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A Phase I Dose-finding Study Based on Polychotomous Toxicity Responses

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SUMMARY

Toxicity issue is always a main concern in phase I study and it is commonly categorized to multiple grades. In this study, the concept of overall maximum tolerated dose (overall MTD) is introduced along with its analytic properties. The traditional definition of MTD is shown to be a special case of the overall MTD. A dose finding strategy is also proposed to find the overall MTD. Motivated by the continual reassessment method (CRM), a cumulative probit model with latent variables is introduced to fit the data. By introducing latent variables, Markov chain Monte Carlo (MCMC) methods are employed to estimate the model parameters. Simulation studies show that the cumulative probit model, which takes into account of the severity level of toxicity, reduces the number of patients allocated to the higher toxicity dose level. This could reduce the risk of toxicity for patients in the phase I study.

KEY WORDS: phase I clinical trial; polychotomous toxicity responses; dose finding; continual reassessment method (CRM); cumulative probit model; latent variable; Markov chain Monte Carlo (MCMC)

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1 Introduction

The primary goal of a phase I clinical trial is to determine the dose of a candidate drug for use in the subsequent phase II trial. Toxicity issue is always a main concern in phase I study and it is commonly categorized to multiple grades by the Common Toxicity Criteria (CTC) (National Cancer Institute, 2003). The general guidelines of the CTC are grade 0 for no toxicity; grade 1, 2, 3, 4 and 5 for minimal toxicity, moderate toxicity, severe toxicity, life threatening and death, respectively. In most dose allocation procedures, such as the traditional "3+3"design [7], CRM [6] and EWOC [2], these grades are dichotomized. For example, if grade 4 fatigue is considered DLT then grades $0-3$ will be non-DLT and treated identically from the point of view of an experimental design. Such dichotomization works for relatively mild toxicities. However, for severe and possibly irreversible effects such as renal, liver, or neurological toxicities, grade 4 renal toxicity is much more dangerous than that for grade 3. Hence, those toxicity grades cannot be treated equivalently. Such concerns need be addressed in the dose escalation process.

During the past ten years, polychotomous toxicity response has been widely discussed. In 2000, Wang *et al.* [8] extended the CRM by incorporating the idea of unequal weights on the assessments of grade 3 and grade 4 toxicity in the dose escalation. The simulation results show that their procedures reduce the chance of recommendation to the higher dose levels by taking into account of the impact of grade 4 toxicity, both for the standard design and for the CRM. Similar trends are observed for patient allocation to the higher !eve!s. Additionally, for CRM which performs more accurately on the estimation of maximum tolerated dose (MTD), the proposed extended CRM maintains the same characteristic.

In 2004, Bekele and Thall [3] proposed a Bayesian method for dose finding in a sarcoma trial based on a vector of correlated, ordinal-valued toxicities with severity levels varying with dose. They also developed a method for jointly eliciting the prior, a vector of weights quantifying the clinical importance of each level of each type of toxicity, and a target total toxicity burden (TTB) acceptable to the physicians.

There are other research related to this type of problem. In 2007, Yuan *et al.* [10] proposed another extension of the continual reassessment method (CRM), called the Quasi-CRM, to incorporate the grade information. They convert the toxicity grades to numeric scores that reflect their impacts on the dose allocation procedure, and then incorporate those scores into the CRM using the quasi-Bernoulli likelihood. A simulation study demonstrates

that the Quasi-CRM is superior to the standard CRM and comparable to a univariate version of the Bekele and Thall method [3].

In Phase I clinical trial, Maximum tolerated dose (MTD) refers to the highest dose of a drug or treatment that does not cause unacceptable side effects and it is determined in clinical trials by testing increasing doses on different groups of people until the highest dose with acceptable side effects is found (*Dictionary of Cancer Terms*. National Cancer Institute). This is a descriptive definition rather than an analytical definition, and it leads to different interpretations and comprehension of MTD in practice.

For most of the model-based designs, MTD is defined as a dose, x^*, at which the probability of DLT is equal to θ, where θ is an aimed-for target DLT probability. This definition of MTD works well under the case of dichotomous toxicity responses. However, it is difficult to directly apply such definition in the case of polychotomous toxicity responses. For example, suppose the probability configurations for toxicity grades $0-5$ at dose level x_1 and x_2 are $p_1 = (0.10, 0.25, 0.35, 0.15, 0.10, 0.05)$ and $p_2 = (0.35, 0.25, 0.10, 0.05, 0.10, 0.15)$, respectively, where the p_{ij} is the probability that the patient suffers the jth toxicity grade at dose x_i, $j = 1, \ldots, 6$, $i = 1, 2$. For instance, $p_{13} = 0.35$ means the chance that the patient suffers a 3rd toxicity grade at dose x_1 is 35 percent. Assume that there is a DLT if the toxicity grade is 4 or above and non-DLT otherwise and set the target DLT probability θ equals to 0.30. Since $P(\text{DLT}|x_1) = P(\text{DLT}|x_2) = 0.30$, both dose levels x_1 and x_2 are MTD according to such definition, i.e. there is no difference between dose levels x_1 and x_2 in the sense of the probability of DLT. It is obvious that these two dose levels are not the same by comparing their probability configurations. For dose x_1, the probability mass concentrates at third toxicity grade with probability 0.35. However, for dose x_2, the probability mass has dispersed concentrations at first and sixth toxicity grades with probabilities 0.35 and 0.15, respectively. Hence, it is hard to generate the definition of the MTD from the case of dichotomous toxicity responses to that of the polychotomous toxicity responses naturally.

In the case of polychotomous toxicity responses, Bekele and Thall [3] define MTD as the dose at which the total toxicity burden (TTB) is equal to a target TTB. A numerical variable, so called severity weight, is defined on the ordered toxicity grade. Then the TTB is obtained by calculating the mean value of the severity weight. Simulation study shows that, on average, this definition performs well under a wide variety of circumstances. However, in practice, the meaning of the target TTB is not quite straightforward (e.g., 3.04 in Bekele and Thall's example [3]) and it requires a great deal of effort to interact with the physicians

for establishing severity weight as well as target TTB.

It is thus important to reconsider the definition of MTD, which can be applied in both cases of dichotomous and polychotomous toxicity responses and meanwhile can be easily interpreted by physicians. In this research, we attempt to give a more rigorous definition for MTD and we also propose an attractable way to deal with the computation of the MTD. In Yang, Ye and Wang, 2011 [9] a probit model with latent variables in the case of dichotomous toxicity responses is studied. In this article, a cumulative probit model with latent variables will be investigated in the case of polychotomous toxicity responses. In next section, we introduce the new definition of overall MTD along with its analytic properties. In Section 3, the cumulative probit model with latent variables and the full conditional distributions are given. The likelihood function and the posterior distribution functions of the model parameters will be given in Section 4. In Section 5, a simulation study exploring operating characteristics of the proposed method is presented. Finally, in Section 6, conclusions and discussions are provided.

2 The Overall MTD

Suppose that, instead of a binary definition of toxicity, we use an M-point ordinal toxicity scale. Denoted by Y the polychotomous toxicity response which takes one of the M values, $\{1, \ldots, M\}$. Define by $p_y(x)$ the probability of suffering toxicity grade $Y = y$, $y = 1, \ldots, M$, at dose x such that $\sum_{y=1}^{M} p_y(x) = 1$ for all $x \in \mathbb{X}$ (where $\mathbb{X}$ is the set of all interesting dose levels). Set a critical toxicity grade m, $m \in \{1, 2, \ldots, M\}$, such that there is a severe toxicity response if the toxicity grade is m or higher, or, simply $Y \geq m$, not a severe toxicity response if the toxicity grade is less than m, or $Y < m$. Such severe toxicity is named as **level-m severe toxicity**, denoted by $T_m = \{Y \geq m\}$. For any level-m severe toxicity T_m, there is a target toxicity probability θ_m, $m \in \{1, 2, \ldots, M\}$. A dose x is said **level-m tolerable** if the probability of level-m severe toxicity T_m at x is less than or equal to θ_m, i.e. $P(Y \geq m|x) \leq \theta_m$, **not level-$m$ tolerable** if the probability of T_m at x is greater than θ_m, i.e. $P(Y \geq m|x) > \theta_m$. Given a critical toxicity grade m, the maximum dose of all level-m tolerable doses is called the **level-m maximum tolerated dose**. To make it clearer, we introduce the following definition.

Definition 2.1. For critical toxicity grade m, $m \in \{1, 2, \ldots, M\}$, associated with its target

severe toxicity probability θ, the **level-m maximum tolerated dose** (or briefly **level-m MTD**), denoted by ${}_m\mathbf{MTD}(\theta)$, is defined as

$$ {}_m\mathrm{MTD}(\theta) = \sup\{x|P(Y \geq m|x) \leq \theta\} = \sup\left\{ x \left| \sum_{y=m}^{M} p_y(x) \leq \theta \right. \right\}, \tag{1} $$

where $\sup\{S\}$ is the supremum of set S.

Here, we take the supremum because of the belief that, given a target toxicity probability, the higher the dosage, the more efficient the chemical compound, i.e. it is assumed that dose-response curves for both toxicity and efficacy are increasing in the dosage, or, simply expressed, "the more pain, the more gain."

The following propositions show some properties of the level-m MTD.

Proposition 2.1. For any critical toxicity grade m, $m \in \{1, 2, \ldots, M\}$, ${}_m\mathrm{MTD}(\theta)$ is increasing in θ, where θ is the target toxicity probability associated with the critical toxicity grade m (See Figure 1 (a)).

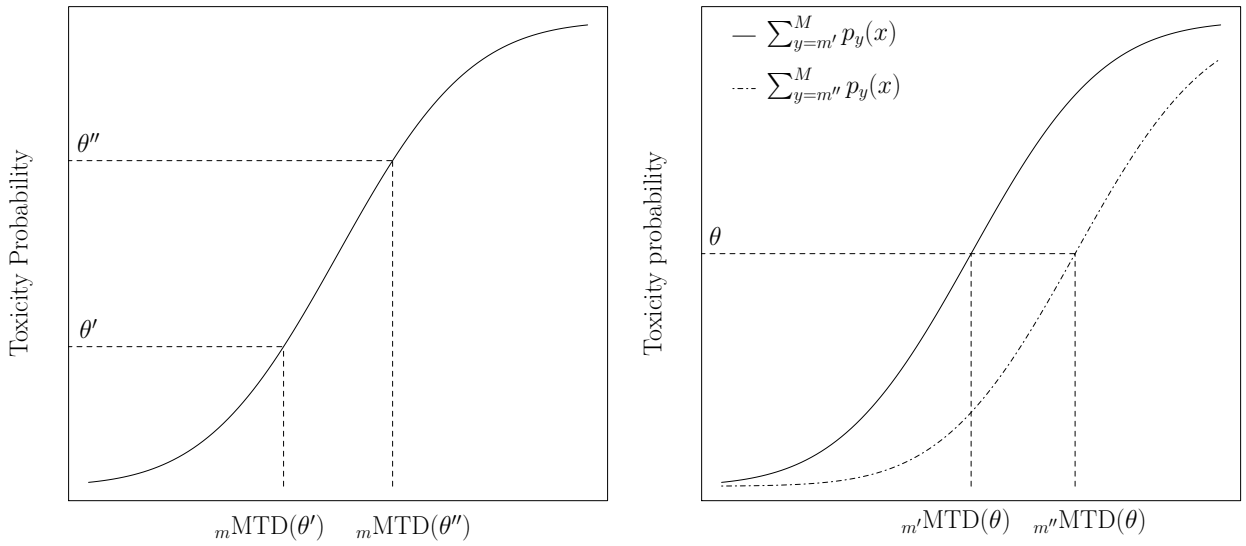
Proof. Suppose $\theta' < \theta''$, then $\sum_{y=m}^{M} p_y(x) \leq \theta'$ implies $\sum_{y=m}^{M} p_y(x) \leq \theta''$, for $m \in \{1, 2, \ldots, M\}$. Hence, $\{x|\sum_{y=m}^{M} p_y(x) \leq \theta'\} \subset \{x|\sum_{y=m}^{M} p_y(x) \leq \theta''\}$. Therefore,

$$ {}_m\mathrm{MTD}(\theta') = \sup\left\{ x \left| \sum_{y=m}^{M} p_y(x) \leq \theta' \right. \right\} \leq \sup\left\{ x \left| \sum_{y=m}^{M} p_y(x) \leq \theta'' \right. \right\} = {}_m\mathrm{MTD}(\theta''). \qquad \square $$

Referring to any level-m maximum tolerated dose, ${}_m\mathrm{MTD}(\theta)$, Proposition 2.1 shows the higher the tolerance probability θ, the larger the amount of the dose should be applied to achieve the maximum efficacy of the drug. The following proposition shows that, on the other side, the higher the toxicity grade which is treated as the DLT, the larger the amount of the drug that can be tolerated.

Proposition 2.2. Given a target toxicity probability θ, ${}_m\mathrm{MTD}(\theta)$ is increasing in toxicity grade m (See Figure 1 (b)), i.e., ${}_{m'}\mathrm{MTD}(\theta) \leq {}_{m''}\mathrm{MTD}(\theta)$, for any $m' < m''$ in $\{1, 2, \ldots, m\}$.

Proof. Suppose $m' < m''$, then $\sum_{y=m'}^{M} p_y(x) \geq \sum_{y=m''}^{M} p_y(x)$, Hence, $\{x|\sum_{y=m'}^{M} p_y(x) \leq$



(a) Proposition 2.1

(b) Proposition 2.2

Figure 1: Graph illustration for Proposition 2.1 and 2.2. (a) shows that the level-m MTD, ${}_m\text{MTD}(\theta)$, is increasing in its corresponding target toxicity probability θ; (b) shows that, for a fixed target toxicity probability θ, ${}_m\text{MTD}(\theta)$ is increasing in the toxicity grade m.

$\theta\} \subset \{x|\sum_{y=m''}^{M} p_y(x) \leq \theta\}$. Therefore,

$$ {}_{m'}\text{MTD}(\theta') = \sup\left\{x \left| \sum_{y=m'}^{M} p_y(x) \leq \theta \right.\right\} \leq \sup\left\{x \left| \sum_{y=m''}^{M} p_y(x) \leq \theta \right.\right\} = {}_{m''}\text{MTD}(\theta). \qquad \square $$

In order to define the overall MTD in the case of polychotomous toxicity responses with M-point ordinal toxicity grade, let us introduce the following notations. Denoted by $\mathbb{Y} = \{1, \ldots, M\}$ the set of ordered grades associated with the polychotomous toxicity response Y. Suppose $\boldsymbol{P} = \{p_1(x), \ldots, p_M(x)|x \in \mathbb{X}\}$ such that $\sum_{y=1}^{M} p_y(x) = 1$, for all $x \in \mathbb{X}$, and $\boldsymbol{\theta} = \{\theta_1, \ldots, \theta_M\}$, where θ_m is the target toxicity probability corresponding to the level-m severe toxicity T_m, $m \in \{1, 2, \ldots, M\}$. The triplet $\{\mathbb{Y}, \boldsymbol{P}, \boldsymbol{\theta}\}$ is called an ***M*-point ordinal toxicity grade system** defined on $\mathbb{X}$.

Example 2.1. Suppose $\mathbb{Y} = \{1, 2\}$, where 1 indicates a non-DLT and 2 a DLT. Let $\boldsymbol{P} = \{1 - p(x), p(x)|x \in \mathbb{X}\}$ and $\boldsymbol{\theta} = \{1, \theta\}$, then $\{\mathbb{Y}, \boldsymbol{P}, \boldsymbol{\theta}\}$ is a 2-point ordinal toxicity grade system, or dichotomous toxicity grade system, defined on $\mathbb{X}$. Furthermore, if $p(x) = [(1 + \tanh x)/2]^a$ and $\theta = 0.2$, then the original CRM by O'Quigley *et.al.* [6] can be reconsidered under this

framework $\{\mathbb{Y}, \boldsymbol{P}, \boldsymbol{\theta}\}$.

Suppose $\{\mathbb{Y}, \boldsymbol{P}, \boldsymbol{\theta}\}$ is an M-point ordinal toxicity grade system defined on $\mathbb{X}$. It is reasonable to define the overall MTD of $\{\mathbb{Y}, \boldsymbol{P}, \boldsymbol{\theta}\}$ as the maximum dose of those dose x such that it is level-m tolerable for any $m \in \{1, \ldots, M\}$. Based on Definition 2.1, dose x is level-m tolerable if and only if dose $x \leq {}_m\text{MTD}(\theta_m)$. Hence, the overall MTD of $\{\mathbb{Y}, \boldsymbol{P}, \boldsymbol{\theta}\}$ should be defined as the minimum of all the level-m MTD. To make it clearer, we introduce the following definition.

Definition 2.2. Given M dimensional vector $\boldsymbol{\theta} = (\theta_1, \theta_2, \ldots, \theta_M)$, whose elements θ_m's are pre-specified target toxicity probabilities with respect to the critical toxicity grade m's, the **overall MTD** of the M-point ordinal toxicity grade system, denoted by ${}^{M}\mathbf{MTD}(\boldsymbol{\theta})$, is defined as

$$ {}^{M}\text{MTD}(\boldsymbol{\theta}) = \min\{{}_m\text{MTD}(\theta_m) | m = 1, 2, \ldots, M\}, \tag{2} $$

where ${}_m\text{MTD}(\theta_m)$ is the level-m MTD associated with its target toxicity probability θ_m, for $m \in \{1, 2, \ldots, M\}$ (See Figure 2).

The following theorem shows that the target toxicity probability θ_m's should be monotone decreasing in practice, i.e., $\theta_1 > \theta_2 > \ldots > \theta_M$. Otherwise, the toxicity grade system can be reduced to a lower dimension system.

Theorem 2.1. Suppose $\{\mathbb{Y}, \boldsymbol{P}, \boldsymbol{\theta}\}$ is an M-point ordinal toxicity grade system with its associated target toxicity probability $\boldsymbol{\theta} = (\theta_1, \theta_2, \ldots, \theta_M)$ and $\boldsymbol{P} = \{p_1(x), \ldots, p_M(x) | x \in \mathbb{X}\}$. If there exists an m_0 such that $\theta_{m_0} \geq \theta_{m_0-1}$, then the M-point ordinal toxicity grade system $\{\mathbb{Y}, \boldsymbol{P}, \boldsymbol{\theta}\}$ is equivalent to the $(M-1)$-point ordinal toxicity grade system $\{\mathbb{Y}^*, \boldsymbol{P}^*, \boldsymbol{\theta}^*\}$, where $\mathbb{Y}^* = \{1, \ldots, M-1\}$, $\boldsymbol{P}^* = \{p_1(x), \ldots, p_{m_0-2}(x), p_{m_0-1}(x) + p_{m_0}(x), p_{m_0+1}(x), \ldots, p_M(x) | x \in \mathbb{X}\}$ and $\boldsymbol{\theta}^* = \{\theta_1, \ldots, \theta_{m_0-1}, \theta_{m_0+1}, \ldots, \theta_M\}$. Hence, the toxicity grade $m_0 - 1$ and m_0 should be combined into one single toxicity grade level $m_0 - 1$. Here, "equivalence"is in the sense of finding the overall MTD.

Proof. Denoted by ${}^{M}\text{MTD}(\boldsymbol{\theta})$ and ${}^{M-1}\text{MTD}^*(\boldsymbol{\theta}^*)$ the overall MTD of $\{\mathbb{Y}, \boldsymbol{P}, \boldsymbol{\theta}\}$ and $\{\mathbb{Y}^*, \boldsymbol{P}^*, \boldsymbol{\theta}^*\}$, respectively. Since $\theta_{m_0} \geq \theta_{m_0-1}$, using Proposition 2.1 and 2.2, we have

$$ {}_{m_0-1}\text{MTD}(\theta_{m_0-1}) \leq {}_{m_0}\text{MTD}(\theta_{m_0-1}) \leq {}_{m_0}\text{MTD}(\theta_{m_0}), $$

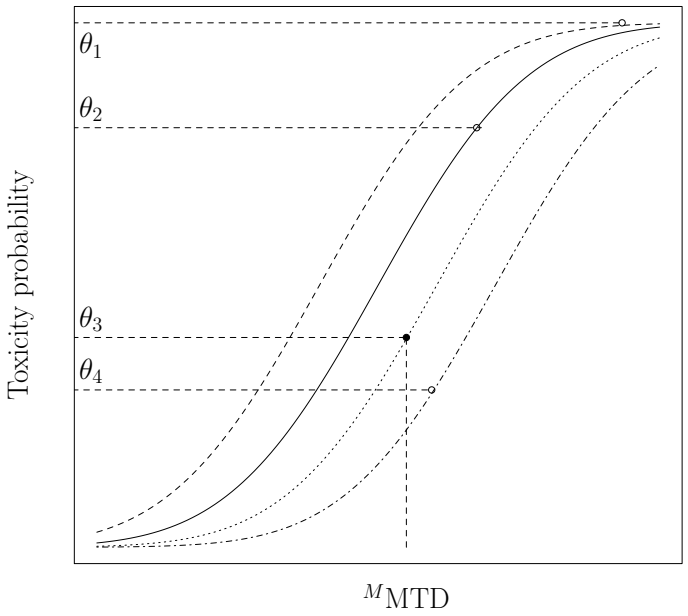


Figure 2: Graph illustration for Definition 2.2. In this graph, there are 4 increasing curves $P(Y \geq m_i|x) = \sum_{y=m_i}^{M} p_y(x), i = 1, \ldots, 4$, where $m_1 < \ldots < m_4$ are some toxicity grades. There is a level-m_i MTD given the target toxicity probability θ_i, denoted by a small circle, $i = 1, \ldots, 4$. The overall MTD, denoted by a dotted circle, is the minimum of all level-m_i MTD's.

where ${}_m\text{MTD}(\theta)$ is the level-m MTD associated with system $\{\mathbb{Y}, \boldsymbol{P}, \boldsymbol{\theta}\}$. Hence,

$$\begin{aligned} {}^M\text{MTD}(\boldsymbol{\theta}) &= \min\{{}_m\text{MTD}(\theta_m)|m = 1, \ldots, M\} \\ &= \min\{{}_m\text{MTD}(\theta_m)|m = 1, \ldots, m_0 - 1, m_0 + 1, \ldots, M\}. \end{aligned} \tag{3}$$

Since $\boldsymbol{P}^* = \{p_1(x), \ldots, p_{m_0-2}(x), p_{m_0-1}(x) + p_{m_0}(x), p_{m_0+1}(x), \ldots, p_M(x)|x \in \mathbb{X}\}$, one has $\sum_{y=m}^{M-1} p_y^*(x) = \sum_{y=m}^{M} p_y(x)$ for $m \leq m_0 - 1$ and $\sum_{y=m}^{M-1} p_y^*(x) = \sum_{y=m+1}^{M} p_y(x)$ for $m > m_0 - 1$. Furthermore, since $\boldsymbol{\theta}^* = \{\theta_1, \ldots, \theta_{m_0-1}, \theta_{m_0+1}, \ldots, \theta_M\}$, one has $\theta_m^* = \theta_m$ for $m \leq m_0 - 1$ and $\theta_m^* = \theta_{m+1}$ for $m > m_0 - 1$. Consequently,

$$\left\{\sum_{y=m}^{M-1} p_y^*(x) \leq \theta_m^*\right\} \text{ is equivalent to } \left\{\sum_{y=m}^{M} p_y(x) \leq \theta_m\right\} \text{ for } m \leq m_0 - 1,$$

and

$$\left\{\sum_{y=m}^{M-1} p_y^*(x) \le \theta_m^*\right\} \text{ is equivalent to } \left\{\sum_{y=m+1}^{M} p_y(x) \le \theta_{m+1}\right\} \text{ for } m > m_0 - 1.$$

Therefore, according to (1), ${}_m\text{MTD}^*(\theta_m^*) = {}_m\text{MTD}(\theta_m)$ for $m \le m_0 - 1$ and ${}_m\text{MTD}^*(\theta_m^*) = {}_{m+1}\text{MTD}(\theta_{m+1})$ for $m > m_0 - 1$, where ${}_m\text{MTD}^*(\theta_m^*)$ is the level-m MTD associated with system $\{\mathbb{Y}^*, \boldsymbol{P}^*, \boldsymbol{\theta}^*\}$. Finally, using (3),

$$\begin{aligned} {}^M\text{MTD}(\boldsymbol{\theta}) &= \min\{{}_m\text{MTD}(\theta_m) | m = 1, \ldots, m_0 - 1, m_0 + 1, \ldots, M\} \\ &= \min\{{}_m\text{MTD}^*(\theta_m^*) | m = 1, \ldots, M - 1\} = {}^{M-1}\text{MTD}^*(\boldsymbol{\theta}^*), \end{aligned}$$

which implies that $\{\mathbb{Y}, \boldsymbol{P}, \boldsymbol{\theta}\}$ is equivalent to $\{\mathbb{Y}^*, \boldsymbol{P}^*, \boldsymbol{\theta}^*\}$ in the sense of finding the overall MTD. □

Repeatedly applying Theorem 2.1, we obtain the following corollary.

Corollary 2.1. Suppose $\{\mathbb{Y}, \boldsymbol{P}, \boldsymbol{\theta}\}$ is an M-point ordinal toxicity grade system with its associated target toxicity probability $\boldsymbol{\theta} = (\theta_1, \theta_2, \ldots, \theta_M)$ and $\boldsymbol{P} = \{p_1(x), \ldots, p_M(x) | x \in \mathbb{X}\}$. If there exists an m_0 such that $\theta_m = 1$, for $m < m_0$ and $\theta_m = \theta < 1$, for $m \ge m_0$, then the M-point ordinal toxicity grade system $\{\mathbb{Y}, \boldsymbol{P}, \boldsymbol{\theta}\}$ is equivalent to the 2-point ordinal toxicity grade system $\{\mathbb{Y}^*, \boldsymbol{P}^*, \boldsymbol{\theta}^*\}$, where $\mathbb{Y}^* = \{1, 2\}$, $\boldsymbol{P}^* = \left\{\sum_{y=1}^{m_0-1} p_y(x), \sum_{y=m_0}^{M} p_y(x) \middle| x \in \mathbb{X}\right\}$ and $\boldsymbol{\theta}^* = \{1, \theta\}$. Furthermore,

$${}^M\text{MTD}(\boldsymbol{\theta}) = {}^2\text{MTD}^*(\boldsymbol{\theta}^*) = \sup\left\{x \middle| \sum_{y=m_0}^{M} p_y(x) \le \theta\right\}.$$

So, for the admissibility requirement, we assume $1 = \theta_1 > \theta_2 > \ldots > \theta_M > 0$. Since $\theta_1 = 1$ and $\sum_{y=1}^{M} p_y(x) = 1$, ${}_1\text{MTD}(1) = \sup\left\{x | \sum_{y=1}^{M} p_y(x) \le 1\right\} = \sup\{\mathbb{X}\}$. Hence, (2) is equivalent to

$${}^M\text{MTD}(\boldsymbol{\theta}) = \min\{{}_m\text{MTD}(\theta_m) | m = 2, \ldots, M\}. \tag{4}$$

The dichotomized response model might be considered as a special case of the polychotomous response model, where $M = 2$, $Y \in \{0, 1\}$ (to provide the notation consistency, we use $\{0, 1\}$ instead of $\{1, 2\}$) and $m = 1$, which is actually a 2-point ordinal toxicity grade

system. The overall MTD, ${}^{2}\text{MTD}(\theta)$ is equal to the level-1 MTD, ${}_{1}\text{MTD}(\theta) = \sup\{x|P(Y = 1|x) \leq \theta\} = \sup\{x|\psi(x,a) \leq \theta\}$, where $\psi(x,a)$ is defined as in the original CRM paper by O'Quigley *et.al.* [6].

3 The Cumulative Probit Model with Latent Variables

To make the problem more interesting, we will assign a model structure on the M-point ordinal toxicity grade system, $\{\mathbb{Y}, \boldsymbol{P}, \boldsymbol{\theta}\}$, in the following context. Define the cumulative probabilities of the toxicity response Y at dose x as

$$\eta_y(x) = P(Y \leq y|x) = \sum_{j=1}^{y} p_j(x), \quad y = 1, \ldots, M-1.$$

Then, (1) is equivalent to

$${}_{m}\text{MTD}(\theta) = \sup\{x|\eta_{m-1}(x) \geq 1-\theta\}. \tag{5}$$

Instead of assigning a model structure on toxicity response Y directly, we will assign a model structure on the cumulative probabilities $\eta_y(x)$, which is the usual way to fit the ordered categorical data. Assume that there exists a latent continuous random variable Z_x with probability density function $f_{Z_x}(z|x,\boldsymbol{\beta})$ or cumulative density function $F_{Z_x}(z|x,\boldsymbol{\beta})$, at dosage x, where $\boldsymbol{\beta}$ is the model parameters. Suppose that we observe toxicity grade $Y = y$, $y \in \{1, 2, \ldots, m\}$, at dose x, where $Y = y|x$ if $\gamma_{y-1} < Z_x \leq \gamma_y$. Here, $\gamma_0, \gamma_1, \ldots, \gamma_{M-1}, \gamma_M$ are unknown bin boundaries (we define $\gamma_0 = -\infty$ and $\gamma_M = \infty$). Hence,

$$p_y(x) = P(Y = y|x) = F_{Z_x}(\gamma_y|x,\boldsymbol{\beta}) - F_{Z_x}(\gamma_{y-1}|x,\boldsymbol{\beta})$$

and the cumulative probabilities at dose x is

$$\begin{aligned}\eta_y(x) = P(Y \leq y|x) &= \sum_{j=1}^{y} p_j(x) = \sum_{j=1}^{y}[F_{Z_x}(\gamma_j|x,\boldsymbol{\beta}) - F_{Z_x}(\gamma_{j-1}|x,\boldsymbol{\beta})] \\ &= F_{Z_x}(\gamma_y|x,\boldsymbol{\beta}).\end{aligned} \tag{6}$$

Therefore, (5) can be modified as

$$ {}_m\text{MTD}(\theta) = \sup\{x | F_{Z_x}(\gamma_{m-1}|x, \boldsymbol{\beta}) \geq 1 - \theta\}. \tag{7} $$

Given the critical value $m \in \{1, 2, \ldots, M\}$, $Y \geq m$ implies that there is a level-m severe toxicity at dosage x. If we define the probability of toxicity as

$$ \psi(x, \boldsymbol{\beta}, \gamma_{m-1}) = P(Y \geq m|x) = 1 - F_{Z_x}(\gamma_{m-1}|x, \boldsymbol{\beta}), $$

then (1) becomes

$$ {}_m\text{MTD}(\theta) = \sup\{x | \psi(x, \boldsymbol{\beta}, \gamma_{m-1}) \leq \theta\}, \tag{8} $$

which is similar to the dichotomized response case. Furthermore, suppose we choose the normal latent variable, $Z_x \sim N(\mathbf{x}^T\boldsymbol{\beta}, 1)$, where $\boldsymbol{\beta} = (\beta_0, \beta_1)^T$ and $\mathbf{x} = (1, x)^T$, then, the probability of toxicity is

$$ \psi(x, \boldsymbol{\beta}, \gamma_{m-1}) = 1 - \Phi(\gamma_{m-1} - \mathbf{x}^T\boldsymbol{\beta}) = \Phi(\mathbf{x}^T\boldsymbol{\beta} - \gamma_{m-1}), \qquad m = 1, \ldots, M-1. \tag{9} $$

Consequently, under the normal assumption, the MTD derived from (8) is

$$ {}_m\text{MTD}(\theta) = \frac{\gamma_{m-1} - \beta_0 - \Phi^{-1}(1-\theta)}{\beta_1}. $$

For an M-point ordinal toxicity grade system, $\{p_1(x), \ldots, p_M(x)\}$, associated with its target toxicity probability $\boldsymbol{\theta} = (\theta_1, \theta_2, \ldots, \theta_M)$, if the normal latent variable is used, then the overall MTD is defined as

$$ {}^M\text{MTD}(\boldsymbol{\theta}) = \min\left\{ \frac{\gamma_{m-1} - \beta_0 - \Phi^{-1}(1-\theta_m)}{\beta_1} \middle| m = 2, \ldots, M \right\} $$

In next section, we will use the Bayes method to fit model (9).

4 The Likelihood Function and the Posterior Distribution

Denoted by $\mathscr{F}_j = \{(x_1, y_1), \ldots, (x_j, y_j)\}$ the history of the first j assignments and responses, where x_l is the dose level of the lth patient (that is $x_l \in \{d_1, \ldots, d_K\}$) and y_l is the observed response which takes one of M ordered categories, 1, ..., M and $l = 1, \ldots, j$. In model (9) of Section 3, both the regression parameter $\boldsymbol{\beta}$ and the bin boundary $\boldsymbol{\gamma} = (\gamma_1, \gamma_2, \ldots, \gamma_{M-1})$ are unknown. To ensure that the parameters are identifiable, it is necessary to impose one restriction on the bin boundary $\boldsymbol{\gamma}$ (See Albert and Chib [1]). Without loss of generality, we take $\gamma_1 = 0$. The likelihood function of $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ is

$$L(\boldsymbol{\beta}, \boldsymbol{\gamma} | \mathscr{F}_j) \propto \prod_{l=1}^{j} \sum_{y=1}^{M} I(y_l = y)[\Phi(\gamma_y - \mathbf{x}_l^T \boldsymbol{\beta}) - \Phi(\gamma_{y-1} - \mathbf{x}_l^T \boldsymbol{\beta})].$$

It is straightforward to find the maximum likelihood estimate of $(\boldsymbol{\beta}, \boldsymbol{\gamma})$ by using Newton-Raphson method and to obtain the approximate standard deviations of $(\boldsymbol{\beta}, \boldsymbol{\gamma})$ by using the second derivative of log likelihood evaluated at the maximum likelihood estimate. But, unfortunately, due to the small sample size in phase I clinical trials the accuracy of the MLE is questionable (see Albert and Chib [1]).

In order to increase the accuracy of the estimation, the Gibbs sampling algorithm (see Gelfand and Smith [5]) for the polychotomized response described in [1] can be generalized to this situation. We introduce j latent variables $Z_1, Z_2, \ldots, Z_j$, where Z_l are independent $N(\beta_0 + \beta_1 x_l, 1)$ and x_l is the dose level of the lth patient.

Define

$$Y_l = y, \qquad \text{if } \gamma_{y-1} < Z_l \leq \gamma_y, \qquad \text{for } y = 1, 2, \ldots, M. \tag{10}$$

The joint likelihood function of $(\boldsymbol{\beta}, \boldsymbol{\gamma}, \mathbf{Z})$ is

$$L(\boldsymbol{\beta}, \boldsymbol{\gamma}, \mathbf{Z} | \mathscr{F}_j) \propto \prod_{l=1}^{j} \left[\sum_{y=1}^{M} I(y_l = y) I(\gamma_{y-1} < Z_l < \gamma_y) \right] \phi(Z_l; \mathbf{x}_l^T \boldsymbol{\beta}, 1).$$

Let $\pi(\boldsymbol{\beta}, \boldsymbol{\gamma}) = \pi(\boldsymbol{\beta})\pi(\boldsymbol{\gamma})$ be the prior on $(\boldsymbol{\beta}, \boldsymbol{\gamma})$, the joint posterior density function of

$(\boldsymbol{\beta}, \boldsymbol{\gamma}, \mathbf{Z})$ given data $\mathscr{F}_j$ is

$$\pi(\boldsymbol{\beta}, \boldsymbol{\gamma}, \mathbf{Z}|\mathscr{F}_j) \propto \pi(\boldsymbol{\beta}, \boldsymbol{\gamma}) \prod_{l=1}^{j} \left[\sum_{y=1}^{M} I(y_l = y) I(\gamma_{y-1} < Z_l < \gamma_y) \right] \phi(Z_l; \mathbf{x}_l^T \boldsymbol{\beta}, 1)$$

$$= \pi(\boldsymbol{\beta}) \pi(\boldsymbol{\gamma}) \prod_{l=1}^{j} \left[\sum_{y=1}^{M} I(y_l = y) I(\gamma_{y-1} < Z_l < \gamma_y) \right] \phi(Z_l; \mathbf{x}_l^T \boldsymbol{\beta}, 1). \qquad (11)$$

Since the probability of DLT is assumed to be increasing in dose level x and the categories of toxicity grade are ordered, we need certain constraints on the prior distribution of $(\boldsymbol{\beta}, \boldsymbol{\gamma})$. The prior $\pi(\boldsymbol{\beta}, \boldsymbol{\gamma})$ should be defined on $\{(\boldsymbol{\beta}, \boldsymbol{\gamma}) | \beta_1 > 0, -\infty < \gamma_1 < \gamma_2 < \cdots < \gamma_{M-1} < \infty\}$.

In order to evaluate (9) at any given dose $x \in \{d_1, \ldots, d_K\}$, parameters $(\boldsymbol{\beta}, \gamma_{m-1})$ need to be jointly generated from (11). Note that this joint posterior distribution (11) is complicated in the sense that it is difficult to normalize and sample from it directly. But computation of the marginal posterior distribution of $(\boldsymbol{\beta}, \gamma_{m-1})$ using the Gibbs sampling algorithm requires only the posterior distribution of $\boldsymbol{\beta}$ conditional on $(\mathbf{Z}, \boldsymbol{\gamma})$, posterior distribution of $\mathbf{Z}$ conditional on $(\boldsymbol{\beta}, \boldsymbol{\gamma})$ and the posterior distribution of $\boldsymbol{\gamma}$ conditional on $(\boldsymbol{\beta}, \mathbf{Z})$, and these full conditional posterior distributions are easy to obtained and easy to sample from.

Based on (11), the full conditional posterior distributions are found as follows.

- $\pi(\boldsymbol{\beta}|\boldsymbol{\gamma}, \mathbf{Z}, \mathscr{F}_j)$

The posterior densities of β_0 and β_1, given $\boldsymbol{\gamma}$ and $\mathbf{Z}$, is given by the follows. If a flat prior $\pi(\beta_0) \propto 1$ is assigned on β_0, then,

$$\beta_0|\beta_1, \mathbf{Z}, \mathscr{F}_j \sim N\left(\frac{\sum_{l=1}^{j} (z_l - \beta_1 x_l)}{j}, \frac{1}{j} \right). \qquad (12)$$

If a proper conjugate prior $N(\bar{\beta}_0, \bar{\sigma}_0^2)$ is assigned, then,

$$\beta_0|\beta_1, \mathbf{Z}, \mathscr{F}_j \sim N\left(\frac{\bar{\sigma}_0^2 \sum_{l=1}^{j} (z_l - \beta_1 x_l) + \bar{\beta}_0}{1 + \bar{\sigma}_0^2 j}, \frac{\bar{\sigma}_0^2}{1 + \bar{\sigma}_0^2 j} \right). \qquad (13)$$

If a flat prior $\pi(\beta_1) \propto I(\beta_1 > 0)$ is assigned, then,

$$\beta_1|\beta_0, \mathbf{Z}, \mathscr{F}_j \sim N\left(\frac{\sum_{l=1}^{j}(z_l - \beta_0)x_l}{\sum_{l=1}^{j} x_l^2}, \frac{1}{\sum_{l=1}^{j} x_l^2}\right) I(\beta_1 > 0). \tag{14}$$

If a proper conjugate truncated normal prior $N(\bar{\beta}_1, \bar{\sigma}_1^2)I(\beta_1 > 0)$ is assigned, then,

$$\beta_1|\beta_0, \mathbf{Z}, \mathscr{F}_j \sim N\left(\frac{\bar{\sigma}_1^2 \sum_{l=1}^{j}(z_l - \beta_0)x_l + \bar{\beta}_1}{1 + \bar{\sigma}_1^2 \sum_{l=1}^{j} x_l^2}, \frac{\bar{\sigma}_1^2}{1 + \bar{\sigma}_1^2 \sum_{l=1}^{j} x_l^2}\right) I(\beta_1 > 0). \tag{15}$$

If a proper, but non-conjugate exponential prior $\exp\{-\beta_1\}I(\beta_1 > 0)$ is assigned, then,

$$\beta_1|\beta_0, \mathbf{Z}, \mathscr{F}_j \sim N\left(\frac{\sum_{l=1}^{j}(z_l - \beta_0)x_l - 1}{\sum_{l=1}^{j} x_l^2}, \frac{1}{\sum_{l=1}^{j} x_l^2}\right) I(\beta_1 > 0). \tag{16}$$

- $\pi(\mathbf{Z}|\boldsymbol{\beta}, \boldsymbol{\gamma}, \mathscr{F}_j)$

Z_l's are latent variables, not parameters. Hence no priors are needed. Using (11), the posterior density of $\mathbf{Z}$, given $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$, is

$$\pi(\mathbf{Z}|\boldsymbol{\beta}, \boldsymbol{\gamma}, \mathscr{F}_j) \propto \prod_{l=1}^{j}\left[\sum_{y=1}^{M} I(y_l = y)I(\gamma_{y-1} < Z_l < \gamma_y)\right]\phi(Z_l; \mathbf{x}_l^T\boldsymbol{\beta}, 1), \tag{17}$$

which implies that $Z_1, Z_2, \ldots, Z_j$ are independent with

$$Z_l|\boldsymbol{\beta}, \boldsymbol{\gamma}, \mathscr{F}_j \sim N(\mathbf{x}_l^T\boldsymbol{\beta}, 1)I(\gamma_{y-1} < Z_l < \gamma_y), \qquad \text{if } y_l = y, \tag{18}$$

where y takes one of the M ordered categories, 1, ..., M and $l = 1, \ldots, j-1$. (18) implies that $Z_l|\boldsymbol{\beta}, \boldsymbol{\gamma}, \mathscr{F}_j$ is a normal random variable truncated at the left γ_{y-1} and right γ_y when $y_l = y$.

- $\pi(\boldsymbol{\gamma}|\boldsymbol{\beta}, \mathbf{Z}\mathscr{F}_j)$

According to (11), the posterior density of $\boldsymbol{\gamma}$, given $\boldsymbol{\beta}$ and $\mathbf{Z}$, is

$$\pi(\boldsymbol{\gamma}|\boldsymbol{\beta}, \mathbf{Z}, \mathscr{F}_j) \propto \pi(\boldsymbol{\gamma}) \prod_{l=1}^{j}\left[\sum_{y=1}^{M} I(y_l = y)I(\gamma_{y-1} < Z_l < \gamma_y)\right], \tag{19}$$

which implies that $\gamma_1, \gamma_2, \ldots, \gamma_j$ are dependent. Suppose a flat prior is assigned on $\boldsymbol{\gamma}$

$$\pi(\boldsymbol{\gamma}) = I(-\infty < \gamma_1 < \gamma_2 < \cdots < \gamma_{M-1} < \infty),$$

then the full conditional posterior distribution of γ_i given $\boldsymbol{\beta}$, $\boldsymbol{\gamma}_{-i} = \{\gamma_y, y \neq i\}$, $\mathbf{Z}$ and $\mathscr{F}_j$, is

$$\pi(\gamma_i|\boldsymbol{\beta}, \boldsymbol{\gamma}_{-i}, \mathbf{Z}, \mathscr{F}_j) \propto \prod_{l=1}^{j} \left[I(y_l = i) I(\gamma_{i-1} < Z_l < \gamma_i) + I(y_l = i+1) I(\gamma_i < Z_l < \gamma_{i+1}) \right].$$

This conditional distribution can be seen to be uniform, i.e.,

$$\gamma_i|\boldsymbol{\beta}, \boldsymbol{\gamma}_{-i}, \mathbf{Z}, \mathscr{F}_j \sim \mathrm{U}(a,\ b), \tag{20}$$

where $a = \max\{\max\{Z_l : y_l = i\}, \gamma_{i-1}\}$ and $b = \min\{\min\{Z_l : y_l = i+1\}, \gamma_{i+1}\}$.

Based on the Gibbs sampler, β_0, β_1, $\mathbf{Z}$ and $\boldsymbol{\gamma}$ could be generated from those full conditional posterior distributions.

After drawing from the marginal joint posterior distribution $\pi(\boldsymbol{\beta}, \gamma_{m-1})$, one can estimate the overall MTD by using the following formula.

$$^{M}\widehat{\mathrm{MTD}}(\boldsymbol{\theta}) = \min \left\{ \frac{E^{\pi(\gamma_{m-1}|\mathscr{F}_j)}\gamma_{m-1} - E^{\pi(\beta_0|\mathscr{F}_j)}\beta_0 - \Phi^{-1}(1-\theta_m)}{E^{\pi(\beta_1|\mathscr{F}_j)}\beta_1} | m = 2, \ldots, M \right\}. \tag{21}$$

The estimates of the expectations in (21) are obtained based on the simulation. Suppose one has obtained N generations of $(\beta_0, \beta_1, \gamma_{m-1})$, which are $(\beta_0^{(i)}, \beta_1^{(i)}, \gamma_{m-1}^{(i)}), i = 1, 2, \ldots, N$, then,

$$\hat{E}^{\pi(\beta_0|\mathscr{F}_j)}(\beta_0) = \frac{1}{N}\sum_{i=1}^{N} \beta_0^{(i)},$$
$$\hat{E}^{\pi(\beta_1|\mathscr{F}_j)}(\beta_1) = \frac{1}{N}\sum_{i=1}^{N} \beta_1^{(i)},$$
$$\hat{E}^{\pi(\gamma_{m-1}|\mathscr{F}_j)}(\gamma_{m-1}) = \frac{1}{N}\gamma_{m-1}^{(i)}.$$

5 Simulation Results

To evaluate the operating characteristics of the polychotomous response model, a simulation study is performed. We use a 5-point ordinal toxicity scale, i.e., the polychotomous toxicity response Y takes one of the 5 values, $\{1, \ldots, 5\}$ at any given dose level, with grade 1 representing no toxicity, grade 2 minor toxicity, grade 3 moderate toxicity, grade 4 severe toxicity, and grade 5 very severe or life threatening toxicity. We suppose there are six ordered dose levels, $x_1, x_2, \ldots, x_6$ and the data are simulated according to the following probabilities,

$$p_{ij} = P(Y = i|\text{Dose} = x_j), \text{ for } i = 1, \ldots, 5 \text{ and } j = 1, \ldots, 6,$$

where $\sum_{i=1}^{5} p_{ij} = 1$ for any $j = 1, \ldots, 6$, and, for any $i_0 = 2, \ldots, 5$, $\sum_{i=i_0}^{5} p_{ij'} < \sum_{i=i_0}^{5} p_{ij''}$, for any $1 \leq j' < j'' \leq 6$. Table 1 show the true probabilities of each grade $(1-5)$ at each dose level $(1-6)$ for four simulation scenarios.

In this simulation study, the probabilities are generated in one of the following two ways.

(1) Normal latent: $p_{ij} = P(\gamma_{j-1} < Z_i \leq \gamma_j)$, for $i = 1, \ldots, 5$ and $j = 1, \ldots, 6$, where $Z_i \sim N(\beta_0 + \beta x_i, 1)$, $\gamma_0 = -\infty, \gamma_5 = \infty$ and $\boldsymbol{\beta} = (\beta_0, \beta_1)$, $\boldsymbol{\gamma} = (\gamma_1, \ldots, \gamma_4)$ are set to different values for different scenarios.

(2) General situation: for any $i_0 = 2, \ldots, 5$, $\sum_{i=i_0}^{5} p_{ij'} < \sum_{i=i_0}^{5} p_{ij''}$, if $1 \leq j' < j'' \leq 6$.

The target toxicity probabilities, $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_5)$, are set in three different combinations. For each scenario we use 200 duplications (trials). In each trial, we recruit 30 patients in 10 cohort with 3 patients per cohort. The first cohort of subjects in each trial was treated at the lowest dose. Additional constraints follow those of Faries [4] where dose escalation was limited to a maximum of 1 dose between consecutive subjects. The dose closest to the final updated MTD was taken to be the final recommended dose. The updated MTD was then calculated by using (21).

The working model is

$$\begin{cases} Y = y|x, \text{ if } \gamma_{y-1} < Z_x \leq \gamma_y, \text{ where } y = 1, 2, \ldots, 5, \\ \qquad\qquad\qquad\qquad \text{and, } -\infty = \gamma_0 < \gamma_1 < \ldots < \gamma_4 < \gamma_5 = \infty, \\ Z_x \sim N(\beta_0 + \beta_1 x, 1), \text{ for } x \in \{x_1, x_2, \ldots, x_6\}. \end{cases}$$

Table 1: True Probabilities of Toxicity for Various Grade and Dose Levels

Scenario	Grade	Dose level					
		x_1	x_2	x_3	x_4	x_5	x_6
A	1	0.87	0.78	0.70	0.51	0.19	0.12
	2	0.08	0.12	0.15	0.19	0.16	0.13
	3	0.03	0.06	0.09	0.15	0.20	0.18
	4	0.01	0.03	0.04	0.09	0.18	0.20
	5	0.00	0.01	0.02	0.06	0.27	0.37
B	1	0.87	0.78	0.70	0.51	0.19	0.12
	2	0.08	0.12	0.15	0.19	0.16	0.13
	3	0.02	0.04	0.05	0.08	0.10	0.09
	4	0.02	0.04	0.06	0.12	0.20	0.19
	5	0.01	0.02	0.04	0.10	0.36	0.47
C	1	0.82	0.73	0.53	0.35	0.23	0.15
	2	0.10	0.14	0.19	0.20	0.17	0.15
	3	0.05	0.08	0.14	0.18	0.20	0.19
	4	0.02	0.04	0.08	0.14	0.17	0.19
	5	0.01	0.02	0.06	0.13	0.23	0.32
D	1	0.83	0.75	0.55	0.37	0.24	0.16
	2	0.09	0.12	0.17	0.18	0.16	0.14
	3	0.03	0.05	0.08	0.10	0.10	0.09
	4	0.03	0.05	0.11	0.16	0.19	0.20
	5	0.02	0.03	0.09	0.19	0.31	0.41

We always set a prior $\pi(\beta_0, \beta_1) \propto \exp(-\beta_1), \beta_1 > 0$ on the parameter in each scenario. To ensure that the parameters are identifiable, it is necessary to impose one restriction on the bin boundary $\boldsymbol{\gamma} = (\gamma_1, \ldots, \gamma_4)$. Since toxicity grade 3, 4 and 5 represent moderate ,severe and very severe or life threatening toxicity, we take $\gamma_2 = 0$. Table 2 is an illustration of the process from one of the simulated trials. We frame those toxicity grades which are grade 3, 4 and 5, since they represent the moderate, severe and very severe or life threatening toxicities.

Figure 3 shows an example of the simulated parameters of $\boldsymbol{\beta} = (\beta_0, \beta_1)$ and $\boldsymbol{\gamma} =$

Table 2: An Illustration of One of the Simulated Trials

		Toxicity Grade		
Cohort	Dose level	Subject 1	Subject 2	Subject 3
1	x_1	1	2	1
2	x_2	2	1	1
3	x_3	1	1	$\boxed{3}$
4	x_4	1	1	$\boxed{3}$
5	x_5	$\boxed{5}$	$\boxed{5}$	1
6	x_4	1	1	$\boxed{4}$
7	x_3	1	1	1
8	x_4	1	1	$\boxed{4}$
9	x_4	1	2	2
10	x_4	$\boxed{3}$	1	2
Recommendation	x_4			

$(\gamma_1, \gamma_3, \gamma_4)$ at the sample size 30. Based on the trace in Figure 3, the MCMC results converge and based on the density in Figure 3, all the constraints on the model parameters, such as $\beta_1 > 0$, $\gamma_1 < 0$, $\gamma_3 > 0$ and $\gamma_4 > 0$, are satisfied.

Table 3 shows the simulation results. In Table 3, we only display target toxicity probabilities $(\theta_3, \theta_4, \theta_5)$, since θ_1 has been always set to be equal to 1 and θ_2 is associated with toxicity grade 2 (which is minor toxicity) and above, hence we also set $\theta_2 = 1$. For $(\theta_3, \theta_4, \theta_5)$, we consider three settings, $(0.3, 0.3, 0.3)$ which is equivalent to the dichotomized model, $(0.3, 0.1, 0.05)$ which indicates that toxicity grades 4 and 5 are considered and differentiated, $(0.3, 0.06, 0.02)$ which indicates that grades 4 and 5 are more severe in toxicity than grade 3. Table 3 shows that both percent of recommended level and percent of patient allocation are toward the lower dose levels in general. For the first scenario, 83% of the recommendations are x_4 for dichotomized model. However, for the polychotomous model, 54% and 21% of the recommendations are x_4 for target toxicity probability settings $(0.3, 0.1, 0.05)$ and $(0.3, 0.06, 0.02)$, respectively. In addition, for $(0.3, 0.06, 0.02)$, 46% of the recommendations are x_3, which is the largest recommendation rate among all six dose levels. As for patient allocation, 34% and 20.4% of them allocate to x_4 for $(0.3, 0.1, 0.05)$ and $(0.3, 0.06, 0.02)$, respectively (decrease from 44.6% for dichotomized model). Similar results are shown for the

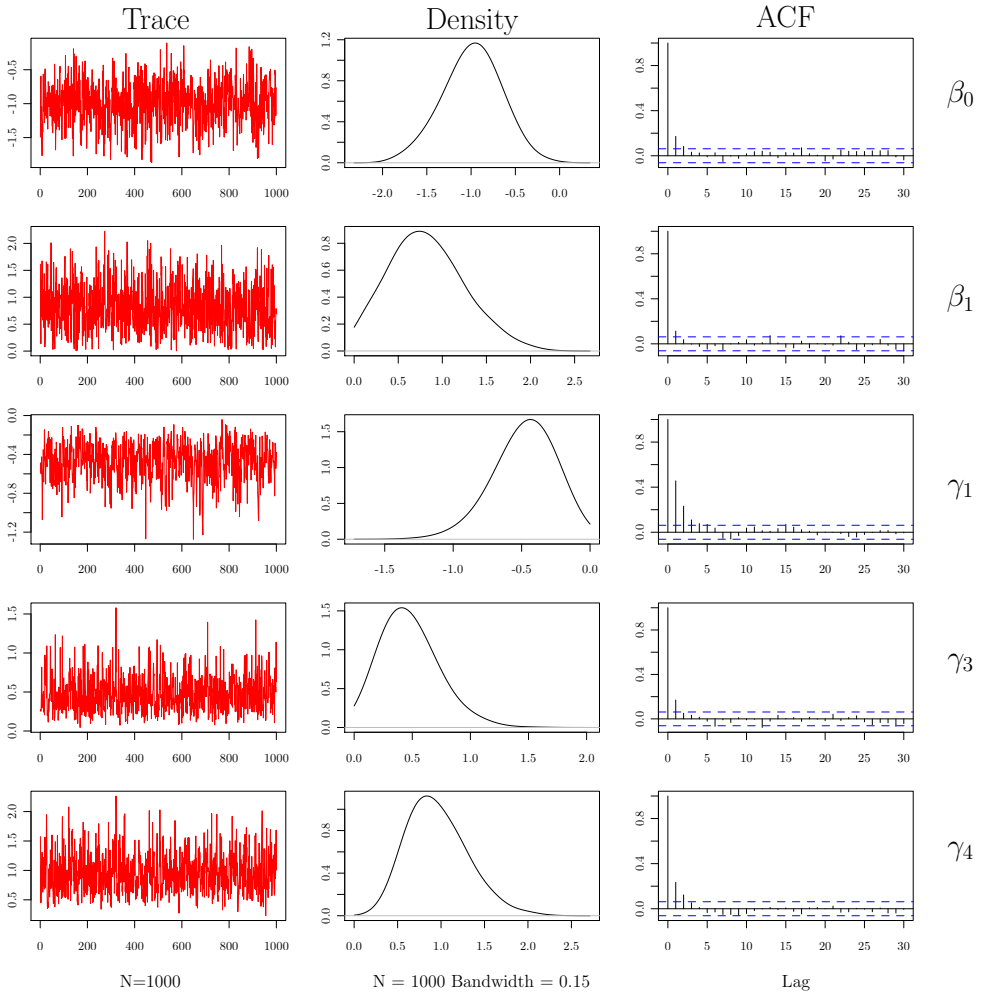


Figure 3: An illustration of simulated $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ (Sample size = 30). The trace column gives the time series plot for each parameter. After burn-in the first 1000 generations and thinning in each 100 generations, the time series plots appear to be stationary. The ACF column gives the autocorrelation function for each parameter and it shows that the parameters are nor significantly autocorrelated. From the density column, it is clear that $\beta_1 > 0$, $\gamma_1 < 0$, $\gamma_3 > 0$ and $\gamma_4 > 0$, which satisfy the constraints on the model parameters.

Table 3: Simulation Results

Scenario	Target $(\theta_3, \theta_4, \theta_5)$		Dose Level x_1	x_2	x_3	x_4	x_5	x_6
A								
	(.30, .30, .30)	Rec.		1.5	11.5	<u>83.0</u>	4.0	
		Exp.	12.1	14.5	21.8	44.6	6.7	0.2
	(.30, .10, .05)	Rec.	3.5	7.0	34.5	<u>54.0</u>	1.0	
		Exp.	16.5	16.8	27.7	34.0	4.9	0.1
	(.30, .06, .02)	Rec.	13.0	20.0	<u>46.0</u>	21.0		
		Exp.	22.1	24.4	29.4	20.4	3.7	
B								
	(.30, .30, .30)	Rec.		0.5	13.0	<u>80.5</u>	6.0	
		Exp.	12.7	13.4	22.9	42.9	7.7	0.4
	(.30, .10, .05)	Rec.	6.5	18.5	<u>47.0</u>	27.5	0.5	
		Exp.	20.6	22.3	31.7	22.2	2.9	0.3
	(.30, .06, .02)	Rec.	28.0	<u>33.5</u>	32.6	6.0		
		Exp.	33.0	26.9	26.4	11.6	1.9	0.1
C								
	(.30, .30, .30)	Rec.	1.0	9.5	<u>67.5</u>	21.0	1.0	
		Exp.	14.4	21.6	42.3	18.0	3.5	0.2
	(.30, .10, .05)	Rec.	6.5	32.5	<u>53.5</u>	8.0		
		Exp.	18.2	32.2	37.1	11.2	1.2	0.1
	(.30, .06, .02)	Rec.	20.5	<u>49.5</u>	29.0	1.0		
		Exp.	28.2	37.3	27.1	6.3	1.1	
D								
	(.30, .30, .30)	Rec.		7.0	<u>68.5</u>	22.5	2.0	
		Exp.	14.1	21.8	42.8	17.6	3.4	0.4
	(.30, .10, .05)	Rec.	17.5	<u>48.0</u>	32.5	2.0		
		Exp.	27.2	35.9	29.6	6.3	1.0	
	(.30, .06, .02)	Rec.	43.0	<u>45.5</u>	11.5			
		Exp.	41.3	34.8	19.1	4.1	0.7	

scenario B, C and D. In conclusion, the polychotomous model, which takes severity level of toxicity into account, reduces the number of patients allocated to the higher toxicity dose level. That reduces the risk of toxicity for patients in the phase I study.

6 Conclusions and Discussions

In this study, we make a new definition of overall MTD, ${}^{M}\text{MTD}(\boldsymbol{\theta})$, in the case of the polychotomous toxicity responses and the analytic properties of the overall MTD are also examined. It is shown that the traditional definition of MTD in the case of the dichotomous (binary) toxicity responses is a special case of the overall MTD. In order to find the overall MTD, ${}^{M}\text{MTD}(\boldsymbol{\theta})$, in practice, the target toxicity probability $\boldsymbol{\theta} = \{\theta_1, \ldots, \theta_M\}$, where θ_m is the target toxicity probability corresponding to the level-m severe toxicity T_m, $m \in \{1, 2, \ldots, M\}$, needs to be pre-specified. The determination of each θ_m, $m = 1, \ldots, M$, is same as the determination of the target probability θ in the dichotomous (binary) toxicity case. Therefore, compared with the existing methods described in [3, 8, 10], there is not much more effort needed to interact with the physicians.

As an illustration of our research, we utilize the cumulative probit model (9) with the normal latent variables as the working model. The simulation studies show that the cumulative probit model, which takes severity level of toxicity into account, reduces the number of patients allocated to the higher toxicity dose level. That reduces the risk of toxicity for patients in the phase I study.

In practice, other working model, such as cumulative logistic model or other suitable models, can be utilized under the same framework. Prior elicitation is also an important issue. In this study, we provide full conditional distributions for the parameters and latent variables for various priors. When more complex models or hard-to-deal-with priors are used, the difficulties might arise when complex full conditional distributions are obtained. However, many simulation methods can be applied to handel those difficulties, such as acceptance-rejection algorithms or Metropolis-Hastings algorithm.

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