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# On the consistency of the continual reassessment method with multiple toxicity constraints

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ABSTRACT

Conventional dose finding methods require the dichotomization of toxicity outcome measures generally collected in an ordinal scale. To improve efficiency and include more information on the gradation of toxicities, a sequential likelihood procedure that accounts for multiple toxicity constraints is proposed to differentiate the tolerance for toxicity of various degrees of severity under a novel class of multiplicative models, and the asymptotic properties of the procedure under certain model misspecification are established.



## 1. Introduction

The main objective of dose finding clinical trials is to estimate the maximum tolerated dose, defined as the dose level associated with a pre-specified probability of dose limiting toxicity. Therefore, the objective is posed as a quantile estimation problem based on a binary outcome. Numerous methods have been proposed under this framework. Among the earliest publications in this area, we have Storer (1989), O'Quigley et al. (1990), Durham et al. (1997), and Babb et al. (1998). To implement any of these methods, the toxicity outcome measured must be dichotomized given that it is collected on an ordinal scale from 0 to 5 based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (National Cancer Institute, 2003). To improve efficiency, several methods have been proposed to allow for ordinal toxicity outcomes. Several of these improved methods incorporate gradations of toxicity, while controlling only the rate of dose limiting toxicity in the objective Simon et al. (1997), Wang et al. (2000), Iasonos et al. (2011), Van Meter et al. (2011, 2012). Others reformulate the problem to find the dose associated with a pre-specified value of the outcome Bekele and Thall (2004), Yuan et al. (2007), and Ivanova and Kim (2009). The method of Lee et al. (2011) retains the quantile estimation objective while controlling the rate of higher toxicities as well to ensure that the identified dose is safe in terms of both dose limiting toxicity and other higher toxicities. This method generalizes the definition of the maximum tolerated dose by imposing multiple constraints on toxicities and proposes a generalized version of the continual reassessment method under the Bayesian framework.

Among the above dose finding methods, the continual reassessment method originally proposed by O'Quigley et al. (1990) is one of the few methods whose theoretical properties have been rigorously investigated. This paper aims to establish the theoretical properties of the multi-parameter models under the multiple toxicity constraint framework. Specifically,

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we investigate the large sample properties of the likelihood procedure for the continual reassessment method with multiple constraints and investigate its asymptotic behaviors. The paper is organized as follows. In Section 2, we describe the probability model, the objective under multiple constraints, and the dose-finding algorithm. In Section 3, we establish the large sample properties of the likelihood procedure under a class of multiplicative models. In Section 4, we conduct a simulation study comparing the proposed method with the Bayesian approach and the likelihood based continual reassessment method that considers only the constraint for dose limiting toxicity. Some discussions are provided in Section 5.

## 2. Methods

Let $D = \{d_1, \ldots, d_K\}$ be the $K$ test doses of ascending dosage $d_1 < \cdots < d_K$. Let $Y^*$ be an ordinal or continuous toxicity outcome such as the NCI-CTCAE or the toxicity burden score Lee et al. (2012). Let $Y$ be the re-defined ordinal toxicity outcome which takes on values $0, 1, \ldots, L$ based on the desired constraints, such that $L$ is less than or equal to the number of possible toxicity outcomes in $Y^*$. For example, suppose the raw outcome $Y^*$ is the NCI-CTCAE, which assumes values 0, 1, 2, 3, 4, 5, and we are interested in only two constraints (i.e. $L = 2$), one on $\text{pr}(Y^* \geq 3)$ and the other on $\text{pr}(Y^* \geq 4)$. In that case, the variable $Y$ is defined as $Y = 0$ if and only if $Y^* = 0, 1, 2$, $Y = 1$ if and only if $Y^* = 3$, and $Y = 2$ if and only if $Y^* \geq 4$. Denote $\text{pr}(Y \geq l|d_k) = R_l(d_k)$, $k = 1, \ldots, K$, $l = 1, \ldots, L$. The unknown toxicity probabilities $R_l(d_k)$ satisfy $0 < R_l(d_1) < \cdots < R_l(d_K) < 1$ for $l = 1, \ldots, L$, and $R_{l_1}(d_k) > R_{l_2}(d_k)$ for any $l_1 < l_2$ and fixed $k$. Thus, it is implicitly assumed that there are $L$ toxicity constraints, where constraint on $\text{pr}(Y \geq l)$ corresponds to the non-zero value $Y = l$, $l = 1, \ldots, L$.

Consider a pre-specified targeting toxicity vector $\theta = (\theta_1, \ldots, \theta_L)^T$ such that $1 > \theta_1 > \cdots > \theta_L > 0$. For each $l = 1, \ldots, L$, we define the optimal dose associated with the $l$th toxicity constraint as

$$d_{v_l} = \underset{x \in D}{\text{argmin}} \, |R_l(x) - \theta_l|.$$

When $l = 1$, $Y \geq 1$ corresponds to the dose limiting toxicity and $d_{v_1}$ corresponds to the original definition for the maximum tolerated dose.

The maximum tolerated dose under multiple toxicity constraints is defined as

$$d_v = \min\{d_{v_1}, \ldots, d_{v_L}\},$$

which is seen as a generalization of definition for the maximum tolerated dose. In this paper, we assume that $d_v$ is uniquely defined.

We note that the objective of the CRM with multiple constraints is the same as the original CRM when a single constraint is specified, that is, it identifies the dose associated with a single target probability of dose limiting toxicity. However, when more than one constraint is specified, the objective differs from that of the original CRM. Previously proposed methods by Iasonos et al. (2011), Van Meter et al. (2011, 2012) have incorporated information on grades of toxicity by including the additional information in the modeling, but keeping the objective the same as the original CRM. Their extensive simulations conclude that only including the grade information in the modeling does not generally improve the accuracy of identification of the MTD. By contrast, our proposed method changes the objective by including toxicity thresholds for the various grades of toxicity.

To estimate the maximum tolerated dose $d_v$, consider a generic working model

$$\text{pr}(Y \geq l) = \psi_l(x, \beta), \quad l = 1, \ldots, L, \tag{1}$$

where $\beta = (\beta_1, \ldots, \beta_L)^T$ is the unknown parameter. We assume that the above model is rich enough in the sense that for any fixed dose $x$ and any given targeting toxicity $\theta$, there exists a $\beta$ such that $\psi_l(x, \beta) = \theta_l$, $l = 1, \ldots, L$. The choice of such models will be discussed in Section 3.1.

We propose to use the maximum likelihood method to estimate the model parameters instead of the Markov chain Monte Carlo method used in Lee et al. (2011). Specifically, the maximum likelihood estimate $\hat{\beta}_n$ based on the toxicity outcomes of the first $n$ subjects is a value maximizing the likelihood

$$L(\beta) = \prod_{i=1}^{n} \psi_L\{x(i), \beta\}^{I(Y_i=L)} \, [1 - \psi_1\{x(i), \beta\}]^{I(Y_i=0)} \prod_{l=1}^{L-1} [\psi_l\{x(i), \beta\} - \psi_{l+1}\{x(i), \beta\}]^{I(Y_i=l)}.$$

If $\hat{\beta}_n$ exists, the recommended dose for the $(n+1)$th patient is

$$x(n+1) = \min\{\underset{x \in D}{\text{argmin}} \, |\psi_l(x, \hat{\beta}_n) - \theta_l|, l = 1, \ldots, L\}.$$

The likelihood approach does not require the specification of priors. In addition, the determination of the maximum likelihood estimator $\hat{\beta}_n$ is much easier to compute as it does not require the Markov chain Monte Carlo method. However, $\hat{\beta}_n$ may not exist, particularly when $n$ is small. In fact, Pratt (1981) indicated that under certain condition on $\psi_l(x, \beta)$, the maximum likelihood estimate $\hat{\beta}_n$ exists when all the $(L+1)$ possible values of $Y$ are observed. Therefore, to make use of all the $L$ constraints, all the $L+1$ possible values of $Y$ must be observed, which we call "full heterogeneity". However, we emphasize that our procedure can be used as long as two or more distinct values are observed, which we call "partial heterogeneity",