Finding Maximum Tolerated Dose in Phase I Oncology Clinical Trials with Bayesian Methods

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Abstract: Maximum tolerated dose (MTD) is a maximal amount of drug or radiation resulting relatively acceptable dose-limiting toxicity (DLT). Accurate value of MTD should be found in Phase I trials in order to create the possibility to conduct successful Phase II (pilot efficacy and safety evaluation) and Phase III (comparative efficacy) trials. The aim of this paper is to review the difficulties of the dose-finding methods including multi-agent problems and late-onset toxicities, and to discuss Bayesian adaptive dose-finding methods which can handle these issues.

Keywords: maximum tolerated dose (MTD); dose-limiting toxicity (DLT); Continual Reassessment Method (CRM); Time-To-Event Continual Reassessment Method (TITE-CRM); copula regression model; logistic regression model; delayed toxicities; late-onset toxicity model

1 Introduction

The main aim of evidence-based medicine is to collect, analyze and critically evaluate research data, and translate systematically collected and evaluated medical knowledge into practice in order to obtain optimal health outcomes [1]. Nowadays, evidence-based approach is fundamental in the field of oncology as well, and biostatistics is an important tool for this.

The aim of Phase I clinical cancer studies from oncological point of view is to find the maximum tolerated dose (MTD) of a drug or radiation which refers to a maximal amount of drug resulting relatively acceptable (typically grade 3) dose-limiting toxicity (DLT) [2]. Knowing the precise value of MTD has a key role in oncological treatment design [3].

Phase I design methods can be divided into three groups: algorithm-based designs, model-based designs and model-assisted designs [4–6].

Algorithm-based designs are conventional designs in the sense that there are prespecified rules to decide on the dose escalation and de-escalation. Algorithm-

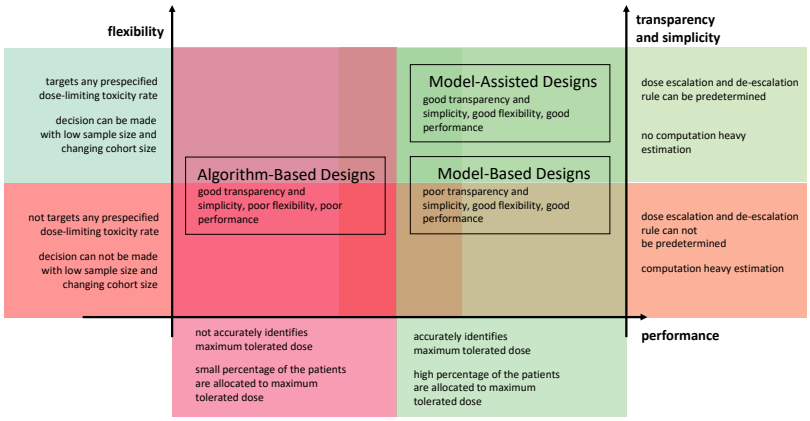

Figure 1
Characteristics of Phase I Design groups.
Transparency and simplicity criterion is defined based on whether dose escalation and de-escalation rule can be predetermined, and the estimation is computation heavy or not. Flexibility refers to the ability that a design targets prespecified dose-limiting toxicity rate, and decision can be made with low sample size and changing cohort size. The good performance criterion is met when the design accurately identifies maximum tolerated dose, and high percentage of the patients are allocated to maximum tolerated dose. In terms of these criteria, algorithm-based designs are the least applicable; model-based designs have good perfomance and flexibility, but these designs can be overly complex; while model-assisted designs combine all the good properties.

based designs group contains the most common Phase I design method, the "$3+3$" design which can be used in a single-agent trial. Albeit it is a simply and easy to use model, it has been widely criticized due to its poor efficiency in terms of treating too many subjects at a suboptimal dose and weakly estimating MTD [7].

Taking into account not a single-agent but a drug combination trial, the process is more challenging due to the complex drug–drug interactions [8]. However, in oncology, combination therapy is often used due to its synergistic treatment effect.

Model-based designs are adaptive designs where a statistical model is used in order to quantify the dose-toxicity relationship, and describe the dose-toxicity curve [9, 10]. Model-based designs have the following dose-finding strategy. The first step is creating a probability model (that can be parametric or non-parametric) in order to quantify the dose-toxicity relationship. The second step is the collection of data from the treated patients, and based on that, the model continuously updates the estimate of the model after each cohort, and this updated estimation is used to find the dose for the next cohort. The final step is the identification of the maximum tolerated dose based on the estimated toxicity probabilities of the dose combinations. Model-based designs group includes the Continuous Reassessment Method (CRM), and the Bayesian copula regression

and logistic regression model.

Model-assisted designs group is a relatively new class of trial designs which were developed in order to combine the advantages of algorithm-based and model-based designs. Before the onset of the trial, dose escalation and de-escalation rule can be predetermined (like in algorithm-based designs), and a statistical model is used in order to quantify the dose-toxicity relationship, and describe the dose-toxicity curve (like in model-based designs). Model-assisted designs group contains e.g. the Bayesian Optimal Interval (BOIN) design [11, 12] and the keyboard design [13] for single-agent dose finding.

According to Yuan et. al [5], Phase I design characteristics can be evaluated on three criteria. Transparency and simplicity criterion is defined based on whether dose escalation and de-escalation rule can be predetermined, and the estimation is computation heavy or not. Flexibility refers to the ability that a design targets prespecified dose-limiting toxicity rate, and decision can be made with low sample size and changing cohort size. The good performance criterion is met when the design accurately identifies maximum tolerated dose, and high percentage of the patients are allocated to maximum tolerated dose. In terms of these criteria, algorithm-based designs are the least applicable; model-based designs have good perfomance and flexibility, but these designs can be overly complex; while model-assisted designs combine all the good properties (Fig. 1). Besides Yuan's evaluation, there are other comparative reviews discussing the pros and cons of algorithm-based designs, model-based designs and model-assisted designs (e.g. [6]).

The paper is organized as follows. The second section discusses the most common dose-finding solution for single-agent trials, namely the Continual Reassessment Method. In the third section, two Bayesian adaptive dose-finding methods for multi-agent trials are shown, a copula-type regression model and a logistic regression model. The fourth section considers the question of late-onset toxicities and presents two different methods to handle this problem. Time-To-Event Continual Reassessment Method offers a solution for single-agent trials, while Bayesian data augmentation approach can be used in multi-agent trials. The paper ends with the conclusion section.

2 Continual Reassessment Method (CRM) for Single-Agent Dose-Finding Trials

In dose-finding studies, the typical procedure is that a sequence of doses is investigated in order to find DLT and the corresponding MTD. The main assumption in Continual Reassessment Method [14–16] is that by increasing drug dose, the probability of therapeutic efficacy is monotonically increasing, as well as the probability of toxicity. Hence, the main purpose of Phase I trials is to find a trade-off solution, viz. finding the most efficacious therapy which results in tolerable toxicity risk. Steps of the CRM are the following [14].

Step 1. Choosing of an *a priori* dose-toxicity model. There are two main

groups of *a priori* dose-toxicity curve models: one-parameter and two-parameter models. In the case of one-parameter models, the intercept of the curve is fixed, and trial data update the slope (s) of the curve from cohort to cohort. In contrast, using two-parameter models, both intercept (i) and slope (s) of the curve is re-estimated step by step. Advantage of the one-parameter models is that they require less information; however, their accuracy is limited due to the fixed intercept parameter. Using two-parameter models, the accuracy can be improved, but a bigger data set is required for good estimation. In the following, the mostly used dose-toxicity models are listed:

- hyperbolic tangent model

$$p_{toxicity}(dose) = \left(\frac{\tanh(dose)+1}{2}\right)^{s}, \tag{1}$$

  where s is the slope of the curve.

- one-parameter logistic model

$$p_{toxicity}(dose) = \frac{\exp(c+s\cdot dose)}{1+\exp(c+s\cdot dose)}, \tag{2}$$

  where s is the slope of the curve, and c is a constant, typically $c=-4$ or $c=3$.

- two-parameter logistic model

$$p_{toxicity}(dose) = \frac{\exp(i+s\cdot dose)}{1+\exp(i+s\cdot dose)}, \tag{3}$$

  where s is the slope, and i is the intercept of the curve. In Fig. 2 (blue solid line), a two-parameter logistic curve is chosen as an *a priori* dose-toxicity model.

Step 2. Choosing of a target toxicity level. By target toxicity level, we can describe what percentage of the investigated patients would be acceptable to have dose-limiting toxicity (DLT). In oncology trials, investigating chemotherapeutic agents which may cause serious side-effects and usually applied in short treatment period, the target toxicity level is typically chosen to be between 0.2 and 0.3. However, if the purpose of the study is to examine the clinical response and efficacy rate of a drug, target toxicity level can be chosen form a wider range, e.g. $[0.3, 0.9]$. In Fig. 2 (gray solid line), the target toxicity level is 0.5, meaning that it is acceptable that 50% of the patients have DLT.

Step 3. Dose levels and mapping. Physiologically relevant dose levels should be chosen for the dose-toxicity model. A typical choice for dose levels is calculated by using the modified Fibonacci sequence. In this case, $dose1$ is chosen based on preliminary data, and the next doses are calculated as follows: $dose2 = 2\cdot dose1, dose3 = 1.67\cdot dose2, dose4 = 1.5\cdot dose3, dose5 = 1.4\cdot dose4, dose6 = 1.33\cdot dose5, dose7 = 1.33\cdot dose6, dose8 = 1.33\cdot dose7$. Finally, the correspond-

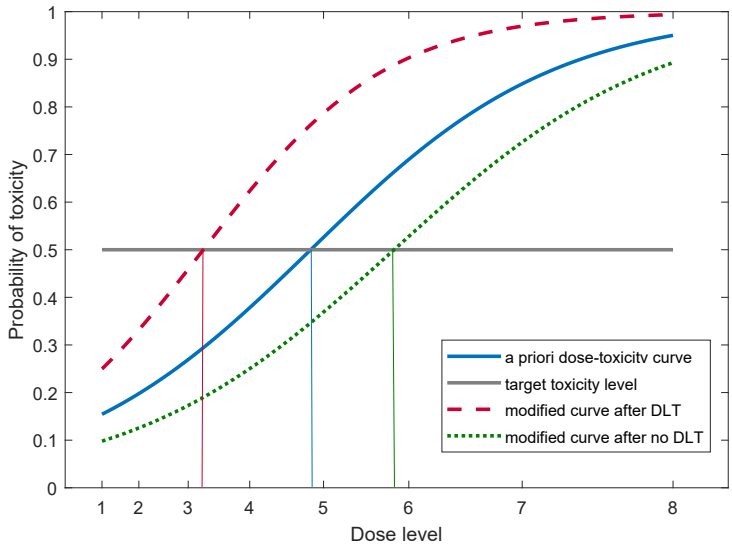

Figure 2
Dose-toxicity models for Continual Reassessment Method.
The *a priori* dose-toxicity curve is shifted up if at least one of the patients from the previous cohort experienced dose-limiting toxicity; if no patient from the previous cohort experienced DLT, the curve is shifted down. The treatment dose of the next cohort is the closest following dose level to the intersection of the dose-toxicity curve and the target toxicity level.

ing toxicity risks should be estimated for every mapped dose value. In Fig. 2 (x axis), modified Fibonacci sequence-based mapped dose levels are shown.

Step 4. Find the optimal starting dose. The optimal starting dose should be chosen based on the intersection of the *a priori* dose-toxicity curve and the target toxicity level. The starting dose is the closest following dose level to the intersection. In Fig. 2, the optimal starting dose is $dose5$.

Step 5. Re-estimation of model parameters of the dose-toxicity curve. Using the optimal starting dose, a given number of patients are treated in the first cohort. Based on the observed toxicity data from this cohort, and using the *a priori* dose-toxicity model, parameters of the original dose-toxicity curve are re-estimated. This method applies the Bayesian approach, i.e. statistically combines *a priori* assumptions with observed data. As a result, the dose-toxicity curve is shifted up or down based on whether the patients experienced DLT in the given cohort or not. Finally, using the updated dose-toxicity curve, the treatment dose of the next cohort can be calculated. From cohort to cohort, as the number of patients involved in the trial is increasing, the dose-toxicity curve is almost only estimated from the observed data, the originally chosen *a priori* dose-toxicity model is substantially changing. In Fig. 2, dashed red curve shows the modified dose-toxicity model if at least one of the patients from the previous cohort

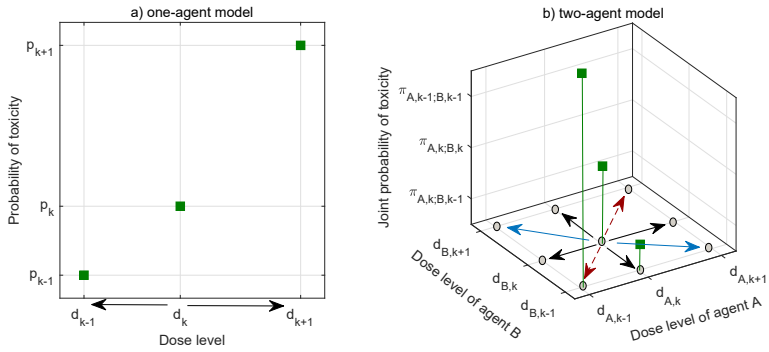

Figure 3
Probability of toxicity as a function of dose level in dose-finding trials.
In one-agent models, there are maximum two adjacent doses for a given dose level, and the probability of toxicity is monotonically increasing as the drug dose is increased. In two-agent models, there are eight adjacent doses; diagonal movements where doses are not changing in the same direction (blue solid arrow) are allowed, but diagonal movements where both doses are changing in the same direction (red dashed arrow) are not allowed. The monotonic order of toxicity is not guaranteed in the case of multi-agent models, the joint toxicity probability is unknown.

experienced DLT (the curve is shifted up, meaning that doses are presumably associated with higher toxicity risks). The treatment dose of the next cohort in this case is *dose*4. In contrast, green dotted curve in Fig. 2 represents the case when the dose-toxicity model was updated due to no patient from the previous cohort experienced DLT (the curve is shifted down, meaning that doses are presumably associated with lower toxicity risks). The treatment dose of the next cohort is *dose*6.

Step 6. Stopping CRM and finding MTD. After each cohort, dose escalation or de-escalation takes place as it is described in Step 5. CRM stops when a predefined stopping criterion is met. In a typical stopping criterion, the total number of the patients who have been treated at a given dose (during the different cohorts) is specified, and an additional condition could be that the next cohort would give the same dose level. This dose is the MTD that was being sought.

3 Bayesian Adaptive Dose-Finding Method for Multi-Agent Trials

Beside the traditional frequentist biostatistical designs, a specific model-based design group, namely Bayesian methods gain more and more importance. Bayes' theorem establishes the relationship between the conditional probability of A given B with the conditional probability of the reverse, i.e. B given A [17]. The advantages of the use of Bayesian biostatistics in clinical oncology are manifold [18–20]. On the one hand, *a priori* knowledge can be incorporated into the trial design and complex statistical methods can be expeditiously handled.

On the other hand, a probability can be assigned directly to the efficiency of the treatment. Also, Bayesian methods have the capacity to naturally integrate evidence from multiple sources [21] and Bayesian methods can provide better results by minimizing risk and maximizing utility [22]. Besides this, Bayesian methods can be used in minimum effective dose (MinED) finding problems as well [23]. However Bayesian methods have significant computational complexity, it is not an obstacle anymore due to modern computing power and available software [24]. Ewings et al. discusses a practical recommendations for implementing a Bayesian adaptive phase I design during a pandemic using AGILE trial which is a randomised seamless phase I/II trial platform [25].

Other important question in Phase I trials is the fact that in most of the cases, oncology protocols recommend multi-modal therapies where a given combination of drugs is used. In these cases, it should be determined which drug is causing the observed toxicity, which is a significant challenge [26].

As we have discussed previously, in single-agent dose-finding trials the main assumption is that the probability of toxicity is monotonically increasing as the drug dose is increased. For a given dose level, there are maximum two adjacent doses where – based on the dose-finding algorithm – the current dose can be escalated or de-escalated (Fig. 3 a) one-agent model), and the order of toxicity level corresponding to the new dose is known (i.e. is it higher or lower than the previous one).

In contrast, using a two-agent model [27, 28], the doses span a 2-dimensional space where for a given dose, there are eight adjacent doses, including diagonal movements when both doses are changing in one step (Fig. 3 b) two-agent model). Such diagonal movements where both doses are changing in the same direction (i.e. both agent doses are increasing or both are decreasing in one step) is not allowed [29]. A special case in two-agent models is when a discrete dose space is used, i.e. several doses of one agent are fixed. A solution for this case can be the parsimonious working model for the dose–toxicity relationship where the aim is to find the MTD of the other agent to be used in combination with each of the doses of agent one [30, 31].

The main problem using multiple agents is that monotonicity of the dose-toxicity curve is not an always valid assumption, namely the monotonic order of toxicity is not guaranteed [32, 33], the joint toxicity probability is unknown, hence deciding on dose escalation or de-escalation is not trivial [34].

3.1 Copula regression model

Yin et al. [29] published a copula-type drug combination regression model where *a priori* information comes from trials in which drugs were investigated individually as single agents. The developed copula-type Bayesian adaptive dose-finding method reduces to the Continual Reassessment Method when a single-agent is investigated.

The (individual) toxicity probability of agent A in the case of the jth dose (A_j) is p_j, and the investigated sequence is $p_1 < p_2 < ... < p_j < ... < p_J$, where

p_J is the toxicity probability of the MTD of agent A (i.e. A_J). Similarly, the (individual) toxicity probability of agent B in the case of the kth dose (B_k) is q_k, and the investigated sequence is $q_1 < q_2 < ... < q_k < ... < q_K$, where q_K is the toxicity probability of the MTD of agent B (i.e. B_K). The individual toxicity probabilities are known. As it was mentioned before, however the individual toxicity probabilities are ordered, the joint toxicity probabilities are not trivially ordered; for instance the relationship between $\pi_{j,k}$ (joint toxicity probability of (A_j, B_k)) and $\pi_{j-1,k+1}$ (joint toxicity probability of (A_{j-1}, B_{k+1})) is not known.

In the next step, a power parameter is assigned to the *a priori* toxicity probabilities in order to reduce the uncertainty of the probabilities; the "true" toxicity probabilities are p_j^α and q_k^β, where $\alpha > 0$ and $\beta > 0$ are unknown parameters with prior means centered at 1. To calculate the joint toxicity probabilities, the following conditions have to be satisfied:

- if $p_j^\alpha = 0$ and $q_k^\beta = 0 \Rightarrow \pi_{j,k} = 0$,
- if $p_j^\alpha = 0 \Rightarrow \pi_{j,k} = q_k^\beta$; and if $q_k^\beta = 0 \Rightarrow \pi_{j,k} = p_j^\alpha$,
- if either $p_j^\alpha = 1$ or $q_k^\beta = 1 \Rightarrow \pi_{j,k} = 1$,

where $j = 1, ..., J$ and $k = 1, ..., K$.

In a copula-type model, the joint toxicity probability distribution can be calculated using the marginal distributions and a dependence parameter. The dependence function in the Archimedean copula family is

$$C_\gamma(u,v) = \psi_\gamma \left\{ \psi_\gamma^{-1}(u) + \psi_\gamma^{-1}(v) \right\}, \tag{4}$$

where $0 \leq u, v \leq 1$, and γ is an association parameter, C_γ is a distribution function on $[0,1]^2$, and ψ_γ is the copula generator with the following properties: $0 \leq \psi_\gamma \leq 1$, $\psi_\gamma(0) = 1$, $\psi'_\gamma < 0$ and $\psi''_\gamma > 0$. Taking into account a specific type from the Archimedean copula family (Clayton copula), the proposed regression model copula is

$$\pi_{j,k} = 1 - \left\{ \left(1 - p_j^\alpha\right)^{-\gamma} + \left(1 - q_k^\beta\right)^{-\gamma} - 1 \right\}^{-\frac{1}{\gamma}}, \tag{5}$$

where $\gamma > 0$ describes the drug–drug interaction. This model is a multivariate generalization of the Continual Reassessment Method, allowing internal learning from other combinations of dose levels.

In the case of multi-agent models, target toxicity level has an intersection curve with the joint toxicity probability surface, this curve defines the required maximum tolerated dose. As a consequence, there could be more than one discrete MTD solution. The final MTD combination should be selected based on the recommendation of medical experts.

The likelihood function can be calculated based on a binomial distribution

$$L(\alpha,\beta,\gamma|\text{data}) \propto \prod_{j=1}^{J}\prod_{k=1}^{K} \pi_{j,k}^{x_{j,k}}(1-\pi_{j,k})^{n_{j,k}-x_{j,k}}, \tag{6}$$

where $n_{j,k}$ represents the patients who are treated with (j,k) dose level combination, and $x_{j,k}$ represents the patients who experienced dose-limiting toxicity.

Assuming independent *a priori* distributions, viz. $f(\alpha,\beta,\gamma) = f(\alpha)f(\beta)f(\gamma)$, joint posterior distribution is

$$f(\alpha,\beta,\gamma|\text{data}) \propto L(\alpha,\beta,\gamma|\text{data})f(\alpha)f(\beta)f(\gamma). \tag{7}$$

After each cohort, Gibbs sampler is used to find the unknown parameters, and hence the $\pi_{j,k}$ joint toxicity probability can be calculated, on which the dose escalation or de-escalation decision for the following cohort can be done.

The dose-finding algorithm has the following steps (denotations: ϕ is the target toxicity level, c_e is the probability cut-off for dose escalation, c_d is the probability cut-off for dose de-escalation, $c_e + c_d > 1$):

- Starting the first cohort: patients are treated with the lowest combination: (A_1, B_1)
- Start-up rule in order to obtain reliable posterior estimates:
  - first, the dose of agent A is fixed, while the dose of agent B is continuously increased based on the predescribed sequence, until the first DLT is experienced: $\{(A_1,B_2),(A_1,B_3),...,(A_1,B_{DLT})\}$
  - second, the dose of agent B is fixed, while the dose of agent A is continuously increased based on the predescribed sequence, until the first DLT is experienced: $\{(A_2,B_1),(A_3,B_1),...,(A_{DLT},B_1)\}$
  - if one patient experiences DLT in both agents, the start-up period is finished
- Investigating joint toxicity probabilities:
  - if $P\left(\pi_{j,k} < \phi\right) > c_e$, then dose escalation takes place to an adjacent dose combination where the corresponding joint toxicity probability is higher than the current one; if the current dose combination is (A_J, B_K) (viz. the individual MTD for both agents), no more dose escalation takes place, dose combination stays at the same level
  - if $P\left(\pi_{j,k} > \phi\right) > c_d$, then dose de-escalation takes place to an adjacent dose combination where the corresponding joint toxicity probability is lower than the current one; if the current dose combination is (A_1, B_1) (viz. the lowest dose for both agents), no more dose de-escalation takes place, the trial is terminated

– otherwise (when no cut-off dose for escalation or de-escalation is reached), the next cohort continues with the same dose combination

– when the predefined maximum cohort size is reached, the trial ends; the dose combination which has the closest value to the target toxicity level is set to be the joint MTD for the investigated agents

For an integrated Bayesian Phase I/II adaptively randomized oncology trial design based on the copula model, see [35].

3.2 Logistic regression model

Riviere et al. [2] proposed a drug combination–toxicity relationship logistic regression model

$$\text{logit}(\pi_{j,k}) = \beta_0 + \beta_1 u_j + \beta_2 v_k + \beta_3 u_j v_k, \tag{8}$$

where $\pi_{j,k}$ is the joint toxicity probability of a two agent drug combination, β_1 is the the toxicity effect of agent A, β_2 is the the toxicity effect of agent B, and β_3 is the interaction between the two agents ($\beta_0 ... \beta_3$ are unknown parameters). Variable u_j represents the standardized dose of the jth level of agent A, v_k is the standardized dose of the kth level of agent B. Standardized doses are defined individually (as if they are administered as a single-agent) using the *a priori* estimates of the toxicity probabilities of the jth dose level of agent A (p_j) and the kth dose level of agent B (q_k)

$$u_j = \log \frac{p_j}{1-p_j} \tag{9}$$

$$v_k = \log \frac{q_k}{1-q_k}. \tag{10}$$

In this model, the likelihood function is a product of the Bernoulli probabilities

$$L(\beta_0, \beta_1, \beta_2, \beta_3 | \text{data}) \propto \prod_{j=1}^{J} \prod_{k=1}^{K} \pi_{j,k}^{x_{j,k}} (1-\pi_{j,k})^{n_{j,k}-x_{j,k}}, \tag{11}$$

where $n_{j,k}$ represents the patients who are allocated at combination (j,k), and $x_{j,k}$ represents the patients who experienced dose-limiting toxicity.

The posterior distribution is sampled using Gibbs sampler, and the *a posteriori* toxicity probabilities are estimated using Monte Carlo simulation

$$\tilde{\pi}_{j,k} = \frac{1}{L} \sum_{l=1}^{L} \frac{\exp\left(\beta_0^{(l)} + \beta_1^{(l)} u_j + \beta_2^{(l)} v_k + \beta_3^{(l)} u_j v_k\right)}{1 + \exp\left(\beta_0^{(l)} + \beta_1^{(l)} u_j + \beta_2^{(l)} v_k + \beta_3^{(l)} u_j v_k\right)}, \tag{12}$$

where $\left(\beta_0^{(l)}, \beta_1^{(l)}, \beta_2^{(l)}, \beta_3^{(l)}\right)_{l=1,\ldots,L}$ are the L posterior samples, assuming that β_0 and β_3 are normal *a priori* distributions ($N(0,10)$), and β_1 and β_2 are exponential

a priori distributions (Exp(1)).

The dose-finding algorithm is the one that was proposed in the copula regression model [29]; however, MTD level is found in a different way. Target toxicity level is extended to a target toxicity interval using parameter δ

$$\phi_{interval} = [\phi - \delta; \phi + \delta], \tag{13}$$

where ϕ is the target toxicity level.

Using the target toxicity interval, the *a posteriori* densities of the toxicity probability can be divided into three groups:

- if the toxicity probability is in the $[0; \phi - \delta]$ interval, the corresponding cumulative density is the probability of under-dosing,
- if the toxicity probability is in the $[\phi - \delta; \phi + \delta]$ interval, the corresponding cumulative density is the probability of target toxicity,
- if the toxicity probability is in the $[\phi + \delta; 1]$ interval, the corresponding cumulative density is the probability of over-dosing (for a specific solution of the over-dosing problem, see e.g. [11] where the Bayesian Optimal Interval (BOIN) design is introduced).

For each (A_j, B_k) dose combination, the probability of being in the targeted toxicity interval can be calculated. The dose combination that has the highest *a posteriori* probability, and have been used previously to treat at least one cohort of the patients, should be chosen as MTD

$$(A_{MTD}, B_{MTD}) = \max \left\{ P\left(\pi_{j,k} \in [\phi - \delta; \phi + \delta]\right) \right\}. \tag{14}$$

For another Bayesian dose-finding method which use logistic regression model, see e.g. [36] where the approach allows the inclusion of covariates.

4 Bayesian Dose-Finding Methods for Trials with Delayed Toxicities

Administering different radiations to the patients, late-onset toxicities can be observed which affect the dose escalation or de-escalation decisions. In order to conduct a complete follow-up after each cohort, in some cases several weeks or even months are required. Late-onset toxicity is an important problem in the non-conventional cancer therapies like Targeted Molecular Therapies (TMTs) [37].

4.1 Time-To-Event Continual Reassessment Method (TITE-CRM) for single-agent trials

The time-consuming nature is a strong limit to the use of Continual Reassessment Method in the case of late-onset toxicities. A short-cut for this problem is to allow patients to enter to the trial in a staged fashion, which extends the CRM to Time-To-Event Continual Reassessment Method (TITE-CRM) that can handle

late-onset toxicities [38, 39].

In the original CRM, the decision of the dose level of the next cohort can be formulated as

$$F\left(d_{n+1},\hat{p}_n\right)-\phi \leq F\left(d_k,\hat{p}_n\right)-\phi \text{for } k=1,...,K, \tag{15}$$

where $F(d,p)$ is the dose-toxicity model, $d_1,...,d_K$ are the dose levels, p is the probability of toxicity, n is the number of observations, $\hat{p}_n$ is an estimate of p, and ϕ is the target toxicity level.

The likelihood function in this case is

$$L_n(p)=\prod_{i=1}^{n} F\left(d_i,p\right)^{y_i}\left\{1-F\left(d_i,p\right)\right\}^{1-y_i}, \tag{16}$$

where y_i is the indicator of toxic response for the ith patient.

In the TITE-CRM, there is a weighted dose-toxicity model $G(d,\omega,p)$ that has the following properties: $G(d,0,p)=0$ and $G(d,1,p)=F(d,p)$, where ω $(0 \leq \omega \leq 1)$ is a function of the time-to-event of a patient, and it is linear in F. The dose escalation or de-escalation decisions are the same as in the original CRM (i.e. (15)), but the likelihood is weighted as well

$$\tilde{L}_n(p)=\prod_{i=1}^{n} G\left(d_i,\omega_{i,n},p\right)^{y_{i,n}}\left\{1-G\left(d_i,\omega_{i,n},p\right)\right\}^{1-y_{i,n}}, \tag{17}$$

where $y_{i,n}$ is the indication of toxic response for the ith patient prior to the entry time of the $(n+1)$th patient, and $\omega_{i,n}$ is the corresponding weight. Using TITE-CRM, patients who have not experienced DLT are weighted by the proportions of their follow-up times compared to the full period of the trial, and patients who have experienced DLT are weighted by 1.

4.2 Late-onset toxicity model for multi-agent trials

Liu et al. [37] proposed a late-onset toxicity model for multi-agent trials using the Bayesian data augmentation approach, treating the late-onset toxicity as missing data. The dose-toxicity model is described by the Finney model

$$\text{logit}(\pi_{j,k})=\beta_0+\beta_1 \log\left(a_j+\rho b_k+\gamma(a_j\rho b_k)^{\frac{1}{2}}\right), \tag{18}$$

where β_1 is the slope of the regression ($\beta_1>0$), ρ is the relative potency of agent B versus agent A to induce toxicity (if $\rho>1 \Rightarrow$ agent B is more likely to cause toxicity than agent A), and γ is the synergy-antagonism parameter describing the drug-drug interaction between the agents ($\gamma<0 \Rightarrow$ antagonism effect, $\gamma=0 \Rightarrow$ dose additivity effect, $\gamma>0 \Rightarrow$ synergy effect). In this model, β_0, β_1, γ and ρ are unknown parameters. The Finney model reduces to the standard logistic model when a single-agent is investigated.

If no late-onset toxicity takes place, the toxicity outcomes are fully observed and

hence the complete-data likelihood function can be described for the ith patient as

$$L(\theta|y) = \prod_{i=1}^{n} \frac{\exp\left\{y_i\beta_0 + y_i\beta_1 \log\left(a_{j_i} + \rho b_{k_i} + \gamma\left(a_{j_i}\rho b_{k_i}\right)^{\frac{1}{2}}\right)\right\}}{1 + \exp\left\{\beta_0 + \beta_1 \log\left(a_{j_i} + \rho b_{k_i} + \gamma\left(a_{j_i}\rho b_{k_i}\right)^{\frac{1}{2}}\right)\right\}}, \quad (19)$$

where n is the total number of patients, y_i is the binary toxicity outcome, a_{j_i} is the jth dose of agent A for the ith patient, and b_{k_i} is the kth dose of agent B for the ith patient. The *a posteriori* distribution of $\theta = (\beta_0, \beta_1, \gamma, \rho)$ in this case is

$$f(\theta|y) \propto f(\theta)L(y|\theta), \quad (20)$$

where $f(\theta)$ is the *a priori* distribution of θ.

If late-onset toxicities take place, the toxicity outcomes are not fully observed due to the missing binary toxicity outcome values. These missing values can be handled using data augmentation which contains two iterative steps:

- imputation (I):
  - in this step, the missing data is imputed by drawing samples from their posterior predictive distribution using Bernoulli probability

    $$f(y_i|t_i > s_i, \theta) = \text{Bernoulli}\left(P\left(y_i = 1|t_i > s_i, \theta\right)\right), \quad (21)$$

    where t_i is the time to toxicity for the ith patient, and s_i is the actual follow-up time;
- posterior (P):
  - in this step, the posterior samples of unknown parameters are simulated based on imputed data
  - here – due to the imputation of the missing data in the previous step – the standard Markov chain Monte Carlo method [26] can be used as in the case of complete-data when no late-onset toxicity takes place.

Iteration-based techniques are well-known not only in model-baesd dose-toxicity modelsbut in fixed point, iteration-based controls as well [40].

5 Discussion and Conclusion

Finding the maximum tolerated dose in Phase I oncology clinical trials is an important and not trivial problem. Beside the safety criterion of the patients (viz. avoiding over-dosing), cost-effectiveness viewpoints should be taken into account as well (e.g. avoiding unnecessary under-dosing experiments), and some-

times even extreme circumstances such as a pandemic [25].

A promising solution of the dose-finding problem is the use of Bayesian methods. In every case, the method is based on an *a priori* dose-toxicity model which gives a preliminary estimation of the toxicity probability for the investigated drug dose levels. In the following steps, these *a priori* assumptions are statistically combined with observed data. The trials consist of cohorts; from cohort to cohort, dose escalation or de-escalation takes place. The trial ends when a pre-defined stopping criterion is met, and maximum tolerated dose can be found which results in relatively acceptable dose-limiting toxicity.

For the simplest dose-finding problem, viz. single-agent trials with fully observed data, the most common solution is the Continual Reassessment Method. In this case the toxicity is monotonically increasing as the drug dose is increased. However, using multiple agents, the monotonic order of toxicity is not guaranteed, the joint toxicity probabilities are unknown, and as a consequence, dose escalation or de-escalation decision is not trivial.

In this paper, two models for multiple agents have been discussed: the copula regression model and the logistic regression model. Both models estimate the joint toxicity probability distribution and define a likelihood function. The dose escalation or de-escalation decision is made after Gibbs sampling, but MTD level is found in different ways in respect of the two methods.

Another incremental problem can be the presence of late-onset toxicities. For a single-agent problem, the use of Time-To-Event Continual Reassessment Method can handle the problem by allowing patients to enter to the trial in a staged fashion. Taking into account multi-agent trials, the Bayesian data augmentation approach can be applied which treats the late-onset toxicity as missing data, and missing values can be handled using data imputation and simulation of posterior samples.

Besides the above discussed Bayesian methods, dose-finding criteria can be calculated using other approaches like toxicity and efficacy odds ratios [41]. In this case, acceptable doses satisfy the following two conditions:

$$\Pr(p_j < \overline{\pi}_T) > p^*, \tag{22}$$

$$\Pr(q_j > \underline{\pi}_E) > q^*, \tag{23}$$

where $\overline{\pi}_T$ is a pre-defined upper toxicity limit, $\underline{\pi}_E$ is pre-defined lower efficacy limit, and p^* and q^* are fixed probability cutoffs.

Dose j has p_j toxicity probability and q_j efficacy probability. Taking into account two-dimensional toxicity and efficacy domain, we expect that p_j and q_j are the closest values to the lower-right corner $(1,0)$. The horizontal and vertical lines which cross point $A(q_j, p_j)$ split the domain into four rectangles.

After that, the odds ratio between the toxicity and efficacy of dose j can be calculated:

$$\omega_j^{(2)} = \frac{p_j/(1-p_j)}{q_j/(1-q_j)} = \frac{p_j(1-q_j)}{(1-p_j)q_j)}. \tag{24}$$

Note that $\omega_j^{(2)}$ is exactly the ratio of the lower-right versus the upper-left rectangle's area. In this way, an equivalent odds ratio contour can be defind: along the curve, all the points have the same toxicity-efficacy odds ratio, namely $\omega_j^{(2)}$.

Furthermore, this two-dimensional probability space can be extended by a third scale, where the new axis is the probability of efficacy given no toxicity. Hence in this three-dimensional domain, the toxicity-efficacy odds ratio trade-offs are arranged with an efficacy value given no toxicity. Compared to the two-dimensional domain, there not an equivalent odds ratio contour, but an equivalent odds ratio surface is defined. All the points on this smooth surface have the same odds ratio, $\omega_j^{(3)}$. Based on this, one can find the best dose to treat the patients in the next cohort.

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