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Optimal designs for multiple treatments with unequal variances

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ABSTRACT

The response of a patient in a clinical trial usually depends on both the selected treatment and some latent covariates, while its variance varies across the treatment groups. A general heteroscedastic linear additive model incorporating the treatment effect and the covariate effects is often used in such studies. In this paper, under D- and D_A-optimality criteria, it is shown that the product of an optimal treatment allocation and an optimal design for covariates is also optimal among all possible designs for this linear additive model. Moreover, the optimal treatment allocation is characterized by a unique set of solutions to a system of equations. The connection between D- and D_A-optimal designs is also revealed. Several examples are presented to illustrate the applications of the above results to some selected models.

1. Introduction

Consider a K-treatment ($K \geq 2$) experiment consisting of a set of independent runs, where in each run one treatment is assigned. Suppose the mean value of the response of each run is determined by the effect of the chosen treatment $t \in \mathcal{T} = \{1, \ldots, K\}$ and also by the effects of m covariates $\boldsymbol{z} = (z_1, \ldots, z_m)^T \in \mathcal{Z}$, where $\mathcal{Z}$ is a compact subset of $\mathbb{R}^m$. The variance of the response varies across the treatment groups and depends only on t. Let $\boldsymbol{f}(\boldsymbol{z}) = (f_1(\boldsymbol{z}), \ldots, f_J(\boldsymbol{z}))^T$ denote a vector of J regression functions defined on $\mathcal{Z}$ satisfying $\{1, f_1(\boldsymbol{z}), \ldots, f_J(\boldsymbol{z})\}$ is a linearly independent set. Then the heteroscedastic linear additive model is

$$y(t, \boldsymbol{z}) = \alpha_t + \sum_{j=1}^{J} \gamma_j f_j(\boldsymbol{z}) + \sigma_t \varepsilon, \tag{1}$$

where $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_K)^T$ and $\boldsymbol{\gamma} = (\gamma_1, \ldots, \gamma_J)^T$ are the vectors of treatment effects and covariate effects, respectively. The unequal variances $\sigma_1^2, \ldots, \sigma_K^2$ are assumed to be known and positive, and ε's are independent random variables, each with mean 0 and unit variance.

For simplicity, rewrite model (1) as $y(t, \boldsymbol{z}) = \boldsymbol{\beta}^T \boldsymbol{g}(\boldsymbol{x}) + \sigma_t \varepsilon$, where $\boldsymbol{x} = (t, \boldsymbol{z}) \in \mathcal{X}$, $\mathcal{X} = \mathcal{T} \times \mathcal{Z}$, $\boldsymbol{g}(t, \boldsymbol{z}) = (\boldsymbol{e}_{K,t}^T, \boldsymbol{f}^T(\boldsymbol{z}))^T$ and $\boldsymbol{\beta} = (\boldsymbol{\alpha}^T, \boldsymbol{\gamma}^T)^T$. Here $\boldsymbol{e}_{K,t}$ is the vector of length K with its tth entry equal to one and all other entries equal to zero. Throughout all designs will be treated as approximate designs, i.e., probability measures on the design region with finite support points. A centre problem is to find optimal designs for model (1) under some optimality criterion. When there is

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no covariate effects in model (1), Wong and Zhu (2008) and Sverdlov and Rosenberger (2013) obtained optimal treatment allocation designs for different inferential purposes. Recently, Atkinson (2015) studied D- and D_A-optimal designs for model (1) with $K = 2, J = m, f_j(\boldsymbol{z}) = z_j$ and $\mathcal{Z} = [-1, 1]^m$, i.e., only the treatment effects and all the linear main effects of m continuous covariates are considered.

The aim of this paper is to generalize the work of Atkinson (2015), by providing a theoretical insight into the design optimality for the general model (1) with multiple treatments. We note that model (1) can be regarded as a multi-factor model, for which optimal designs are usually obtained by the method of product design. See Schwabe (1996), Rodríguez and Ortiz (2005) and Graßhoff et al. (2007) for examples. We will show certain product design is D- or D_A-optimal for model (1) and present a further investigation of the optimal treatment allocation rules.

The remainder of this paper will unfold as follows. Section 2 proves that the product of an optimal treatment allocation and an optimal design for covariates is D-optimal for model (1). The characterization for the optimal treatment allocation of any D-optimal design is established, some numerical results are also presented. When the goal is to estimate some treatment contrasts and certain covariate effects, parallel results are obtained with respect to D_A-optimality in Section 3. Moreover, the connection between the two optimal treatment allocations under D- and D_A-optimality criteria is built. Applications of the theories to selected models are given in Section 4. Section 5 concludes this paper with some remarks.

2. *D*-optimal designs for model (1)

For model (1), the information matrix of a given design ξ on $\mathcal{X}$ is

$$M(\xi) = \int_{\mathcal{X}} \boldsymbol{g}(\boldsymbol{x})\boldsymbol{g}^T(\boldsymbol{x})/\sigma_t^2 \, d\xi. \tag{2}$$

Define $\Xi = \{\xi \mid \det M(\xi) > 0\}$, i.e., the set of all designs on $\mathcal{X}$ with non-singular information matrix. Typically we are going to find optimal designs over Ξ which maximize some concavity criterion function of the information matrix, see Pukelsheim (2006) and Atkinson et al. (2007) for examples. A design is said to be D-optimal for model (1) if it maximizes $\det M(\xi)$ over Ξ. Any D-optimal design minimizes the volume of the confidence ellipsoid for $\boldsymbol{\beta}$, the vector of total unknown parameters in model (1).

The D-optimal designs found by Atkinson (2015) are essentially special product designs (see Example 2 in Section 4). In this section a further characterization of D-optimal designs for the more general linear model (1) with multiple treatments will be presented by using the techniques in the theory of optimal product designs.

Firstly, in addition to the full model (1) we consider two reduced marginal models: the heteroscedastic one-way layout for treatment effects

$$y_1(t) = \alpha_t + \sigma_t \varepsilon, \tag{3}$$

and the homoscedastic marginal model for covariate effects with an explicit intercept term

$$y_2(\boldsymbol{z}) = \gamma_0 + \sum_{j=1}^{J} \gamma_j f_j(\boldsymbol{z}) + \varepsilon. \tag{4}$$

Let ξ_1 and ξ_2 be designs on $\mathcal{T}$ and $\mathcal{Z}$, respectively, i.e., ξ_1 is a treatment allocation design and ξ_2 is a design for covariates. Since a treatment allocation design always provides K nonnegative weights $w_1, \ldots, w_K$ for the K treatments with $\sum_{k=1}^{K} w_k = 1$, ξ_1 can be equivalently described by a $K \times 1$ vector of weights $\boldsymbol{w} = (w_1, \ldots, w_K)^T$. For the two marginal models, the corresponding information matrices of ξ_1 and ξ_2 are

$$M_1(\xi_1) = \operatorname{diag}\left\{w_1\sigma_1^{-2}, \ldots, w_K\sigma_K^{-2}\right\}$$

and

$$M_2(\xi_2) = \begin{pmatrix} 1 & \int_{\mathcal{Z}} \boldsymbol{f}^T(\boldsymbol{z})\, d\xi_2 \\ \int_{\mathcal{Z}} \boldsymbol{f}(\boldsymbol{z})\, d\xi_2 & \int_{\mathcal{Z}} \boldsymbol{f}(\boldsymbol{z})\boldsymbol{f}^T(\boldsymbol{z})\, d\xi_2 \end{pmatrix},$$

respectively.

Given ξ_1 on $\mathcal{T}$ and ξ_2 on $\mathcal{Z}$, the product design is defined as the product measure $\xi_1 \otimes \xi_2$ on $\mathcal{X} = \mathcal{T} \times \mathcal{Z}$. Hence $\xi_1 \otimes \xi_2$ assigns the weight $\xi_1(t)\xi_2(\boldsymbol{z})$ to every point $(t, \boldsymbol{z})$ in the Cartesian product of the supports of ξ_1 and ξ_2. The information matrix (2) of $\xi_1 \otimes \xi_2$ for model (1) can be rewritten as

$$M(\xi_1 \otimes \xi_2) = \begin{pmatrix} M_{11}(\xi_1 \otimes \xi_2) & M_{12}(\xi_1 \otimes \xi_2) \\ M_{12}^T(\xi_1 \otimes \xi_2) & M_{22}(\xi_1 \otimes \xi_2) \end{pmatrix}, \tag{5}$$

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