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Randomization of subjects to study-arms of a parallel study in the presence of multiple covariates

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RESEARCH

Randomization of subjects to study-arms of a parallel study in the presence of multiple covariates

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Abstract

Background: Parallel intervention studies involving healthy volunteers usually require a procedure to allocate the subjects to study-arms. Statistical models to evaluate the different outcomes of the study-arms will include study-arm as a factor along with any covariate that might affect the results. To ensure that the effects of the covariates are confounded to the least possible extent with the effects of the arms, stratified randomization can be applied. However, there is at present no clear-cut procedure when there are multiple covariates.

Methods: We propose a D-optimal blocking procedure to allocate subjects with known values of the covariates to the study arms. We prove that the procedure minimizes the variances of the baseline differences between the arms corrected for the covariates. The procedure uses standard statistical software.

Results: We demonstrate the potential of the method by an application to a human parallel intervention trial with three arms and 162 healthy volunteers. The covariates were gender, age, body mass index, an initial composite health score, and a categorical indicator called first-visit group, defining groups of volunteers who visit the clinical centre on the same day (17 groups). Volunteers were allocated equally to the study-arms by the D-optimal blocking procedure. The D-efficiency of the model connecting an outcome with the study-arms and correcting for the covariates equals 99.2%. We simulated 10,000 random allocations of subjects to arms either unstratified or stratified by first-visit group. Intervals covering the middle 95% of the D-efficiencies for these allocations were [82.0, 92.0] and [93.2, 98.4], respectively.

Conclusions: Allocation of volunteers to study-arms with a D-optimal blocking procedure with the values of the covariates as inputs substantially improves the efficiency of the statistical model that connects the response with the study arms and corrects for the covariates.

Trial registration: Dutch Trial Register NL7054 (NTR7259). Registered May 15, 2018, https://www.trialregister.nl/trial/7054.

Keywords: D-efficiency; Randomization; Blocking

Background

A clinical trial involving volunteers usually focuses on comparing the effect of different interventions or treatments of the subjects. The main instrument for the comparison is a statistical model that links clinical outcomes to the intervention or treatment that was applied. An important concern when evaluating the treatment differences is the possibility of bias in the treatment effects. For example, if the subjects allocated to one of the arms in a parallel or between-subjects study design are on average older than those allocated to another arm, the crude difference in average responses of these arms may be biased by age.

There are well-known methods to obtain unbiased estimates of the treatment effects. First, for biases due to subject-specific covariates, one could consider using a cross-over or within-subjects design, in which any subject receives all of the treatments, separated by a wash-out period. However, the treatments may be incompatible with such a design. For example, lifestyle interventions such as weight reduction studies should involve a between-subjects rather than a within-subjects design, because effects are not easily washed out.

For parallel or between-subjects studies, each subject is allocated to one of the arms. Bias due to covariates can be reduced in two ways. First, the randomization procedure to allocate the subjects to the arms could be made to address specific sources of bias. For example, one could use a stratified randomization [1] to reduce bias due to age. This involves defining age classes, determining the age class for each subject and randomizing the allocation of the subjects of each age class to the arms of the study. As a consequence, the arms of the study have about the same average value of the covariate involved so that differences in treatment outcome means hardly need adjustment for differences in a covariate among the arms. Stratified randomization is a study design-based measure to reduce bias.

The second way to reduce bias in between-subjects studies is to include the potential sources of bias in the statistical model to evaluate study outcomes. The statistical model then provides estimates of the treatment effects corrected for co-

variates such as age. Inclusion of the covariate in the statistical model in addition to stratified randomization hardly removes bias, but it does reduce the unexplained variation within the arms. Therefore, the effects of the different treatments are estimated more precisely than without the inclusion of the covariate in the model.

It might be possible to define homogeneous study groups based on multiple covariates. When these groups are sufficiently large, stratified randomization could proceed in the same way as for a single covariate. However, with an increasing number of covariates the groups become too small for a stratified randomization. Nevertheless, it is desirable that the arms of a human study have about the same average value for all of the covariates, or, in case of a categorical covariate, shows a proportional distribution of that covariate for the respective arms. The motivating example for this paper is a human intervention study with three study-arms, in which gender, age, boy mass index (BMI), and a composite health score are continuous covariates. Subsequently, a categorical covariate called first-visit group defines groups of subjects whose initial visit of the clinical center was on the same day. There are 17 different first-visit groups so that a stratified randomization addressing all the covariates would be impossible to perform.

The purpose of this paper is to propose a method to allocate subjects to the arms of a study using multiple covariates. The method is model-based such that the variances of the intervention effects corrected for the covariate are minimized. It can be conducted using commercially available statistical software, requiring as input a list specifying for each subject the covariates that need to be addressed, and the number of arms in the study. The output is an allocation table where each subject is allocated to one of the arms. We further propose a quantitative measure of the effectiveness of any allocation. We show the effectiveness of the proposed allocation method for the motivating example using both this measure and tables of mean values or frequencies of the covariates for the three study-arms. We compare the effectiveness of our procedure with results on 10,000 completely random allocations and 10,000 stratified random allocations within each of the 17 levels of the first-visit group. Finally, we sum up benefits and possible drawbacks of the procedure.

Methods

Allocation procedure

Our method to allocate subjects to the arms of a study is based on a statistical model that relates any parameter of interest to the arms of the study and the covariates considered to be relevant for that study. We assume that these parameters are continuous so that we can use linear-model methodology. Let y be the $N \times 1$ vector of observed values of these parameters. Further, let X be the $N \times p$ matrix of covariates and T the $N \times (t-1)$ matrix of contrasts modelling the differences between the t arms of the study. The statistical model of the data is then

$$y = X\beta + T\gamma + \epsilon, \quad (1)$$

where β is a $p \times 1$ vector of coefficients corresponding to the covariates, γ is a $(t-1) \times 1$ vector of coefficients quantifying the differences between the arms, and ϵ $N(0, \sigma^2 I_N)$ is a vector of identically and independently distributed normal variables with mean 0 and variance σ^2, and I_N is the $N \times N$ identity matrix.

The purpose of the study is to estimate γ as precisely as possible. [2] show that the precision of the estimator of γ is maximized if

$$\mathcal{D}_s = |T^T(I - X(X^TX)^{-1}X^T)T| \quad (2)$$

is maximized, where $|.|$ denotes the determinant. This is determinant of the residual sums of squares and products matrix after regressing the contrast vectors making up the differences between the $t-1$ arms of the study effects in T on the covariates collected in X. Denoting the full matrix of parameters with $F = [XT]$, it can be shown that (2) is equivalent to

$$\mathcal{D}_s = |F^TF|/|X^TX| \quad (3)$$

The matrix X is fixed when allocating the subjects to the arms of the study. The only way to affect D is in the allocation of the subjects to the arms as expressed with the matrix T. We propose optimizing this allocation using the blocking procedure of [3]. This procedure groups the rows of a pre-existing matrix T with treatment columns into groups, or blocks, of a specified size such that the precision of the

estimator of γ is maximized. Denoting the blocking allocation matrix by X and using $F = [TX]$, the procedure maximizes

$$D^* = |F^T F|/|T^T T|. \quad (4)$$

The blocking factor is a categorical covariate added by the procedure. In the present case, however, we have a pre-existing matrix of covariates X and we want to allocate the rows to groups corresponding to the arms. If we fix the number of subjects in each arm, we can nevertheless use the blocking procedure to obtain an optimal allocation. Fixing the number of subject per arm does not fix the matrix T, but it does fix $|T^T T|$. Therefore, $|F^T F|$ is maximized by the procedure. By 4, maximization of $|F^T F|$ implies maximization of D so that the procedure can be used to optimize the allocation of subjects to the arms of a study.

Measuring effectiveness

By writing the determinant in (2) as

$$\mathcal{D}_s = |T^T T - T^T X (X^T X)^{-1} X^T T|, \quad (5)$$

it can be seen that the maximum is reached if X and T are orthogonal to each other, and $D_s = |T^T|$. Without loss of generality, T can be made to include $t-1$ orthogonal contrasts with length $\sqrt{N}$. Therefore, $|T^T T| = N^{t-1}$. Following [4], we define the D_s efficiency of the study design with respect to the covariates as $\mathcal{D}_s^{1/(t-1)}/N$. Its value equals 1 if the allocation is such that the treatment contrasts are orthogonal to the covariates. Its value equals 0 if one or both of the treatment contrasts are completely aliased with one of the covariates.

Results

Performance of the allocation procedure

The motivating example for this paper is a clinical study to assess the effects of general nutritional advice versus personalized nutritional advice to control a set of health parameters in volunteers. There were three study arms: (1) a control arm where no advice was offered, (2) a general nutritional advice arm and (3) a personalized nutritional advice arm. The study included a total of 162 subjects. Each of the subjects visited the clinical center three times. The initial visit involved collecting

baseline information of the subjects such as BMI. Subjects furthermore consumed a mixed meal challenge test drink and multiple blood samples were obtained afterwards to analyse the physiological response. Based on this response, an initial health score was calculated [5]. The intervention started on the second visit to the clinical center. The main interest of the study is in the relation between the study arm and changes in health score between second and third visit.

Gender, age, BMI and initial health score may affect the change in health parameters between the second and third visit. Therefore, they should be included as covariates in a statistical model relating the change in health score between second and third visit to the arm of the study. We decided also to include the grouping variable that indicates which participants initially visited the clinical center on the same day. There are 17 first-visit groups indicated by this variable. These groups of subjects remain largely the same for the second and third visits. Therefore, including the first-visit group as a variable in a statistical model accounts for different changes in health parameters for people starting early in the study when compared to those starting later on, for example by seasonal variation.

In view of the main interest of the study, the differences between the arms as regards the changes in health parameters between the second and third visit should be confounded to the least possible extent with differences between gender, age, BMI, initial health score and first-visit group. The matrix X in equation 1 thus includes one column for each of the parameters gender, age, BMI and initial health score and 17 columns indicating whether a subject belongs to first-visit group 1 up to 17 (an entry 1 for subject i in column j indicates that subject i belongs to first-visit group j).The matrix T is a 162×2 matrix of normalized contrasts making up the differences between the 3 arms of the study. An allocation of subjects to the arms of the study corresponds to a permutation in the rows of T against a fixed matrix X. We impose the restriction that each arm is to include 54 subjects. Therefore, $|T^T T|$ in equation 4 equals 162^2.

We used SAS/QC procedure OPTEX with 5000 iterations to allocate the subjects to the arms. The D_s-efficiency of the allocation is 0.992. Table 1 shows the distribution over the arms for female (F) and male (M) subjects. The table shows that the 104 female subjects are allocated as evenly as possible to the three arms. The same is the case for the 58 male subjects. Neither 104 nor 58 is divisible by

3 so that the distribution cannot be perfectly even. The distribution is such that each arm includes 54 subjects and the ratio of female over male is as close to constant as possible. Table 2 shows the distribution over the arms for each first-visit group. Note that these groups are of unequal size. It is clear that the subjects of one and the same first-visit group are allocated as evenly as possible to the three arms. Finally, the means and standard deviations of the continuous covariates age, BMI and initial health score are shown in Table 3. The three arms have nearly the same mean values of these covariates, while their standard deviations are also close. We conclude that the randomization procedure was very successful in returning an efficient study design.

Discussion

Comparison with complete and restricted randomization

To assess the amount of improvement due to the proposed procedure, we performed 10,000 random allocations of the subjects to arms and evaluated for each allocation the D_s efficiency for the study design with respect to the covariates. We considered a completely random allocation and a random allocation stratified by first-visit group. For the latter case, we assumed that, for each first-visit group, the numbers of subjects assigned to each of the arms correspond to the numbers in Table 2.

The results of the random allocation are shown in Figure 1. The blue bars show a frequency distribution of the 10,000 random allocations. The proposed procedure, addresses all covariates simultaneously. The small red bar denotes the D_s-efficiency of 99.2 obtained in this way. Intervals covering 95% of the D_s-efficiencies for the completely random and stratified random allocations were [0.80, 0.90] and [0.93, 0.98], respectively. Maximum values were 0.97 and 0.99 respectively. We conclude that it is very likely that a random allocation returns a substantially worse D_s-efficiency for the study design than a model-based allocation. Even in case the numbers of subjects per arm are predetermined for each first-visit group, the stratified randomization generally produces inferior study designs.

Restriction to specific study designs

The allocation procedure proposed here is appropriate for a parallel study design in which the subjects are simultaneously allocated to the arms. This implies that the procedure is not compatible with studies where an immediate choice among

treatments is required such as clinical trials that enrol subjects gradually. Sajobi et al. [6] provide a heuristic method to balance multiple covariates as much as is feasible over the arms of the study. The method presented in that paper employs an updated table of the current distribution of each individual covariate over the arms to allocate a new subject to one of these arms. Instead, our method operates directly on the precision of the parameter estimators modeling the differences between the arms when corrected for the joint effects of the covariates.

The procedure is also not compatible with a cross-over design, because such a design features several treatments per subject. Therefore, a correction for the covariates determined prior to the actual start of the study affects these treatments in the same amount. As a result, treatment differences in cross-over studies are unaffected by covariates measured at the start.

Conclusions

In this paper, we proposed a model-based procedure to allocate subjects with known values of a set of covariates to the study-arms of a parallel study. The procedure can be viewed as an extension of stratified randomization to the case of multiple covariates. It operates using standard statistical software. Its goal function is such that the allocation results in a maximum precision for the effects of the study-arms after correction for the covariates. The success of the procedure can be measured by the D_s-efficiency of the resulting design and by summary tables classified by the covariate values and the study-arm. An application to a human intervention trial with three arms and 162 volunteers showed that the procedure is highly effective.

Abbreviations

BMI: Body Mass Index.

Declarations

Ethics approval and consent to participate

Before entering the study, all participants provided written informed consent. The study was approved by the French medical Ethics Committee, Comité de Protection des Personnes (CPP) and agreed upon by the French health agency (ANSM, Competent Regulatory Authority). The study was conducted in accordance with the Declaration of Helsinki as revised in 1983 and was registered in the Dutch Trial Register NL7054 (NTR7259) on May 15, 2018; see https://www.trialregister.nl/trial/7054.

Consent for publication

Not applicable.

Availability of data and materials

Data used for the allocation are available upon reasonable request. SAS code for the allocation is provided as a supplementary file.

Competing interests

The authors declare that they have no competing interests.

Funding

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Author's contributions

EDS and SW developed the study design; EDS developed the randomization procedure; SW supervised the study; EDS and SW wrote the paper; both authors read and approved the final paper.

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Figure ledends

Figure 1 D_s-efficiencies for potential complete randomizations in the motivating example. Based on a model with gender, age, BMI, a composite health score and membership of one of 17 first-visit groups as covariates, efficiencies of the estimators of the effects of 3 study arms are shown for 10,000 random allocations of subject to arms, not stratified by any covariate. The red bar denotes the efficiency obtained with the proposed procedure, which addresses all covariates simultaneously.

Figure 2 D_s-efficiencies for potential stratified randomizations in the motivating example. Based on a model with gender, age, BMI, a composite health score and membership of one of 17 first-visit groups as covariates, efficiencies of the estimators of the effects of 3 study arms are shown for 10,000 random allocations of subject to arms, stratified by first-visit group. The red bar denotes the efficiency obtained with the proposed procedure, which addresses all covariates simultaneously.

Tables

Table 1 Allocation of subjects to study arms according to gender in the motivating example. The table shows the numbers of female (F) and male (M) subjects allocated to the arms A, B and C, respectively.

Gender	Arm		
	A	B	C
F	34	35	35
M	20	19	19

Table 2 Allocation of subjects to study-arms according to first-visit group in the motivating example. A first-visit group comprises the subjects that had their intake visit on the same day. The table shows for each first-visit group the numbers of subjects allocated to the arms A, B and C, respectively.

Visit	Arm		
	A	B	C
1	3	4	3
2	3	3	4
3	4	4	3
4	3	2	2
5	4	3	4
6	3	3	4
7	3	2	2
8	4	4	3
9	2	3	3
10	3	3	3
11	3	3	3
12	3	4	4
13	3	3	4
14	4	3	3
15	4	4	4
16	2	2	2
17	3	4	3

Table 3 Allocation of subjects to study-arms according to age, BMI and initial health score in the motivating example. The table shows means and standard deviations of the covariates in the arms A, B and C, respectively.

Covariate	Arm					
	A		B		C	
	mean	sd	mean	sd	mean	sd
Age	42.63	12.59	42.33	12.36	42.93	11.87
BMI	25.28	3.15	25.31	3.68	25.27	3.97
Health Score	1.476	0.135	1.475	0.121	1.478	0.133

Additional Files

Randomization.txt

SAS code to allocate the subjects to the three arms of the motivating example study.

figure 1

Click here to access/download;Figure;fig1-eps-converted-to.pdf

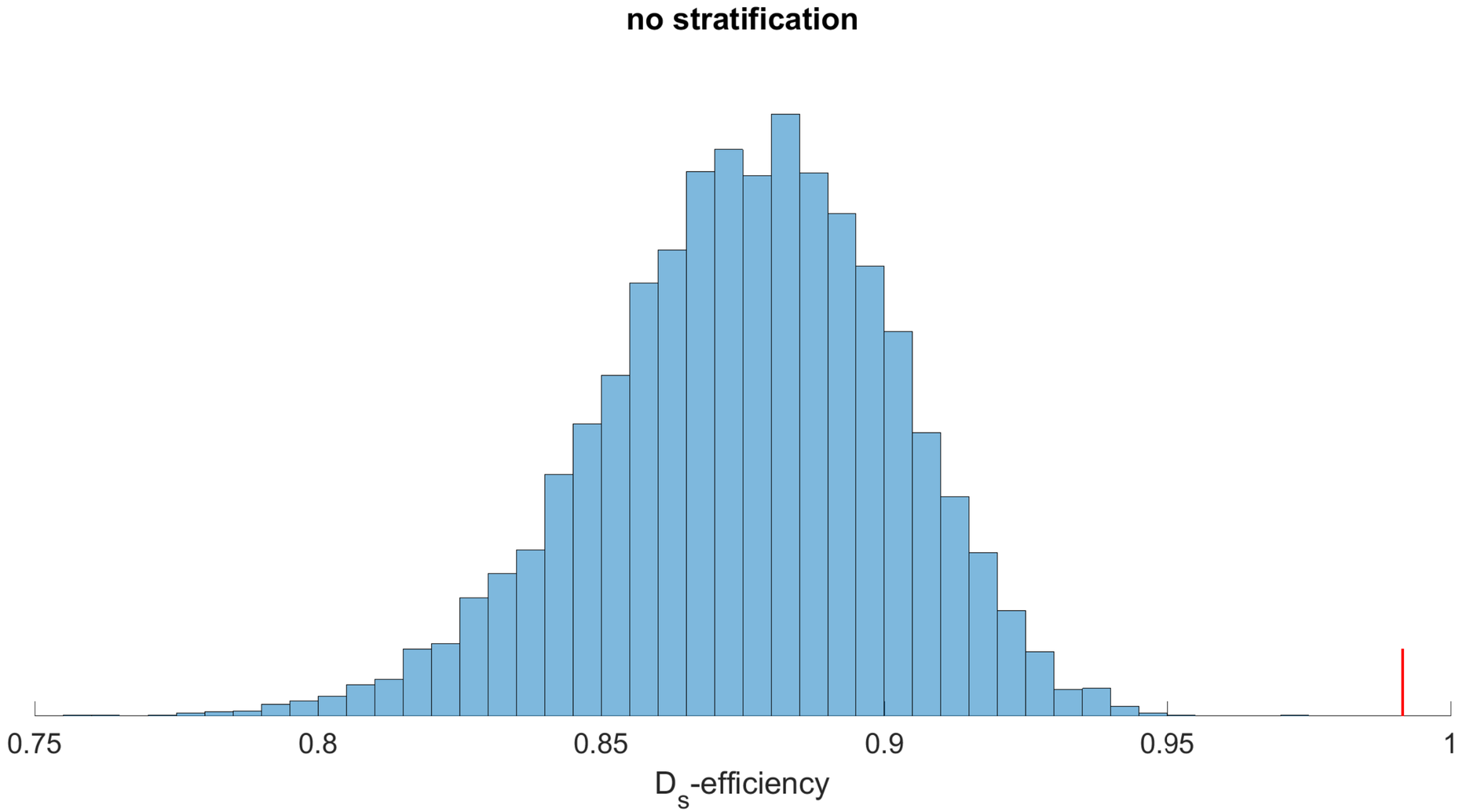

figure 2

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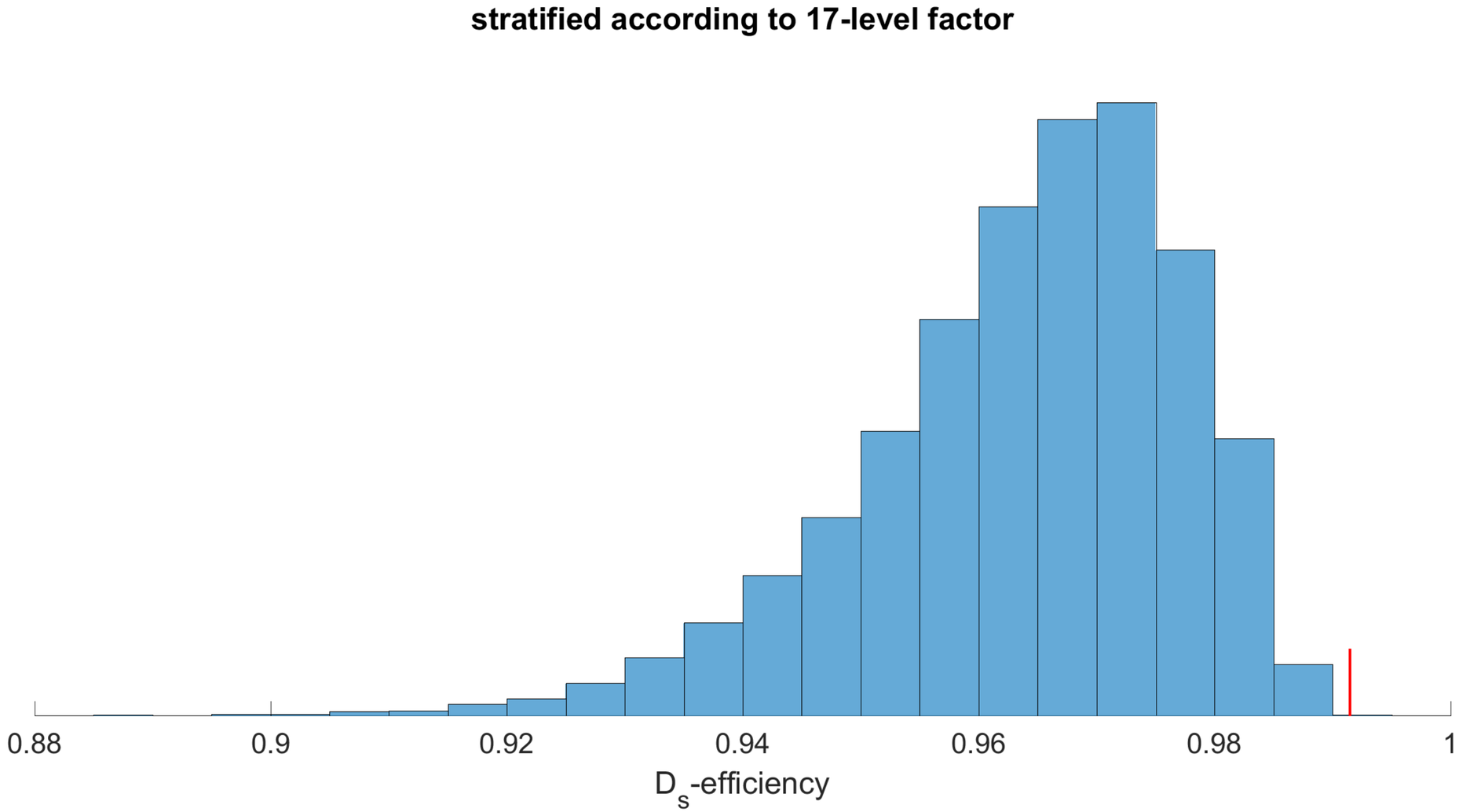

text file with SAS code for randomization