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Adaptive designs for selecting drug combinations based on efficacy–toxicity response

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Abstract

We propose a new adaptive procedure for dose-finding in clinical trials with combination of two drugs when both efficacy and toxicity responses are available. We model the distribution of this bivariate binary endpoint using the bivariate probit model. The analytic formulae for the Fisher information matrix are obtained, that form the basis for derivation of the locally optimal, minimax, Bayesian, and adaptive designs in the framework of optimal design theory.

Keywords: Adaptive design; Bivariate probit model; Dose-finding; Dose–response; Drug combination; Early phase clinical trials; Information matrix; Optimal experimental design; Optimal safe dose

1. Introduction

Our major aim is the implementation of optimal design techniques in dose-finding studies when several endpoints can be observed simultaneously on each subject. While our narrative is built for the case of two-dimensional endpoint, the generalization for a higher dimension is straightforward. We assume that the first endpoint corresponds to efficacy and the second to toxicity, the two endpoints being defined specifically for the study in question. The bivariate binary model has four possible outcomes: efficacy without toxicity, efficacy with toxicity, failure without toxicity, and failure with toxicity.

The primary goal of a dose-finding study is to establish the dose–response relationship. The optimal experimental design framework provides enough structure to make this goal attainable. It is assumed that the available dose combinations (*the design region*) and the response variables have been defined and there exists a known structure for the mathematical model describing the dose–response relationship (*the model*). The focus is on choosing the dose levels in some optimal way to enhance the process of estimating the unknown parameters of the model $\boldsymbol{\theta}$. The experimental designs are represented by a set of design points (support points) and a corresponding set of weights representing the allocations to the design points: $\xi = \{x_i, \lambda_i\}_1^k$. An important element in optimal design is the information matrix, say $M(\xi, \boldsymbol{\theta})$, which is an expression of the accuracy of the $\boldsymbol{\theta}$ estimate based on observations at k design points of design ξ. A "larger" value of M reflects more information (more precision, lower variability) in the estimate. A natural goal in

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picking the design ξ is to find the design that "maximizes" the matrix M. Unfortunately, it is not possible, in general, to find such a design, therefore, weaker criteria that are the functions of this matrix are often used. The *D-optimal criterion*, is one of the most popular in determining an optimal design ξ^*. The D-optimal criterion is the determinant of the information matrix. This criterion has several desirable properties, for instance, any invertible transformation of $\boldsymbol{\theta}$ does not affect ξ^*; it has a minimax property (cf. Fedorov and Hackl, 1997), and it is closely related to the efficiency in hypotheses testing.

A major challenge in design for nonlinear (in $\boldsymbol{\theta}$) models is that the optimal design ξ^* depends on $\boldsymbol{\theta}$—a conundrum: one is looking for the design ξ with the aim of estimating the unknown $\boldsymbol{\theta}$, and yet one has to know $\boldsymbol{\theta}$ to find the best ξ. This conundrum leads to various ways of coping with the dependence on $\boldsymbol{\theta}$. These include the *locally optimal design* based on one's best guess at $\boldsymbol{\theta}$, *Bayesian design* by augmenting the criterion to reflect the uncertainty in a prior knowledge about $\boldsymbol{\theta}$, *minimax design* by finding the design that is optimal under the worst parameter $\boldsymbol{\theta}$ value, and *adaptive design* by alternating between forming estimates of $\boldsymbol{\theta}$ and choosing a locally optimal design for that value of the parameter. We discuss these approaches below.

Heise and Myers (1996) were one of the first to construct the locally D-optimal design for two correlated binary responses using Gumbel model. Fan and Chaloner (2001) discussed the locally D-optimal design and Bayesian optimal designs for a continuation-ratio model with ordinal trinomial outcome: efficacy, toxicity, or neutral. Rabie and Flournoy (2004) also studied D-optimal designs for trinomial outcome using contingent response model. These designs, as all D-optimal designs in general, are concerned mainly with *collective ethics*: doing in the dose-finding study what is best for future patients who stand to benefit from the results of the trial.

In contrast, alternative procedures for dose-finding studies have been proposed that are mainly concerned with *individual ethics*: doing what is best for current patients in the trial. The continual reassessment method (CRM) of O'Quigley et al. (1990) was the first such method that formulates the goal of a dose escalation in Phase I trial as to maximize patient gain. Thall and Russell (1998) used a similar method with a proportional odds ratio to model the trinomial outcome case. Also for this case, Whitehead et al. (2004) have considered recently Bayesian procedures for dose escalation with the objective to determine the therapeutic range of acceptable dose combinations that have a sufficiently large probability of a efficacy response accompanied by a small enough probability of toxicity. Similar procedures are considered in Thall et al. (2003), O'Quigley et al. (2001), Braun (2002), Thall and Cook (2004), Bekele and Shen (2005), Wang et al. (2005), Whitehead and Williamson (1998), Whitehead et al. (2001). Notice, however, that although these designs rely on a noble intention to maximize individual gain by allocating the patient to the "best" known dose, the individual ethics may be well compromised by the "poor learning" about the "best" dose with such a design.

Pocock (1983) (see also Palmer and Rosenberger, 1999) points out that each clinical trial involves a balance between individual and collective ethics and such a balance is never simple but complex. Of course, the collective ethics should never usurp the individual ethics. Dragalin and Fedorov (2006) made one of the first attempt to formalize the goal of a dose-finding study as a penalized D-optimal design problem: find the design that maximizes the information (collective (society) ethics) but under the control of the total penalty for treating patients in the trial (individual (all individuals in the trial) ethics). Rather general results have been developed that allow to quantify the compromise between individual and collective ethics for Gumbel model as well as Cox bivariate binary model.

In this paper, we consider the multivariate probit model for the response (see Ashford and Sowden, 1970; Bock and Gibbons, 1996; Ochi and Prentice, 1984; Lesaffre and Molenberghs, 1991; Molenberghs and Verbeke, 2005). While for a single endpoint the logistic model is more attractive than the probit model (calculations are simpler, many results can be derived in closed form), in the case of several endpoints both the Gumbel and the bivariate binary Cox models look rather artificial when one tries to introduce correlation between different responses. At the same time, the probit model being based on the multivariate normal distribution incorporates this correlation very naturally. With the existing hardware, computing of normal distribution function is not a substantially more difficult problem than computing of logistic function. This paper can be viewed as an extension of our previous publication (Dragalin and Fedorov, 2006) in two directions: the use of multivariate probit model and generalization of the results to combinations of two drugs.

In Section 2, we introduce the bivariate probit model and derive the information matrix. Locally optimal designs are presented in Section 3. In Section 4, we provide a numerical example of locally optimal designs for the bivariate probit model. The adaptive designs for the same model are also discussed. All codes are written in SAS and can be obtained from the authors, see also Fedorov et al. (2006).