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A New Sequential Randomization Procedure for Comparative Experiments

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Abstract. For comparative experiments with several treatments, balancing the arms optimizes inference about the treatment effects under homoscedasticity. Moreover, ensuring that treatment groups are comparable in terms of key covariates is another critical aspect. Often, this translates into the equality of the covariate distributions in the treatment arms; while in the presence of heteroscedasticity the optimal design may induce a more complex structure that generally depends on the unknown model parameters. In all these cases, the optimal designs are characterized by a set of equality constraints involving, for instance, the percentage of allocations to each treatment and the empirical moments of the covariates in the different arms. We propose a new sequential randomization procedure for implementing optimal designs based on equality constraints across the treatment groups; the suggested sequential design is aimed at minimizing the variances of the group-specific elements involved in the optimal design. A simulation study shows the validity of the approach, which guarantees a significant improvement in the convergence to the optimum.

Keywords: Balance, Covariate-adaptive procedures, CARA, Optimal designs

1 Introduction

In the design of comparative experiments aimed at comparing the efficacy of $K > 2$ treatments, it is often required to globally balance the treatment groups in order to optimize inference about the treatment effects (see, e.g., [1, 2]). Another critical requirement is to ensure that treatment arms are comparable in terms of key baseline characteristics and this concept of covariate-balance is usually matched with the global balance to avoid loss of efficiency in the estimation of the treatment effects, reduced statistical power, and ultimately, misleading conclusions. Due to the label switching of the treatments (which guarantees that the drugs are treated symmetrically), the optimal designs in comparative experiments are often represented by set of equality constraints involving, for instance, the percentage of allocations to each arm as in the classical one-way ANOVA;

under the linear homoscedastic model with covariates, these constraints also regard the empirical moments of the covariates across the different arms (see, e.g., [5]), while for more complex model they may also involve the unknown model parameters [3]. To address this challenge, several sequential allocation procedures have been proposed to asymptotically approach the optimum; these rules ranging from simple randomization to more sophisticated ones falling into the classes of i) Allocation-Adaptive (AA) designs, where each assignments is based on the previously allocated treatments, ii) Covariate-Adaptive (CA) procedures, where the allocation process also depends on the observed covariates of previous subjects (as well as those of the current one) and iii) Covariate-Adjusted Response-Adaptive (CARA) rules, where the entire accrued information is considered, taking into account the previous responses as well (see [6, 7] for a review).

Although the simplified scenarios of $K = 2$ treatments usually allows one to derive a functional form of the optimal design (namely the desired allocation proportion of each treatment) globally and/or at each level of the covariates, in the case of several treatments this is not generally possible. In this case, suitable extensions of the Sequential Efficient Design (SED) [5] could be employed. The key idea of this CA procedure is to sequentially minimize the Euclidean norm of an imbalance vector representing the current distance between the statistics involved in the optimum across the two arms. However, as K and/or the number of considered covariates grows, the size of this imbalance vector rapidly increases, since it should consider each of the treatment contrasts across the arms for every statistics, which could strongly damages the convergence to the optimum.

In this paper, we propose a new sequential randomization procedure for implementing optimal designs characterized by equality constraints across the treatment groups based of the variances across arms; in particular, the suggested proposal is aimed at minimizing the variance of each group-specific elements involved in the optimal design; according to these quantities, the suggested procedure could become of AA, CA or CARA nature, and so displaying extreme flexibility. A simulation study under both ANOVA, linear and logistic models illustrate the benefits of our approach.

2 Optimal Designs

For each subject i , let $\delta_{i,k} = 1$ if treatment k is assigned and $\delta_{i,k} = 0$ otherwise; thus, $\pi^{(k)} = n^{-1} \sum_{i=1}^n \delta_{i,k}$ represents the percentage of allocation to treatment k (with $k = 1, \dots, K$) after n steps, where clearly $\sum_{k=1}^K \pi^{(k)} = 1$. Without covariates, in many experimental scenarios (like, e.g., the homoscedastic one-way ANOVA) the optimal design consists in balancing the assignments across treatment groups, i.e.,

$$\pi^{(1)} = \dots = \pi^{(K)}, \quad (1)$$

leading to $\pi^{(k)} = K^{-1}$ for every $k = 1, \dots, K$ due to the unitary constraint. In the presence of a continuous covariate X available for each subject prior to

randomization, let x_i be the covariate value of the i th subject, so that

$$m_j^{(k)} = \left(\sum_{i=1}^n \delta_{i,k} x_i^j \right) / \left(\sum_{i=1}^n \delta_{i,k} \right), \quad \text{for } k = 1, \dots, K$$

denote the moments of order $j = 1, 2$ of X observed in group k after n steps. Under the linear homoscedastic model with treatment-by-covariate interaction, besides (1) optimality also requires to balance first and second moments of the covariate between the arms [5], i.e.,

$$\pi^{(1)} = \dots = \pi^{(K)}, \quad m_1^{(1)} = \dots = m_1^{(K)}, \quad m_2^{(1)} = \dots = m_2^{(K)}. \quad (2)$$

In more complex models, the equality constraints defining the optimum could be more tricky, possibly involving the unknown model parameters. Assuming for instance a binary outcome under the logistic model with treatment-by-covariate interaction

$$\Pr(Y_i = 1 \mid \delta_{i,k} = 1, X_i = x_i) = p^{(k)}(x_i) = \left\{ 1 + e^{-(\alpha_k + \beta_k x_i)} \right\}^{-1}, \quad (3)$$

the optimal design is (see [3]):

$$\pi^{(1)} \tilde{m}^{(1)} = \dots = \pi^{(K)} \tilde{m}^{(K)}, \quad \tilde{m}_1^{(1)} = \dots = \tilde{m}_1^{(K)}, \quad \tilde{m}_2^{(1)} = \dots = \tilde{m}_2^{(K)}, \quad (4)$$

where $v_i = \sum_{k=1}^K \delta_{i,k} p^{(k)}(x_i) [1 - p^{(k)}(x_i)]$ is the variance of the outcome of the i th subject assigned to treatment k , while

$$\tilde{m}^{(k)} = \frac{\sum_{i=1}^n \delta_{i,k} v_i}{\sum_{i=1}^n \delta_{i,k}} \quad \text{and} \quad \tilde{m}_j^{(k)} = \frac{\sum_{i=1}^n \delta_{i,k} v_i x_i^j}{\sum_{i=1}^n \delta_{i,k} v_i}, \quad \text{for } j = 1, 2; k = 1, \dots, K.$$

Thus, optimum (4) depends on the observed allocations and covariates and also on the unknown parameters.

3 Variance-Based Sequential Procedure

For $K = 2$ treatments, the optimal designs in (1), (2) and (4) can be achieved sequentially via adaptive randomization by suitably choosing AA, CA, CARA procedures, respectively (see, e.g., [2, 7]). Within the most recent proposals, SED [5] is CA rule aimed at converging to the optimum in (2), namely in the case of just one available covariate. This is based on the sequential minimization of the Euclidean norm $\|\cdot\|$ of an imbalance vector, whose components are the differences between each group-specific observed statistics involved in the optimum. When the next patient arrives, SED evaluates the potential imbalance obtained if he/she will be assigned to each of the two arms and then the allocation is forced to the treatment minimizing the potential imbalance through a biased coin. A possible extension of this procedure to the case of several treatments and covariates could be performed by considering, within each of the equality

constraint of the optimum, the $K - 1$ contrasts across the groups instead of the single difference between the two arms. However, as K and/or the number of considered factors grows, the size of the imbalance vector rapidly increases, that affects the speed of convergence to the optimum.

To overcome this problem, we introduce a new randomization procedure - denoted by VSD - which is able to target optimal designs consisting of $c \geq 1$ equality constraints. More specifically, at each step n we define a c -dim vector ϕ_n , whose elements are the variances of the quantities involved in the optimum evaluated after n assignments; clearly, $\|\phi_n\|$ represents the distance between the design actually employed and the optimal one (that could be expressed by the c -dim vector of zeros), that should be minimized sequentially. For instance, taking into account optimum in (2),

$$\phi_n = \left(\text{Var}_b(\pi_n), \text{Var}_b(m_{1n}), \text{Var}_b(m_{2n}) \right),$$

where $\text{Var}_b(z) = \text{Var}(z^{(1)}, \dots, z^{(K)})$. Starting with at least one observation for every treatment, when the $(n + 1)$ th patient (with covariate x_{n+1}) is ready to be randomized, we compute each distance $\|\phi_{n+1}^{(k)}\|$ that would result if he/she will be assigned to treatment k (for $k = 1, \dots, K$); thus, VSD randomly favours the treatments inducing the smallest distances from the optimum by assigning the $(n + 1)$ th subject to treatment k with probability

$$\left\| \phi_{n+1}^{(k)} \right\|^{-\gamma} / \sum_{k=1}^K \left\| \phi_{n+1}^{(k)} \right\|^{-\gamma}, \quad \text{for } k = 1, \dots, K \quad \text{and } n \geq K, \quad (5)$$

where the non-negative parameter γ governs the degree of randomness: when γ is close to 0 complete randomization is approached, while the allocations tend to be deterministic as γ tends to infinity.

Under (1), no covariates are involved and the goal simply consists in balancing the K treatments. Instead of considering, as usually suggested in the literature, the K differences $\pi_n^{(k)} - K^{-1}$ to randomize the assignment, under our proposal $\phi_n = \text{Var}_b(\pi_n)$ captures the overall imbalance through a scalar measure. Adopting (4), the constraints depend on the unknown parameters of the logistic model in (3), which should be estimated sequentially. After n assignments, the procedure evaluates the MLEs $(\hat{\alpha}_{kn}, \hat{\beta}_{kn})$ of (α_k, β_k) for $k = 1, \dots, K$, in order to estimate $v_1, \dots, v_n$. Then, $\tilde{m}_n$, $\tilde{m}_{1n}$ and $\tilde{m}_{2n}$ are estimated by the corresponding MLEs $\hat{\tilde{m}}_n$, $\hat{\tilde{m}}_{1n}$ and $\hat{\tilde{m}}_{2n}$, so that $\phi_n = \left(\text{Var}_b(\pi_n \hat{\tilde{m}}_n), \text{Var}_b(\hat{\tilde{m}}_{1n}), \text{Var}_b(\hat{\tilde{m}}_{2n}) \right)$.

4 Simulations

We evaluate the performance of the proposed procedure in comparison to the complete randomized design (CR) in the case of $K = 4$. The simulations are performed by assuming the classical one-way ANOVA without covariates, i.e., $Y_i \mid \delta_{i,k} = 1 \sim N(\alpha_k; 1)$, the linear homoscedastic model (LM) with one covariate

under treatment-by-covariate interaction, i.e., $Y_i \mid \delta_{i,k} = 1, X_i = x_i \sim N(\alpha_k + \beta_k x_i; 1)$, (with $\alpha_1 = 0, \alpha_2 = 0.2, \alpha_3 = 0, \alpha_4 = -0.2, \beta_1 = 1, \beta_2 = 0.6, \beta_3 = 0.8, \beta_4 = 1$) and the logistic model in (3) with $\alpha_1 = -1.5, \alpha_2 = 0, \alpha_3 = -0.5, \alpha_4 = -1, \beta_1 = 1, \beta_2 = 0.6, \beta_3 = 0.8, \beta_4 = 1$. The observed covariates values are generated from a standard normal $\mathcal{N}(0, 1)$ and Gamma distribution $\Gamma(0.5, 1)$. Since the level of complexity changes on the basis of the chosen optimum, VSD is performed by letting $\gamma = 1$ in the AA framework induced by (1) for ANOVA model (where only the assignments should be controlled), $\gamma = 2$ for the CA case induced by (2) (in addition, also the patient's covariates are taken into account) and $\gamma = 3$ for the CARA procedure induced by (4) (where all the assignments, covariates and responses should be considered).

Tables 1 and 2 show D and A -efficiency for VSD and CR under the one-way ANOVA, LM and logistic model (respectively), as the sample size n varies.

Table 1: D and A -efficiency for the one-way ANOVA model.

n	$\ \phi_n\ $	D_{eff}	A_{eff}
50 VSD	.003	.963	.962
CR	.005	.939	.937
100 VSD	.002	.979	.979
CR	.003	.969	.969
150 VSD	.001	.985	.985
CR	.002	.980	.980
200 VSD	.001	.988	.988
CR	.001	.985	.985
300 VSD	≈ 0	.992	.992
CR	.001	.990	.990

In the absence of covariates, $\phi_n = \text{Var}_b(\pi_n)$ is essentially null even for small samples; the gain in terms of efficiency wrt CR is evident for small samples, while it vanishes as n increases. The same conclusion could be also drawn in the presence of covariates, for both the linear model and the logistic one, where VSD still outperforms CR, especially for the Gamma case. As showed by further simulations (omitted here for brevity), the gain tends to be more relevant as K and the number of chosen covariates grows). As expected, the logistic scenario requires an increased sample size to guarantee a good approximation of the optimal design.

5 Conclusions

In general, the fast convergence of the suggested VSD to the chosen optimum induces an improvement in terms of inferential precision, especially for small-moderate samples. Moreover, the robustness of the procedure across different covariate distributions suggests its potential utility in a wide range of experiments, where deviations from standard assumptions may occur.

Table 2: D and A -efficiency with one covariate under different distributions and models.

LM, $\mathcal{N}(0, 1)$				LM, $\Gamma(0.5, 1)$				Logit, $\mathcal{N}(0, 1)$				Logit, $\Gamma(0.5, 1)$			
n	$\ \phi_n\ $	D_{eff}	A_{eff}	$\ \phi_n\ $	D_{eff}	A_{eff}		n	$\ \phi_n\ $	D_{eff}	A_{eff}	$\ \phi_n\ $	D_{eff}	A_{eff}	
50 VSD	.119	.916	.837	.242	.845	.667		100 VSD	.052	.924	.834	.076	.885	.726	
CR	.206	.896	.793	.521	.799	.577		CR	.100	.918	.810	.152	.866	.680	
100 VSD	.055	.961	.925	.104	.925	.831		150 VSD	.032	.958	.904	.042	.935	.835	
CR	.099	.949	.901	.248	.889	.754		CR	.067	.950	.884	.102	.915	.788	
150 VSD	.035	.974	.951	.062	.952	.890		200 VSD	.024	.970	.933	.028	.954	.882	
CR	.066	.966	.935	.166	.921	.822		CR	.051	.963	.915	.079	.936	.839	
200 VSD	.027	.981	.963	.041	.966	.921		300 VSD	.017	.980	.956	.019	.969	.922	
CR	.049	.975	.951	.124	.939	.861		CR	.036	.975	.944	.056	.956	.889	
300 VSD	.018	.987	.976	.025	.978	.949		400 VSD	.013	.985	.966	.014	.976	.940	
CR	.033	.983	.968	.081	.958	.903		CR	.028	.981	.956	.045	.967	.916	

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