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Algorithm for balancing both continuous and categorical covariates in randomized controlled trials

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ABSTRACT

Minimization as proposed by Pocock and Simon for balancing categorical covariates in clinical trials with individual-level, consecutive randomization has been increasingly used. An extension of the method exists that uses the symmetric Kullback–Leibler divergence index to balance both categorical and continuous covariates, albeit for two-arm randomized controlled trials only. To date, the algorithm has not been made widely available to researchers via publicly accessible software.

We adapted Endo et al.'s algorithm to randomized trials with two or more arms. In addition, our algorithm incorporates Efron's biased coin method to decrease the predictability of assignment even when a predefined threshold of difference in the numbers of subjects between treatment arms is reached, whereas Endo et al.'s algorithm assigns the next subject to the treatment of smaller size with certainty. We developed code in the free statistical software R to make the algorithm readily available to trialists. While there are no definitive answers regarding the optimal choices for certain statistical parameters that must be defined prior to algorithm application (P_k, D_n, and p_D_n), we provide guidance on these.

We conducted simulations with actual data from a three-arm randomized trial to compare the modified algorithm and R code to another published biased coin minimization method that can accommodate continuous and categorical covariates in multi-arm trials. The three-arm trial used three categorical covariates (sex, race/ethnicity, and online personal health record access) and four continuous covariates (age, fasting blood glucose, body mass index, and waist circumference). All of the continuous and categorical covariates were well balanced, and the results were comparable to the comparison method.

1. Background

Random allocation of subjects to treatments independent of baseline characteristics, measured or unmeasured, including characteristics that are the current values of the outcomes of interest, is one of the hallmarks of randomized controlled trials (RCTs) [1]. The chance procedure in randomization helps to control selection bias and allocation predictability [1]. Although unrestricted randomization provides the basis of validity of statistical inference, it cannot by itself prevent the possibility of unbalanced distributions of subjects with respect to both the numbers in each treatment arm and the characteristics of each group. Such chance imbalances between treatments are more likely to occur in smaller trials and lead to a loss of power. To address these concerns,

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various alternative methods of restricted randomization have been proposed. Pocock and Simon developed a method that minimizes the total imbalance between treatments across important prognostic factors, i.e., baseline covariates known to affect outcome [2]. This method has been recognized for achieving dynamic allocation without the drawbacks of restricting to deterministic assignments by setting the probability at one, as in Taves' minimization method, or to only a very small number of covariates, as in stratified randomization [3]. Some implementation tools [4,5] have been developed based on Pocock and Simon's algorithm. However, this approach only permits categorical covariates; continuous covariates must be categorized – a process that is often arbitrary and can lead to a loss of important information. Further extensions of the Pocock–Simon method have been introduced by other authors [3,6,7]. Recently, Endo et al. published a minimization allocation procedure that is based on the symmetric Kullback–Leibler divergence (KLD) (i.e., Jeffery's divergence) [8,9] and accommodates continuous and categorical covariates. The authors reported that their method produced better balance and more robust estimates than Pocock–Simon's [10]. However, Endo et al.'s algorithm only applies to two-arm RCTs, and no public domain software has been made available to facilitate its adoption.

In this study, we adapted that algorithm [10] to RCTs with two or more arms and added features to decrease the predictability of assignment. We also developed code in the free statistical software R [11] to make the algorithm publicly available. We tested our modified algorithm and R code and compared them to another published biased coin minimization method that can accommodate continuous and categorical covariates [12] in a simulation study using actual baseline data from our recent three-arm RCT, Evaluation of lifestyle interventions to treat elevated cardiometabolic risk in primary care (E-LITE) [10].

2. Implementation

In our modified algorithm, we use a combination of approaches to achieve balance between treatments in both the number of subjects and important baseline covariates while maintaining allocation concealment among consecutively enrolled subjects in RCTs with two or more arms.

As in Endo et al. [10], our algorithm randomly allocates subjects in the first block of $2T$ (T is the number of treatment arms) with two subjects per arm. Subsequently, treatment allocation of a new subject depends on whether the maximum difference between any two treatment arms in the numbers of subjects previously assigned exceeds a pre-defined fixed number, D_n.

2.1. Symmetric KLD index for covariate balance

The algorithm measures the "amount of imbalance" between treatments over multiple covariates by computing a symmetric KLD index [10]. Let treatment be coded i ($i = 1, 2, \ldots, T$). Consider any arbitrary point with the number of subjects $n > 2T$. Let x_{ijk} be the value of covariate for kth ($k = 1, 2, \ldots, n_i$) subject assigned to the ith treatment with the jth ($j = 1, 2, \ldots, j'$) continuous covariate (assuming a normal distribution), and p_{ijm} be the proportion of subjects assigned to the level m ($m = 1, 2, \ldots, M$) of the jth ($j' + 1, \ldots, J$) categorical covariate in treatment i. The difference in the distributions of covariates between any two treatments i and i' can be measured as:

$$d_{ii'} = \frac{1}{2}\sum_{j=1}^{j'} \left\{ \left(\overline{x_{ij}} - \overline{x_{i'j}}\right)^2 + \left(V_{ij} + V_{i'j}\right) \right\} \left(\frac{1}{V_{ij}} + \frac{1}{Vi'j} \right) - 2j' + \sum_{j=j'+1}^{j} \sum_{m=1}^{M_j} (p_{ijm} - p_{i'jm}) \log \frac{p_{ijm}}{p_{i'jm}} \quad (1)$$

where $\overline{x_{ij}} = \frac{1}{n_i}\sum_{k=1}^{n_i} x_{ijk}$ and $V_{ij} = \frac{1}{n_{i-1}}\sum_{k=1}^{n_i}\left(xi_{jk} - \overline{x_{ij}}\right)^2$.

When the new subject $n+1$ is enrolled $\sum_{i=1}^{T} n_i$, $d_{ii'}$ is calculated by assuming that this new subject is allocated to i where i can be any of the treatments under study. Hence, the total number of subjects for treatment i becomes $n_i + 1$, and the number of subjects for all other treatments i' (n_i') remains unchanged. $d_{ii'}$ is produced for all possible pairwise comparisons between treatments i and i' where $i' \neq i$. d_i is defined as:

$$\sum_{i' \neq i} d_{ii'} \quad (2)$$

Therefore, $D = (d_1, d_2, \ldots, d_T)$ represents the "amount of imbalance" in treatment i ($i = 1, 2, \ldots, T$) assuming the new subject is assigned to that treatment. Expression (2) adapted Endo et al.'s algorithm [10] to RCTs with more than two treatments. Begg and Iglewicz [6] suggested using a similar approach to extend their method of minimizing covariate imbalance based on the approximated variances of pairwise treatment comparisons, from two treatments to multiple treatments, and reported it to be an 'extremely efficient" process in a number of completed trials.

2.2. Allocation probability, P_k, for covariate balance

The probability of assigning a new subject to a treatment determines the level of biasing of treatment assignment in favor of those treatments with smaller d_i as follows:

$$\text{Prob}(i = k) = P_k \quad \text{where} \quad P_1 \geq P_2 \geq \cdots \geq P_r \quad \text{and} \quad \sum P_k = 1.$$

P_k in descending order corresponds with d_i in ascending order, indicating that treatments with smaller values of d_i have a higher probability to be assigned. Equal probability is assigned to the treatments with equal values of d_i, where the average of the corresponding probabilities P_k will be used [10].

2.3. Allocation probability, p_D_n, for balancing the number of subjects

If the maximum imbalance in the numbers of subjects between any treatments reaches or exceeds the pre-defined tolerable threshold, D_n, an alternative allocation strategy is desirable to balance the numbers of subjects without necessarily balancing the covariates between treatments. Let $\widetilde{D_n} = \max\{|n_{i'} - n_{i''}|\}$ where i' and i'' are any two treatments. Then, if $\widetilde{D_n} \geq D_n$, the new subject is allocated to the treatment with the smallest number of subjects with a high probability (e.g., $p\_D_n > 0.8$). Endo et al.'s algorithm sets $p\_D_n = 1$, whereas we

provide users the option to define their preferred value considering acceptable tradeoffs between the degree of balance in the numbers of subjects and the predictability of assignment. The two parameters, D_n and p_D_n, determine the degree of deviation in the numbers of subjects between treatments.

2.4. Allocation procedures

Step 1: Define the values of P_k, D_n, and p_D_n.
Step 2: The first $2T$ subjects are formed as a permuted block, where any two subjects are randomly assigned to each treatment.
Step 3: When a new subject is enrolled who is the $(n+1)$th subject ($n \geq 2T$), differences in the numbers of subjects between treatments are calculated. If $\max\{|n_{i'} - n_{i''}|\} \geq D_n$, then the new subject is allocated to the treatment with the smallest number of subjects given the pre-defined probability, p_D_n. If the new subject fails to be assigned to the treatment with the smallest number of subjects or if $\max\{|n_{i'} - n_{i''}|\} < D_n$, then one goes to step 4; otherwise one jumps to step 5.
Step 4: Calculate d_i and order d_i from the smallest to the largest, and the new subject is allocated to treatment i at the kth rank of d_i with allocation probability, P_k. If $d_i = d_{i'}$ for any two or more treatments, the corresponding probability P_k is obtained by averaging the probabilities predefined for these two or more ranks, so that treatments with equal d_i are assigned with the same probability.
Step 5: Repeat steps 3 and 4 until the target sample size is reached.

2.5. Parameter selections and data distribution

(1) P_k. The choice of P_k implies a tradeoff between the degree of covariate balance and the unpredictability of assignment. Balance is maximized whereas unpredictability is removed as P_1 approaches 1; the reverse is true as P_k approaches equal probability across all treatments. There is no optimal choice of P_k. As others have suggested [2,13,14], the choice depends on the sample size, number of covariates, number of treatments, and concealment circumstances of a given RCT.

(2) *D_n and p_D_n.* In order to prevent an undesirable large imbalance in the numbers of subjects between treatments, D_n is predefined to ensure that the maximum possible deviation in the numbers is less than that specified [10]. In Endo et al.'s algorithm [10], whenever the maximum deviation in the numbers of subjects between treatments reaches or exceeds D_n, the next assignment can be predicted with certainty as it is, by default, to the treatment arm with the fewest subjects. To overcome this problem, we apply Efron's biased coin principle as discussed above for the selection of P_k [13] and define p_D_n as the probability of biasing toward the treatment arm with the fewest subjects. Efron [13] proposed $D_n = 1$ and p_$D_n = 2/3$, while Endo et al. [10] suggested choosing a value of D_n between 2 and 6 for two-arm RCTs with a sample size of about 100 and p_$D_n = 1$. Efron's choice of p_$D_n = 2/3$ may be too conservative for small trials (e.g., $n < 100$) that have several covariates [2], whereas p_$D_n = 1$ indicates deterministic allocation. There are no "optimal" D_n and p_D_n values for any trial; instead, their selection should seek a reasonable compromise between ensuring balanced numbers of subjects across treatments and ensuring assignment unpredictability within a given trial. We recommend that, whenever feasible, randomization be carried out by study personnel who have no substantive knowledge of the method used, including the actual values of critical parameters such as P_k, D_n, and p_D_n.

(3) *Data distribution.* The symmetric KLD algorithm assumes a normal distribution for continuous covariates. Data transformation may be needed when the distribution of a covariate is substantially skewed based on prior knowledge, although Endo et al. [10] demonstrated the robustness of their algorithm for non-normally distributed data.

2.6. Simulation study

We programmed the code (additional file 1) for the modified algorithm described above in the free statistical software R. We tested the code in a simulation study using actual baseline data from our recent three-arm RCT, E-LITE, which compared two behavioral weight management interventions to usual care in a primary care setting [10]. The protocol specifies seven covariates for randomization: three categorical (sex, race/ethnicity, and pre-trial online access to personal health records) and four continuous (age, fasting blood glucose, body mass index, and waist circumference).

We compared our modified symmetric KLD method and the one by Frane, which similarly applies a biased coin approach and can accommodate continuous and categorical covariates in multi-arm trials [12]. Differences in the allocation procedures of these two methods are outlined below.

Step 1: Frane's method requires D_n to be defined but lets p_$D_n = 1$ and P_k vary depending on the degree of imbalance each time a new subject is to be randomized (see step 4 below).
Steps 2 and 3: No difference between methods.
Step 4: Instead of defining d_i and P_k as in the modified symmetric KLD method, Frane's method uses p-values from t-tests or analysis of variance for continuous covariates and chi-square tests for categorical covariates to determine treatment allocation probabilities. $P_i = \min(q_{i1}, q_{i2}, \ldots, q_{ij})$ where q_{ij} denotes the p-value for the jth covariate assuming assignment of the new subject to the ith treatment arm. This determines that the subject is assigned to treatment i with probability $p_i / \sum_{i=1}^{T} p_i$.
Step 5: No difference between methods.
Using the E-LITE randomization variables and data, we ran 1000 simulations with $D_n = 4$ and each of four possible combinations given p_$D_n = 0.9$ or 1 and $P_k = c(0.8, 0.1, 0.1)$ or $P_k = c(0.9, 0.05, 0.05)$ for the modified symmetric KLD algorithm and with $D_n = 4$ for the Frane method. We compared the two methods on the following balance measures:

(1) Imbalance score (B): Raab and Butcher [15] suggested a simple imbalance criterion for measuring balanced allocation

for all covariates between two arms. Such a criterion is defined as

$$B = \sum_{j=1}^{j} \left(\sum_{s=1}^{n} (x_{si} w_{sj}) \right)^2$$

where x_{si} is the sth subject of ith allocation (i.e., 0 for one arm and 1 for the another arm), w_{sj} is sth subject of jth baseline covariate ($j = 1, \ldots, J$), and n is the total number of allocated subjects. We adapted this criterion to our three-arm RCT by using the average of the imbalance scores across all pairwise comparisons.2) Significance of imbalance (p-value and I_{pj}): We tested differences in randomization covariates by treatment (Pearson chi-square tests for categorical covariates and F tests for each continuous covariate). I_{pj} indicates the significance of the test for covariate j ($I_{pj} = 1$, where p-value <0.05; $I_{pj} = 0$, otherwise).

In the following section, we illustrate our application of the R code and report the simulation results.

3. Results

Dataset 'covariate.csv' consisted of baseline data for the seven covariates from all 241 E-LITE participants.

We executed the following steps:

1. Download R software from www.r-project.org and install it on a local computer.
2. Create a folder called 'KLD_random' in a chosen directory.
3. Save the R code in Additional file 1 as "Minimization_KLD.R" in folder "KLD_random".
4. Launch R and then:
   (i) on the **FILE** tab, click **Open script** in the drop-down menu.
   (ii) in the open script wizard, browse to select the file "Minimization_KLD.R".
5. Run "Minimization_KLD.R" by clicking **Run all** in the drop-down menu on the **EDIT** tab.
6. Separate the file 'covariate.csv' into two files: one with all continuous variables (e.g., 'convar.csv'), which included studyID in the first column and the four continuous variables in columns 2–5 and variable names in the first row and the corresponding data for each subject in subsequent rows; and the other with all categorical variables (e.g., 'catvar.csv'), which had the same structure as 'convar.csv.' Two sample records in these two files are shown below. These files should include the data for all allocated and ready-to-be-allocated subjects. Categorical variables may be coded as text or numerals.
   Convar.csv:

StudyID	Age	Fasting blood glucose	Body mass index	Waist circumference
01	61	101	26.95	39.69
02	66	91	25.14	35.34

StudyID	Female	Online status	Race/ethnicity
01	1	0	3
02	0	1	3

7. Input the function names and parameter values after "=" in R prompted command line as follows:
   random.allocation (folder="C:\\KLD_random\\", ntrt=3, continuous_covariates="convar.csv", categorical_covariates="catvar.csv", nassigned=0, group_old=, outfile="KLD_assigned.csv", D_n=4, p_D_n=0.9, P_k=c(0.8,0.1,0.1))
   The input data for *folder* was the directory in which the files for continuous covariates (convar.csv) and categorical covariates (catvar.csv) and the outfile (KLD_assigned.csv) were saved. (Please note the special notation required in R for the program to properly identify the specified directory, namely, that one must enter the folder location using a double backslash ("\\") rather than the usual single backslash ("\").) Parameter *nassigned* is the number of subjects that have already been allocated. If nassigned = 0 then *group_old* does not need to be specified; otherwise, *group_old* should be the file containing all previously allocated subjects. The file specified for *outfile* includes columns studyID (unique study subject identification numbers), group (treatment assignments), and random_number (random numbers, which are needed for replication of the randomization) for previously and newly allocated subjects.
8. Repeat step 7 for p_D_n = 0.9 and P_k = c(0.9, 0.05, 0.05); p_D_n = 1 and P_k = c(0.8, 0.1, 0.1); and p_D_n = 1 and P_k = c(0.9, 0.05, 0.05).

Table 1 shows the distribution statistics of imbalance scores (B), the number of significant p-values comparing seven baseline covariates among treatments ($\Sigma_j I_{pj}$), and the distribution statistics of p-values for individual baseline covariates from the two methods. For the symmetric KLD method, the imbalance scores and the total number of significant p-values decreased and the quartiles of p-values for individual covariates mostly increased with increasing P_k and p_D_n values, as expected. The results were comparable when P_k = (0.9,0.05,0.05) for the symmetric KLD method and holding the other parameters (D_n = 4 and p_D_n = 1) equal for the symmetric KLD and Frane methods.

4. Discussion

The modified symmetric KLD algorithm that we developed based on Endo et al. [10] and the free R code can be applied to minimize imbalance across multiple continuous and categorical covariates in RCTs with two or more arms in which subjects are randomized consecutively as they are enrolled. It also eliminates the need to categorize continuous covariates as in Pocock–Simon's minimization method. Our simulation results show that the modified algorithm can produce comparably good balance overall and for individual covariates as the Frane method. All randomization methods to improve the prospects for balance make a tradeoff and the nature of the tradeoff depends on the details of individual trial [16].

Table 1 – Comparisons of imbalance scores *B*, total numbers of significant *p*-values, and *p*-values for individual covariates between the modified symmetric KLD and Frane methods.

	Imbalance score				
	Modified symmetric KLD method				Frane's method
	P_k = (0.8,0.1,0.1)		P_k = (0.9,0.05,0.05)		
	p_D_n = 0.9	p_D_n = 1	p_D_n = 0.9	p_D_n = 1	p_D_n = 1
Median (Q1, Q3)	253.7 (180.9, 343.8)	243.4 (181.8, 324.6)	241.6 (178.5, 324.1)	218.7 (159.8, 286.9)	221.6 (165.0, 286.7)
p value					
# of *p*-value <0.05	228	184	190	139	136
Median (Q1, Q3)					
Age	0.55 (0.31, 0.80)	0.60 (0.34, 0.81)	0.55 (0.30, 0.78)	0.65 (0.38, 0.84)	0.61 (0.39, 0.83)
Fasting blood glucose (mg/dL)	0.56 (0.33, 0.79)	0.57 (0.35, 0.79)	0.59 (0.35, 0.81)	0.60 (0.38, 0.79)	0.62 (0.42, 0.82)
Body mass index (kg/m2)	0.58 (0.31, 0.79)	0.58 (0.35, 0.81)	0.60 (0.34, 0.81)	0.66 (0.44, 0.85)	0.65 (0.42, 0.85)
Waist circumference	0.55 (0.31, 0.79)	0.63 (0.39, 0.84)	0.60 (0.32, 0.81)	0.66 (0.41, 0.84)	0.65 (0.43, 0.84)
Female	0.53 (0.29, 0.76)	0.56 (0.33, 0.80)	0.59 (0.33, 0.80)	0.62 (0.35, 0.81)	0.59 (0.35, 0.81)
Online status	0.5 (0.28, 0.73)	0.48 (0.25, 0.73)	0.48 (0.28, 0.73)	0.50 (0.30, 0.73)	0.48 (0.21, 0.73)
Race/ethnicity	0.62 (0.37, 0.82)	0.62 (0.38, 0.83)	0.69 (0.42, 0.86)	0.68 (0.43, 0.87)	0.62 (0.39, 0.82)

Unlike Frane's method, which uses maximum predictability to control group size balance and varying data-driven probabilities to control covariate balance, our modified symmetric KLD method allows users to specify P_k, D_n, and p_D_n considering acceptable tradeoffs between balance and unpredictability for a given trial. Minimization has been most commonly adopted in patient randomized trials [3]. Future studies are needed to empirically evaluate the application of our modified symmetric KLD method and other minimization methods to different types of studies.

5. Conclusions

We successfully developed, tested, and made easily available an algorithm for balanced randomization with both categorical and continuous covariates in RCTs with two or more treatments. Our algorithm and R code provide an easy-to-use and valuable tool for statisticians as well as medical researchers who may have limited access to a statistician.

Availability and requirements

Project name: Randomization allocation algorithm,
Operation systems: Windows,
Programming language: R,
License: Code provided free for non-commercial use with absolutely no warranty,
Restrictions: Commercial organizations should contact the author prior to use.

List of abbreviations

Randomized controlled trial: RCT
Kullback–Leibler divergence: KLD

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LX carried out the literature review, extended the methodology, developed the R code and drafted the manuscript. VY helped to test the R code and revised the manuscript. JM made substantial contributions to conception and design and revised it critically for important intellectual content. All authors read and approved the final manuscript.

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