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Optimal designs for dose–response models with linear effects of covariates

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HIGHLIGHTS

- This article introduces a new dose–response models with linear effects of covariates.
- An equivalence theorem of the locally ϕ_s-optimal designs is established.
- Computational issues are also studied and presented with theoretical backups.
- The locally optimal designs are illustrated robust to the moderate misspecification of the prespecified parameters.

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ABSTRACT

Personalized medicine is becoming more and more important nowadays since the efficacy of a certain medicine vary among different patients. This requires to combine the effects of the prognostic factors or covariates along with different dosages when planning a dose–response experiment. Statistically, this corresponds to the construction of optimal designs for estimating dose–response curves in the presence of covariates. Some characteristics of the optimal designs are derived in order to search such optimal designs efficiently, and an equivalence theorem of the locally ϕ_s-optimal designs is established accordingly. Computational issues are also studied and presented with theoretical backups. As applications of the above theories, the locally optimal designs are searched out in several situations. Some simulations reveal that the searched locally optimal designs are robust to the moderate misspecification of the prespecified parameters.

1. Introduction

The dose–response relationship, which illustrates the medicine efficacy under different dosages, is an important issue in the investigation of new medicines. Constructing optimal designs for evaluating the dose–response relationship has been studied by many authors in the past few years (see Bretz F and Branson, 2005; Bornkamp et al., 2007; Dragalin et al., 2007). Some researchers constructed optimal designs for several specific regression models which are commonly used to describe the dose–response relationship. For example, Dette et al. (2010) derived the locally D- and ED_p- optimal designs for the Emax, exponential and linear-in-log models.

In clinical trails, the response to a fixed kind of medicine not only depends on treatments and dosages, but also depends on some prognostic factors which vary from person to person. For example, in the schizophrenia study in Ishigooka et al.

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(2000), patients who took the same antipsychotic (olanzapine) gave very different responses. This phenomenon motivated researchers to consider individualized treatments for patients. Qian and Murphy (2011) introduced a two-stage regression-based approach, named as Q-learning, to solve this problem. The first stage of their method estimates the conditional mean for any treatment and covariates, and the second stage derives the optimal treatment rule from the relationship established in the first stage. It is obvious that the efficiency of Q-learning is determined by the estimation of the dose–response relationship in the first stage, which can be improved by using an appropriate design scheme. This motivates us to construct efficient designs which consider the effects of different dosages and covariates.

This paper focuses on the design problem for dose–response models with linear effects of covariates. Although the optimal designs for dose–response relationships have been widely discussed, individual prognostic factors are usually excluded from the considered models since they increase the complexity of analysis. The most related work is given by Atkinson (2015) who studied the D-optimal designs for comparing two treatments. Wang and Ai (2016) generalized the work of Atkinson (2015) by providing the D-optimal designs with multiple treatments.

Finding the optimal designs for dose–response models with linear effects of covariates is not trivial because there are infinite candidate dose levels and the methodologies used in Atkinson (2015) and Wang and Ai (2016) cannot be extended directly. To infer the optimal individualized dose rule, a good design should ensure that both the effect of each candidate dose level and the effect of covariates are well estimated. To the best of our knowledge, there is no previous work on the design problem for dose–response curves when the covariates are included. The purpose of this article is to find the optimal designs in such situations.

The rest of this paper is organized as follows. Section 2 formulates the problem and gives some notations which will be used later. In Section 3, we derive upper bounds on the number of support points for the designs which cannot be improved upon the Loewner ordering. In Section 4, we characterize the ϕ_s-optimal designs introduced by Kiefer (1974), which contains A-, D-, E- optimality criteria as special cases, for our model and provide the corresponding searching algorithms. Some further results for the commonly used dose–response models are also presented. Section 5 illustrates our methodology through several examples. The robustness of our proposed designs is also evaluated in this section. Section 6 concludes this paper with discussions. All proofs are postponed to the Appendix.

2. Statistical model and approximate designs

Consider the dose–response regression model with linear effects for the ith observation:

$$Y_i = f(d_i, \boldsymbol{\theta}) + \boldsymbol{\beta}^T \boldsymbol{x}_i + \varepsilon_i, \tag{1}$$

where Y_i is the response at dose d_i and covariate vector $\boldsymbol{x}_i$, $\boldsymbol{\beta}$ is the p-dimensional unknown parameter vector, and ε_i's are independent and normally distributed with zero mean. The $f(\cdot, \boldsymbol{\theta})$ in (1), which describes the effects of different dosages, is a known function up to the unknown parameter vector $\boldsymbol{\theta} \in \mathbb{R}^q$. The variance of ε_i depends on d_i and is modeled by $\sigma^2(d_i) = cg(d_i)$, where c is a positive real number and $g(d)$ is a known positive function. The homoscedastic case corresponds to $g(d) \equiv 1$. We assume that the $f(\cdot, \boldsymbol{\theta})$ is differentiable with respect to $\boldsymbol{\theta}$ throughout this paper. For instance, the $f(\cdot, \boldsymbol{\theta})$ can be selected as some commonly used dose–response models, namely the Emax, exponential and linear-in-log models, i.e.,

$$f(d, \boldsymbol{\theta}) = \theta_1 + \theta_2 d/(\theta_3 + d), \tag{2}$$

$$f(d, \boldsymbol{\theta}) = \theta_1 + \theta_2(\exp(d/\theta_3) - 1), \tag{3}$$

$$f(d, \boldsymbol{\theta}) = \theta_1 + \theta_2 \log(d/\theta_3 + 1), \tag{4}$$

respectively (see Feller et al., 2017). Let $\boldsymbol{\Theta} = (\boldsymbol{\theta}^T, \boldsymbol{\beta}^T)^T \in \mathbb{R}^{q+p}$, which represents the vector of unknown parameters. Suppose the dosage ranges from 0 to $d_{\max}$ as in Feller et al. (2017) and the covariate, x_{ij}, ranges from L_j to U_j for each j. Note that the optimal designs do not depend on the scaling of the linear factors. Hence, the experimental region, denoted by χ, is assumed to be $[0, d_{\max}] \times [-1, 1]^p$ throughout this paper.

Following Kiefer (1974), we define the approximate design ξ_d on the sub-space $\chi_d = \{d\} \times [L, U]^p$ of χ as a probability measure with masses $\omega_{d,j}$ at the point $(d, \boldsymbol{x}_{d,j}) \in \chi_d$, and μ as a probability measure on $[0, d_{\max}]$. Note that $\xi = \int \xi_d d\mu$ is a probability measure on χ. Hence, ξ is a well-defined approximate design on the experimental region χ. For $\mu = \{(d_i, \omega_{d_i}) : i = 1, \ldots, m\}$, design $\xi = \sum_{i=1}^m \omega_{d_i} \xi_{d_i}$ implies that ξ puts weight ω_{d_i} on design ξ_{d_i} for $i = 1, \ldots, m$. In the theory introduced by Kiefer (1959), the approximate design ξ can be represented as $\xi = \{(\xi_{d_i}, \omega_{d_i}) : i = 1, \ldots, m\}$, where ξ_{d_i} is the design over the covariates at the dose level d_i for $i = 1, \ldots, m$. When only two dose levels exist, the design ξ in this paper has the same form with the designs given in Atkinson (2015). Comments on the exact designs for a specified number of patients can be found in Atkinson (2015).

By standard methods, the information matrix of $\boldsymbol{\Theta}$ in model (1) for $\xi = \{(\xi_{d_i}, \omega_{d_i}) : i = 1, \ldots, m\}$ can be written as

$$I(\xi) = \sum_{i=1}^{m} \frac{\omega_{d_i}}{\sigma^2(d_i)} \sum_{j=1}^{l_{d_i}} \omega_{d_i,j} \begin{pmatrix} \frac{\partial}{\partial \boldsymbol{\theta}} f(d_i, \boldsymbol{\theta}) (\frac{\partial}{\partial \boldsymbol{\theta}} f(d_i, \boldsymbol{\theta}))^T & \boldsymbol{x}_{d_i,j} (\frac{\partial}{\partial \boldsymbol{\theta}} f(d_i, \boldsymbol{\theta}))^T \\ \frac{\partial}{\partial \boldsymbol{\theta}} f(d_i, \boldsymbol{\theta}) \boldsymbol{x}_{d_i,j}^T & \boldsymbol{x}_{d_i,j} \boldsymbol{x}_{d_i,j}^T \end{pmatrix}, \tag{5}$$