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A note on continual reassessment method

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ABSTRACT

A widely used approach in designing the phase I clinical trial is continual reassessment method (CRM). In this paper, we prove that under simple power model and logistic model, the way CRM selects the next dose level is highly efficient from the perspective of optimal design. More specifically, for simple power model, we show that the optimal design selects the dose level such that the corresponding toxicity rate is around 0.2; as for logistic model, we show that CRM is indeed optimal, which will justify the efficiency of the algorithm in theory.

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1. Introduction

Finding an accurate maximum tolerated dose (MTD), the most efficacious dose whose risk of toxicity is tolerable, is a critical step in development of medicine. A poor estimation of MTD has a direct negative impact on the subsequent clinical trial, where over-estimation will induce safety and ethical issues; and under-estimation may make it difficult to establish adequate efficacy. Thus it is ultra-important to identify MTD accurately. But the vague knowledge of the underlying characterization of the dose–response relationship makes accurate identification of MTD hard to achieve. The conventional 3 + 3 dose-escalation design, as described by Storer (1989), was among the earliest dose-escalation and de-escalation schemes utilized. However, some argue that this method of dose escalation may result in a high proportion of patients being treated at subtherapeutic doses (Simon et al., 1997, O'Quigley et al., 1990).

The continual reassessment method (CRM), first introduced by O'Quigley et al. (1990), is a study design and analytic method for Phase I clinical trial. The article has proved that CRM has a better performance compared with the traditional 3 + 3 approach under various situations. Since then many modified CRMs have been proposed to address varied raising criticisms regarding the classical CRM. However, the main structure of all the variations is still based on the CRM proposed by O'Quigley et al. (1990). The general idea behind CRM is that a dose–toxicity curve would be fitted to the data and that each patient would be assigned the dose most likely to be associated with the target toxicity rate, designated as MTD. During the process, it treats the dose–toxicity curve as a function of d and p, where they represent dose level and toxicity probability, respectively. Then the function is solved for d, at the target toxicity rate p_0, which is usually fixed before the study. The excellent performance of CRM and its variations have been demonstrated through many simulation studies (Garrett-Mayer, 2006). However, little is known as to why CRM strategy is so effective.

The aim of this paper is to answer this question. As mentioned above, the uncertainty of the underlying dose–response model is a significant obstacle in achieving the goal of determination of the target dose, i.e., the MTD. With more and more knowledge and experiences in related fields, simple power model (Wages et al., 2011; O'Quigley and Conaway, 2011; Piantadosi et al., 1998) and logistic model (Goodman et al., 1995, Piantadosi et al., 1998) have shown themselves to work well in practice of single-agent dose-finding designs. For simple power model, we show that optimal design selects the dose

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level such that the corresponding toxicity rate is around 0.2, which is exactly the commonly used target toxicity rate. We also demonstrate that even if the target toxicity rate takes some value other than 0.2, but within a reasonable range (0.1 to 0.35), CRM strategy is still highly efficient. Moreover, through simulations under varied scenarios, we show that by incorporating the idea of optimal design into the study, when the target toxicity rate is beyond 0.2, the percentage of toxicity occurrence in the trial will drop by a great amount. As for logistic model, we prove that CRM approach is indeed optimal, which justifies the efficiency of CRM theoretically.

The present paper is organized as follows: Some basic concepts about statistical optimal design theory and how it is related to the CRM setup will be presented in Sections 2–4 will focus on deriving optimal designs for MTD under simple power model and two-parameter logistic model, respectively; Section 5 provides a brief discussion.

2. About optimal design and its connection to CRM

Design of experiments concerns the way of data collection. An optimal design can reduce the sample size and cost needed for achieving a specified precision or improve the precision for a given sample size.

In a dose-finding study, a specified total number of observations, n, can be taken at any available dose level, and the parameters from the dose–response model are to be estimated. The purpose of optimal design here is to select k distinct dose levels $x_1, \ldots, x_k$, and n_i observations on each level so that the resulting design is best with respect to some optimality criterion. Since such problem is in general intractable, the corresponding approximate design, in which $n_i's$ are replaced by weight $\omega_i = n_i/n$, $i = 1, \ldots, k$, is considered. An approximate design can be expressed as:

$$\xi = \{(x_1, w_1), \ldots, (x_k, w_k)\}, \quad \text{where } \sum_{i=1}^{k} w_i = 1, \text{ and } x_i \in \mathcal{X}, i = 1, \ldots, k.$$

In order to identify optimal dose levels and their corresponding weights, one has to consider the effect of dose levels on the precision of parameter estimates, which is generally reflected by the variance of the estimators. Based on Searle (2012), the variance–covariance matrix of the maximum likelihood estimator (MLE) of the parameter of interest, say $g(\theta)$, can be written as

$$\left(\frac{\partial g(\theta)}{\partial \theta}\right) \mathrm{I}^{-} \left(\frac{\partial g(\theta)}{\partial \theta}\right)^T,$$

where I is the Fisher information matrix. On one hand, an optimal design aims minimizing the variance–covariance matrix under some optimality criterion; on the other hand, the Fisher information matrices for nonlinear models usually depend on the unknown parameters. Thus, the challenge in designing an experiment under such situation is that while one is looking for the best design with the aim of estimating the unknown parameters, one has to know the parameters to identify the best design. A common approach to tackle this dilemma is to use "locally" optimal design, where it initiates the design process on the best guess of the unknown parameters (Biedermann and Woods, 2011; Yang, 2010). This approach fits the sequential design method perfectly: the underlying model is refitted once we have new observed outcomes and optimal design can be chosen based on the updated parameter values. Therefore, CRM strategy is a sequential approach, which corresponds to the methodology adopted in a "locally" optimal design. Hereafter, the word "locally" is omitted for simplicity.

Recall that in a CRM-based design, we start with an assumed dose–toxicity curve with the unknown parameter θ, and a chosen target toxicity rate p_0. Then the estimated dose–toxicity curve is refitted under Bayesian structure after each patient's toxicity outcome is observed. For a given design d, by standard asymptotic theory, the MLE of θ has approximately multivariate normal distribution with covariance matrix $\mathrm{I}^{-1}(\theta, d)$. We consider MTD as a function of θ, i.e., MTD $= b(\theta)$, then the variance of the estimator of MTD based on $\hat{\theta}$ can be written as

$$\mathrm{V}(\widehat{\mathrm{MTD}}) = \mathrm{V}(b(\hat{\theta})) = \left(\frac{\partial b(\theta)}{\partial \theta}\right) \mathrm{I}^{-1}(\theta, d) \left(\frac{\partial b(\theta)}{\partial \theta}\right)^T.$$

A design d^* minimizing $\mathrm{V}(\widehat{\mathrm{MTD}})$ results in an accurate estimation of MTD. This design criterion is justified in the Bayesian framework: the asymptotic normal distribution of $\widehat{\mathrm{MTD}}$ approximates the posterior distribution of the $\widehat{\mathrm{MTD}}$ under a Bayesian structure. Hence, minimizing the log-variance of $\widehat{\mathrm{MTD}}$ is equivalent to minimizing the (approximate) Shannon entropy of the posterior distribution of the $\widehat{\mathrm{MTD}}$ (Chaloner and Verdinelli, 1995).

Next, we will study optimal design for simple power model and two-parameter logistic model separately. We denote response Y to be a binary random variable where 1 indicates patient experiencing dose-limiting toxicity (DLT) and 0 otherwise. We also consider X to be the dose level assigned to each entered patient, where its realization x, determined by the algorithm, will take value from m possible dose levels $\{d_1, \ldots, d_m\}$. Moreover, p is denoted as the corresponding toxicity rate for each x.

3. Simple power model

A simple power model is given by

$$Y_j \sim \mathrm{Ber}(p_j), \qquad p_j = \mathrm{E}(Y_j|X_j = x_j) = x_j^{\exp(\alpha)}, \quad j = 1, \ldots, n \tag{1}$$

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