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Optimal experimental designs for estimating the drug combination index in toxicology

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ABSTRACT

When studying combination treatments made up of different substances, the interaction of these treatments is of primary research interest. One way to express the interaction is through a combination index τ based on Loewe additivity. Regarding the statistical optimal design of trials to estimate τ, the problem generally corresponds to a *c*-optimality design problem. Unfortunately, *c*-optimal designs have several practical problems, commonly including an inability to also estimate the underlying dose–response parameters in the same trial. It is demonstrated how optimal designs for combination indices can be generated as well as how these designs can be adapted to guarantee that at least a satisfactory degree of precision can be maintained for all parameter estimates. This is achieved by introducing secondary constraints on efficiency regarding the *D*-criterion, and optimizing within these constraints only. All of the proposals are demonstrated using a practical toxicological example. Furthermore, it is also investigated how the performance of the proposed designs is affected by misspecifications regarding the a priori parameter assumptions used to generate the designs.

1. Introduction

The research here was motivated by an experimental design problem we encountered when analyzing ongoing substance interaction experiments performed at our institution (extension of Morgen et al., 2016). There, a possible interaction between two treatments was investigated in in-vitro experiments on 96-well plates. Aim of the experiments was the estimation of the combination index for the two treatments at various mixture proportions. The combination index τ (see Chou and Talahay, 1983 or Lee et al., 2007 for the theory or Bayer et al., 2012 for a standard application) is a quantity that measures whether a combination of two substances/treatments results in an effect that is either additive, synergistic or antagonistic. Usually, this index is not constant but varies depending on the mixture proportion of substances in the combination treatment as well as on the total dose level. Estimating these indices requires multiple dose–response trials where the substances are applied as singular treatments as well as in various combinations. A common setup for combination trials is a ray design, where one or more fixed combination ratios (rays) are each investigated under different levels of combination dose. Obviously, there is a major incentive to conduct these trials as efficiently as possible. If estimation of τ is performed in the context of a parametric model, statistical optimal design theory is a helpful tool towards this end. While some research in this area already exists (Casey et al., 2005; Fang et al., 2008; Almohaimeed and Donev, 2014 among others), to our knowledge none of the existing literature actually provides optimal designs specifically for the estimation of combination indices. The paper by Almohaimeed and Donev (2014) comes closest, but only proposes designs which are

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D-optimal for each of the individual sub trials at specific combination ratios. While this should result in solid designs, they are not necessarily optimal for the combination index as well.

In the context of treatment interactions, the experimental conditions to be optimized are (a) the distribution of available observations among the different single-substance and combination treatment sub studies and (b) the dose levels to be used in each. Consequently, the endpoints to be estimated are the combination indices and, as a secondary but still essential endpoint, the actual dose–response parameters for each of the single substance and combination treatments.

Usually, a balanced estimation of all parameters corresponds to a D-optimality design problem. Estimation of the combination index, however, can be represented in the context of c-optimality if a single combination index is to be estimated or as so-called D_K-optimality if several combination indices are to be estimated simultaneously for several rays and/or dose levels. Unfortunately, these design philosophies produce quite divergent results. Furthermore, purely c- and D_K-optimal designs commonly do not even allow estimation of all dose–response parameters of interest (Pronzato, 2009). We therefore propose using designs that combine both approaches by introducing lower constraints on D-efficiency (say, D-efficiency at least 90%) into the c-/D_K-problem as well as providing solutions for both basic criteria.

The basic model and standard results from optimal design theory are shown in Section 2. In Section 3 we show how estimating the combination index corresponds to c-/D_K-optimality problems and how optimality regarding these criteria can be combined with lower constraints on D-efficiency. In Section 4 we apply these results to generate optimal designs for a practical toxicological example. As these designs depend on an a priori assumption about the parameters, we conclude with an investigation regarding the robustness of our results towards the parameter assumptions, which can be found in Section 5.

2. Optimal experimental designs in compound combination trials

2.1. Model

We consider a set of three or more connected nonlinear regression models, corresponding to experiments to establish the dose–response relationship of a first treatment A, an alternative second treatment B and finally p different combinations of the two treatments at dose fractions v_l and $(1-v_l)$ ($v_l \in (0,1)$, $l = 1,\ldots,p$). These dose fractions v_l refer to the raw dose proportion of the treatment A in the combination treatment, irrespective of the relative potencies of the treatments. In total, observations can be taken on n different experimental units (subjects, wells, etc.) distributed among the $(p+2)$ experiments. To start with, we define the model for each of the experiments as follows:

$$Y_{ij} = \eta_j(x_{ij}, \boldsymbol{\theta}_j) + \varepsilon_{ij} \quad i = 1,\ldots,n_j, j = 1,\ldots,(p+2), \sum_{j=1}^{p+2} n_j = n. \tag{1}$$

The sub-experiments $j = 1$ and $j = 2$ refer to the two singular treatments, while $j = 3,\ldots,p+2$ correspond to the p combination experiments. Observations can be taken at any measurement condition x_{ij}, distributed among any of the experiments in such a way that the total number of observations is n. Each observation x_{ij} in any one of the experiments is selected from an identical finite set $\mathcal{X}$ consisting of r different potential dose levels. This design space $\mathcal{X}$ must be defined in a way that includes all relevant available dose levels for both individual treatments as well as the combination treatments. Of course, not all of them will actually be used in the actual experiment. The vectors $\boldsymbol{\theta}_j = (\theta_{j1},\ldots,\theta_{jk}) \in \Theta, j = 1,\ldots,(p+2)$ are unknown parameters describing the dose–response relationship in every sub study, one length k parameter vector for each of the sub studies. The dose–response functions $\eta_j : \mathcal{X} \times \Theta \to \mathbb{R}, j = 1,\ldots,(p+2)$ are assumed to be known and twice continuously differentiable with respect to $\boldsymbol{\theta}_j$. We allow these functions to be of a different type for each experiment, but in order to avoid needless over-complication, we assume they all depend on the same number k of parameters. Finally $\boldsymbol{\varepsilon}_{ij}$ represents the random errors for each individual observation, assumed to be independently normally distributed with expectation 0 and variance $\sigma_{ij}^2 \in \mathbb{R}, i = 1,\ldots,n_j, j = 1,\ldots,(p+2)$.

The aim of the study is not just the estimation of the combined parameter vector $\boldsymbol{\theta} = (\boldsymbol{\theta}_1,\ldots,\boldsymbol{\theta}_{p+2}) \in \Theta^{p+2}$ but also the estimation of a combination index τ (Lee et al., 2007), which for any given combination ratio and response level tells us whether, when given in combination, the two treatments will have an additive ($\tau = 1$), synergistic ($\tau < 1$) or antagonistic ($\tau > 1$) effect. Of course, this property can change based on both the dose of the combination treatment and on the proportion of the two treatments in the combination. Thus, the index τ depends on the dose–response parameters of the individual treatments, a specific, given desired response level y and the combination ratio of the treatment. Usually (Lee et al., 2007) it is defined as follows for a single combination treatment:

$$\tau(y, d_1, d_2) = \frac{d_1}{D_{y,1}} + \frac{d_2}{D_{y,2}}, \tag{2}$$

where $D_{y,1}$ and $D_{y,2}$ are the doses of substances A and B in single treatment form required for an effect of y, while d_1 and d_2 are the doses of the same substances in a combination treatment required to obtain the same effect y.

Observing our model (1), we see that the total dose of a combination treatment at mixture proportion v_l required for an effect of y can be determined through the inverse function $\eta_{l+2}^{-1}(y, \boldsymbol{\theta}_{l+2})$ and thus $d_1 = v_l \eta_{l+2}^{-1}(y, \boldsymbol{\theta}_{l+2})$ as well as