete randomization has the largest standard errors. As we include more covariate into the working model, the standard error gradually decreases. This is because the covariate imbalance is partially adjusted by the linear regression. When all covariates are included in the working model (i.e., W4), the standard errors becomes the smallest. Note that the W4 under all randomization methods are almost the
Table 3: Comparison of standard errors of estimated treatment effect for working model W1, W2, W3, and W4 under different randomization methods. This table is a verification of Table 1.

| Randomization method | Working model for estimating $\mu_1 - \mu_2$ |
|----------------------|---------------------------------------------|
|                      | W1   | W2   | W3   | W4   |
| CR                   | 6.604616 | 5.622748 | 4.006424 | 1.970360 |
| RR                   | 4.036759 | 3.544364 | 2.769106 | 1.987251 |
| Proposed             | 2.051219 | 2.031727 | 2.003411 | 1.985727 |

same. This is because covariate imbalance from the randomization methods have been completely adjusted, therefore, the standard error reaches its minimum.

5 Real Data Example

In this section, we illustrate our proposed method using a real clinical study of a Ceragem massage (CGM) thermal therapy bed, a device for treating lumbar disc disease. In total, there are 186 patients with $p = 50$ covariates. There are 30 continuous covariates, such as age and baseline measurements of the patient’s current conditions, e.g., lower back pain and leg numbness, all measured on 0-10 scales. The outcome variable $y_i$, representing the measurements of the lower back pain after the treatment or control experiment, was recorded to study the treatment effect.

In the original study, the patients were randomly assigned to the treatment or control groups. The corresponding Mahalanobis distance was 57.67, which indicates a moderate covariate imbalance. To compare, we repeatedly assigned these patients to treatment groups using the proposed method, complete randomization, and reran-
Figure 7: Comparison of the distributions of the Mahalanobis distance obtained using the proposed method, complete randomization, and rerandomization. Note that rerandomization is represented by the portion of the complete randomization distribution that lies to the left of the vertical line \((M = 20, 30, 40)\).

As seen from the figure, the Mahalanobis distances of the proposed method on the original data \((n = 186)\) are consistently lower than those of complete randomization. If we had \(n = 744\) patients, the Mahalanobis distance of the proposed method further decreases toward 0. Few allocations of complete randomization could achieve the same level of balance as the proposed. Rerandomization produces the Mahalanobis distances to the left of the vertical lines \((M = 20, 30, 40)\), which are still not comparable with the proposed.

For each randomization method, we further simulated the outcome variable \(\hat{y}_i^{\text{sim}}\) according to \(\hat{y}_i^{\text{sim}} = \hat{\mu}_1 T_i^{\text{sim}} + \hat{\mu}_2 (1 - T_i^{\text{sim}}) + x_i^T \hat{\beta} + \epsilon_i^{\text{sim}}\), where \(T_i^{\text{sim}}\) is the simulated
patient allocation, $\epsilon_i^{\text{sim}}$ is sampled from the residuals of the regression fitted to the original data. $\hat{\mu}_1$, $\hat{\mu}_2$, and $\hat{\beta}$ are the corresponding estimated regression coefficients.

Using the simulated outcome variable, we obtained the average treatment effect using $\hat{\tau}$. The performance comparison is summarized in Table 4. The proposed method exhibits the best performance compared with other methods especially under large sample size. It yields the largest PRIV and the lowest variance. For rerandomization, a smaller threshold results in better performance; however, this comes at the cost of a longer computational time and a lower acceptance probability. Note that the $R^2$ for the regression fitted to the original data is only 0.33, therefore, the maximum of PRIV is 0.33. Because of the finite sample size, the optimal PRIV cannot be achieved. We can see that if we increase the sample size, the PRIV of the proposed method is greatly improved and is close to optimal, whereas that of the rerandomization method does not improve at all. The gain from the proposed method is quite substantial.

6 Discussion

In this article, we have introduced a new randomization procedure for balancing the covariates to improve the estimation accuracy for causal inference and clinical trials. Compared with traditional methods, the proposed method can cope with a large number of covariates and a large sample size, which is especially advantageous in the era of big data. The proposed method also shows superior performance in terms of computational time. In addition, it achieves optimality under the linear regression framework, in the sense that, asymptotically, the proposed method can balance the covariates so well that the imbalance adjustment provided by linear regression is not needed.

Although the proposed method is different from the minimization methods (Wei, 1978; Begg and Iglewicz, 1980; Smith, 1984a,b), it can be extended to such settings.
### Table 4: Comparison of the proposed method with rerandomization and complete randomization for real data analysis.

Instead of selecting a pair of units, we can select only one unit to allocate. However, the behavior of the Mahalanobis distance in such a scenario will be further complicated, because the proportion of the treatment group (i.e., $\sum_{i=1}^{n} T_i/n$) then becomes a random variable. We believe that the allocation procedure should be slightly modified such that both the Mahalanobis distance and the proportion are controlled. In such a scenario, we anticipate that the rate of convergence of the Mahalanobis distance can be further improved. We leave this possibility as a topic for future investigation.

The proposed method is following the similar spirit of the minimization methods used in clinical trials (Taves, 1974; Pocock and Simon, 1975; Hu and Hu, 2012). However, the focus and context of these methods are different from ours. Their methods are applicable for patients sequentially enrolled in a clinical trial. On the other hand, our

| Sample Size | Method     | PRIV | MSE (or Var) | $u_n$ or $v_a$ |
|-------------|------------|------|--------------|----------------|
| $n = 186$   | Proposed   | 19.7%| 0.081        | 0.502          |
|             | RR ($M < 40$) | 12.2%| 0.090        | 0.730          |
|             | RR ($M < 30$) | 15.1%| 0.085        | 0.562          |
|             | RR ($M < 20$) | 20.3%| 0.081        | 0.501          |
|             | CR         | -    | 0.100        | -              |
| $n = 744$   | Proposed   | 27.4%| 0.018        | 0.205          |
|             | RR ($M < 40$) | 10.9%| 0.022        | 0.718          |
|             | RR ($M < 30$) | 14.6%| 0.021        | 0.556          |
|             | RR ($M < 20$) | 20.6%| 0.018        | 0.380          |
|             | CR         | -    | 0.025        | -              |
proposed method can be applied both in clinical trials where units enrolled sequentially, and also in causal inference where all units are collected before the randomization and experiment starts. Another significant difference is that the minimization methods are suitable for discrete covariates, minimizing the margin and stratum imbalance. The proposed method, in contrast, is suitable for both discrete and continuous covariates.

Throughout the article, we have focused on equal proportion allocation. However, the proposed method can be easily extended to accommodate unequal proportions. For example, to achieve a ratio of $1 : 2$, in each iteration, we can allocate three units at a time to maintain the targeted proportions.

Many other potential directions for further research remain as well. For example, we have shown the optimality of the estimated treatment effect. An extension to hypothesis testing is also of interest (Ma et al., 2015). The optimality of the estimator hints at the most powerful test for the treatment effect. In addition, as the number of covariates increases, it is more efficient to balance only the most important covariates (Morgan and Rubin, 2015); therefore, the selection of the important covariates to balance in our proposed framework is an interesting topic. The proposed method may also be applied to balance important covariates in the field of crowdsourced-internet experimentation.

7 APPENDIX

We provide outlines of the key proofs in the Appendix. The supplementary materials contain detailed proofs of all theorems.

Proof of Theorem 2.1. We first convert the covariates to canonical form (Rubin and Thomas, 1992). Let $\Sigma = \text{cov}(x)$ and $z_i = \Sigma^{-1/2} x_i$ where $\Sigma^{-1/2}$ is the Cholesky square
root of $\Sigma^{-1}$. Suppose that $n$ is even. By the assumption, $\text{cov}(z_i) = I$, and

$$M^*(n) = np_n(1 - p_n)(\bar{z}_1 - \bar{z}_2)^T(\bar{z}_1 - \bar{z}_2).$$

We further define

$$y_n = \frac{n}{2}(\bar{z}_1 - \bar{z}_2) = \sum_{i:T_i=1} z_i - \sum_{i:T_i=0} z_i,$$

$$\Delta_{n+2} = (-1)^{T_n+2}(z_{n+1} - z_{n+2}).$$

We can see that $\{y_n, y_{n+2}, y_{n+4} \ldots\}$ is a Markov process and $y_{n+2} = y_n + \Delta_{n+2}$. Define the test function $V(y_n) = y_n^T y_n$. By denoting $E[\cdot | y_n] = E_n[\cdot | y_n]$, we have

$$E_n[V(y_{n+2})] - V(y_n) = E_n[y_{n+2}^T y_{n+2}] - y_n^T y_n = 2E_n[y_n^T \Delta_{n+2}] + E_n[\Delta_{n+2}^T \Delta_{n+2}],$$

where $E_n[\Delta_{n+2}^T \Delta_{n+2}] = E_n[(-1)^{2T_n+2}(z_{n+1} - z_{n+2})^T(z_{n+1} - z_{n+2})]$ is a positive constant.

For the first term on the right, we have

$$E_n[y_n^T \Delta_{n+2}] = E_n[y_n^T (-1)^{T_n+2}(z_{n+1} - z_{n+2})]$$

$$= E_n\left\{ E[y_n^T (-1)^{T_n+2}(z_{n+1} - z_{n+2}) | z_{n+1}, z_{n+2}] \right\}$$

$$= E_n\left\{ (1 - 2q) |y_n^T(z_{n+1} - z_{n+2})| \right\}$$

$$= E_n\left\{ (1 - 2q) |y_n| |z_{n+1} - z_{n+2}| \cos \theta \right\}$$

$$= (1 - 2q) |y_n| E_n[|z_{n+1} - z_{n+2}|] E_n[|\cos \theta|],$$

where $\theta$ is the angle between $y_n$ and $z_{n+1} - z_{n+2}$. Note that $E_n[|z_{n+1} - z_{n+2}|]$ and $E_n[|\cos \theta|]$ are two positive constants. Since $1 - 2q < 0$, there exist a constant $b > 0$ and $c < 0$, such as when $|y_n| > b$, $E_n[y_n^T \Delta_{n+2}] + E_n[\Delta_{n+2}^T \Delta_{n+2}] < c$. Therefore, $E_n[V(y_{n+2})] - V(y_n) < c$ for $|y_n| > b$. Similarly, we have $E_n[V(y_{n+2})] - V(y_n) < E_n[\Delta_{n+2}^T \Delta_{n+2}]$ for $|y_n| \leq b$. By the “drift conditions” (Meyn and Tweedie, 2009), we know $y_n$ has a stationary distribution. Therefore, $nM^*(n)/(4p_n(1 - p_n)) = y_n^T y_n$ has a stationary distribution and $M^*(n) = O_p(n^{-1}).$
In practice, covariance matrix $\Sigma$ is not known and is sequentially estimated as $\hat{\Sigma}_n$.

We write the Mahalanobis distance as

$$
M(n) = np_n(1 - p_n)(\bar{x}_1 - \bar{x}_2)^T\hat{\Sigma}_n^{-1}(\bar{x}_1 - \bar{x}_2).
$$

$$= np_n(1 - p_n)(\bar{x}_1 - \bar{x}_2)^T(\hat{\Sigma}_n^{-1} + \Sigma^{-1} - \Sigma^{-1})(\bar{x}_1 - \bar{x}_2).
$$

$$= M^*(n) + np_n(1 - p_n)(\bar{x}_1 - \bar{x}_2)^T(\hat{\Sigma}_n^{-1} - \Sigma^{-1})(\bar{x}_1 - \bar{x}_2)
$$

$$= M^*(n) + np_n(1 - p_n)(\bar{x}_1 - \bar{x}_2)^T\Sigma^{-1/2}\Sigma^{1/2}(\hat{\Sigma}_n^{-1} - \Sigma^{-1})\Sigma^{1/2}\Sigma^{-1/2}(\bar{x}_1 - \bar{x}_2)
$$

$$= M^*(n) + np_n(1 - p_n)(\bar{x}_1 - \bar{x}_2)^T(\Sigma^{1/2}\hat{\Sigma}_n^{-1}\Sigma^{1/2} - I)(\bar{x}_1 - \bar{x}_2)
$$

Note that $(\bar{x}_1 - \bar{x}_2)^T(\Sigma^{1/2}\hat{\Sigma}_n^{-1}\Sigma^{1/2} - I)(\bar{x}_1 - \bar{x}_2)$ can be considered as the weighted norm of $\bar{x}_1 - \bar{x}_2$, i.e., $||\bar{x}_1 - \bar{x}_2||_W$ where $W = \Sigma^{1/2}\hat{\Sigma}_n^{-1}\Sigma^{1/2} - I = \Sigma^{1/2}(\hat{\Sigma}_n^{-1} - \Sigma)\Sigma^{1/2}$. Since $\hat{\Sigma}_n \xrightarrow{p} \Sigma$, we have $M(n) = O_p(M(n))$. 

**Proof of Theorem 3.3.** We first convert the covariates to canonical form (Rubin and Thomas, 1992). Let $\Sigma = \text{cov}(x)$ and $z_i = \Sigma^{-1/2}x_i$ where $\Sigma^{-1/2}$ is the Cholesky square root of $\Sigma^{-1}$. Suppose $n$ is even. By the assumption of normality, $z_i \sim N(0, I)$.

Define

$$
Y = \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix}, \ Z = \begin{bmatrix} z_1^T \\ z_2^T \\ \vdots \\ z_n^T \end{bmatrix}, \ T = \begin{bmatrix} T_1 \\ T_2 \\ \vdots \\ T_n \end{bmatrix}, \ T = \begin{bmatrix} T_1 & 1 - T_1 \\ T_2 & 1 - T_2 \\ \vdots & \vdots \\ T_n & 1 - T_n \end{bmatrix},
$$

and $Z = [T; Z]$, $\gamma = (\gamma_1, ..., \gamma_p)^T = (\Sigma^{-1/2})^T\beta$, $\mu = (\mu_1, \mu_2)^T$ and $\gamma^* = (\mu^T, \gamma^T)^T = (\mu_1, \mu_2, \gamma_1, ..., \gamma_p)^T$.

Then true model, equation (2), can be rewritten as

$$
Y = X\beta^* + \epsilon = T\mu + X\beta + \epsilon = T\mu + Z\gamma + \epsilon = Z\gamma^* + \epsilon.
$$

**Part I:** $\hat{\gamma}_{PSR}$

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Suppose $K = (1, -1)$, then $\hat{\tau}_{\text{PSR}}$ can be obtained by running the regression, $Y = \tilde{T}\mu + \epsilon$, even though the true model is $Y = \tilde{Z}\gamma^* + \epsilon = \tilde{T}\mu + Z\gamma + \epsilon$. In particular, we can write $\hat{\tau}_{\text{PSR}}$ as

$$\hat{\tau}_{\text{PSR}} = \sum_{i=1}^{n} T_i y_i / \sum_{i=1}^{n} T_i - \sum_{i=1}^{n} (1 - T_i) y_i / \sum_{i=1}^{n} (1 - T_i) = K \left( \frac{\tilde{T}^T \tilde{T}}{n} \right)^{-1} \frac{\tilde{T}^T Y}{n} = K \left( \frac{\tilde{T}^T \tilde{T}}{n} \right)^{-1} \frac{\tilde{T}^T (\tilde{Z}\gamma^* + \epsilon)}{n} = K \left[ \mu + \left( \frac{\tilde{T}^T \tilde{T}}{n} \right)^{-1} \tilde{T}^T (\tilde{Z}\gamma + \epsilon) \right] = \mu_1 - \mu_2 + K \left( \frac{\tilde{T}^T \tilde{T}}{n} \right)^{-1} \frac{\tilde{T}^T (Z\gamma + \epsilon)}{n}.$$

We know, as $n \to \infty$,

$$\frac{\tilde{T}^T \tilde{T}}{n} \overset{p}{\to} \begin{bmatrix} 0.5 & 0 \\ 0 & 0.5 \end{bmatrix} = M.$$

We further define

$$A = KM^{-1} \left[ \frac{\tilde{T}^T (Z\gamma + \epsilon)}{n} \right],$$

$$B = K \left[ \left( \frac{\tilde{T}^T \tilde{T}}{n} \right)^{-1} - M^{-1} \right] \left[ \frac{\tilde{T}^T (Z\gamma + \epsilon)}{n} \right],$$

so that $\hat{\tau}_{\text{PSR}} = A + B$.

For $A$, with some algebra, we can show

$$A = \frac{2}{n} \left[ \sum_{j=1}^{p} \sum_{i=1}^{n} (2T_i - 1)\gamma_j z_{i,j} + \sum_{i=1}^{n} (2T_i - 1)\epsilon_i \right].$$

For the first term on the right, we have

$$\sum_{j=1}^{p} \sum_{i=1}^{n} (2T_i - 1)\gamma_j z_{i,j} = \sum_{j=1}^{p} \gamma_j \left[ \sum_{i \in \{i:T_i=1\}} z_{i,j} - \sum_{i \in \{i:T_i=0\}} z_{i,j} \right].$$
where \( \{ i : T_i = 1 \} \) and \( \{ i : T_i = 0 \} \) represent the two treatment groups. From the proof of Theorem 2.1, we understand that \( \sum_{i \in \{ i : T_i = 1 \}} z_{i,j} - \sum_{i \in \{ i : T_i = 0 \}} z_{i,j} \) is a stationary process under the proposed method (i.e. a mean reverting process as \( n \to \infty \)). Therefore,

\[
\sum_{i \in \{ i : T_i = 1 \}} z_{i,j} - \sum_{i \in \{ i : T_i = 0 \}} z_{i,j} = O_p(1),
\]

\[
\sum_{j=1}^{p} \gamma_j \left[ \sum_{i \in \{ i : T_i = 1 \}} z_{i,j} - \sum_{i \in \{ i : T_i = 0 \}} z_{i,j} \right] = O_p(1).
\]

In addition, note that \((2T_i - 1)^2 = 1\), we have

\[
\text{Var} \left( \frac{2}{n} \sum_{i=1}^{n} (2T_i - 1) \epsilon_i \right) = \mathbb{E} \left( \frac{4}{n^2} \sum_{i=1}^{n} (2T_i - 1)^2 \epsilon_i^2 \right)
= \mathbb{E} \left( \frac{4}{n^2} \sum_{i=1}^{n} \epsilon_i^2 \right)
= \frac{4\sigma^2}{n}.
\]

Therefore,

\[
\sqrt{n} A \xrightarrow{D} N(0, 4\sigma^2).
\]

Similarly, for \( B \), we will show \( \sqrt{n} B \xrightarrow{p} 0 \). First note that

\[
\left( \frac{\tilde{T}^T \tilde{T}}{n} \right)^{-1} - M^{-1} \xrightarrow{p} 0.
\]

Therefore, showing \( \sqrt{n} B \xrightarrow{p} 0 \) is equivalent to show

\[
\frac{\tilde{T}^T (Z\gamma + \epsilon)}{\sqrt{n}} = O_p(1).
\]

First, notice that

\[
\frac{\tilde{T}^T (Z\gamma + \epsilon)}{\sqrt{n}} = \frac{1}{\sqrt{n}} \left[ \sum_{j=1}^{p} \sum_{i=1}^{n} T_i \gamma_j z_{i,j} + \sum_{i=1}^{n} T_i \epsilon_i \right. \\
\left. - \sum_{j=1}^{p} \sum_{i=1}^{n} (1 - T_i) \gamma_j z_{i,j} + \sum_{i=1}^{n} (1 - T_i) \epsilon_i \right].
\]
Since
\[
\frac{1}{\sqrt{n}} \left( \sum_{j=1}^{p} \sum_{i=1}^{n} T_i \gamma_{j, i} + \sum_{i=1}^{n} T_i \epsilon_i \right) = \frac{1}{2} \left[ \frac{1}{\sqrt{n}} \left( \sum_{j=1}^{p} \sum_{i=1}^{n} \gamma_{j, i} + \sum_{i=1}^{n} \epsilon_i \right) + \frac{1}{\sqrt{n}} \left( \sum_{j=1}^{p} \sum_{i=1}^{n} (2T_i - 1) \gamma_{j, i} + \sum_{i=1}^{n} (2T_i - 1) \epsilon_i \right) \right].
\]

By central limit theorem, we have
\[
\frac{1}{\sqrt{n}} \left( \sum_{j=1}^{p} \sum_{i=1}^{n} \gamma_{j, i} + \sum_{i=1}^{n} \epsilon_i \right) = O_p(1).
\]

In addition,
\[
\frac{1}{\sqrt{n}} \left( \sum_{j=1}^{p} \sum_{i=1}^{n} (2T_i - 1) \gamma_{j, i} + \sum_{i=1}^{n} (2T_i - 1) \epsilon_i \right) = \frac{\sqrt{n}A}{2}.
\]

Since \( \sqrt{n}A \) converges to a normal distribution,
\[
\frac{1}{\sqrt{n}} \left( \sum_{j=1}^{p} \sum_{i=1}^{n} (2T_i - 1) \gamma_{j, i} + \sum_{i=1}^{n} (2T_i - 1) \epsilon_i \right) = O_p(1).
\]

Therefore,
\[
\frac{1}{\sqrt{n}} \left( \sum_{j=1}^{p} \sum_{i=1}^{n} T_i \gamma_{j, i} + \sum_{i=1}^{n} T_i \epsilon_i \right) = O_p(1).
\]

By symmetry, we have
\[
\frac{1}{\sqrt{n}} \left( \sum_{j=1}^{p} \sum_{i=1}^{n} (1 - T_i) \gamma_{j, i} + \sum_{i=1}^{n} (1 - T_i) \epsilon_i \right) = O_p(1).
\]

Therefore,
\[
\frac{\tilde{\tau}^T (Z\gamma + \epsilon)}{\sqrt{n}} = O_p(1).
\]

Hence, \( \sqrt{n}B \overset{p}{\to} 0 \), together with \( \sqrt{n}A \overset{D}{\to} N(0, 4\sigma^2) \), by Slutsky’s theorem, we have
\[
\sqrt{n}(\hat{\tau}_{PSR} - (\mu_1 - \mu_2)) \overset{D}{\to} N(0, 4\sigma^2).
\]

For \( \hat{\tau}_{CR} \), \( \hat{\tau}_{PSR} \), and \( \hat{\tau}_{CR} \), we can obtain their asymptotic distributions in similar ways. Please see supplementary materials for details. \( \square \)
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