A Bayesian decision-theoretic approach to leverage preclinical information into a phase I first-in-man trial

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Context

Leveraging preclinical animal data for a phase I trial is appealing yet challenging. A prior determined based on animal data may place large probability mass on values of the dose-toxicity model parameters, which appear infeasible in light of data from the ongoing first-in-man trial. In this work, we propose a Bayesian approach to incorporating animal data via a **robust mixture prior** for the model parameters that underpin a human trial. We assume a two-parameter logistic regression model is adequate to describe the dose-toxicity relationship: $\text{logit}(p) = \theta_1 + \exp(\theta_2)\log(d)$.

- A bivariate normal prior for $\boldsymbol{\theta} = (\theta_1, \theta_2)$
  - Traditionally, operational priors are considered
  - However, **animal data** $\rightarrow$ **informative prior**
- The dose for the next patient will be determined based on the posterior probabilistic inference

Methods

We consider a robust mixture prior with dynamically chosen weights

$$f_k(\boldsymbol{\theta}) = \omega_k \times \underbrace{g(\boldsymbol{\theta})}_{\text{preclinical info}} + (1-\omega_k) \times \underbrace{h(\boldsymbol{\theta})}_{\text{weakly-informative}},$$

where the prior mixture weight ω_k will be informed by the degree of **commensurability** between animal and human data at stage k.

- **On deriving the informative component** $g(\theta)$

First, summarise preclinical information as pseudo-observations on the lowest and highest doses. The corresponding probabilities of dose-limiting toxicity (DLT) can be described by two beta distributions. With Jacobian transformation, the joint prior can be re-parameterised using θ_2 and p_j, the probability of DLT at dose d_j. The probability density function of p_j can be derived by integrating out θ_2, and the 2.5th, 50th and 97.5th percentiles of prior distributions for p_j will be available. Finally, a bivariate normal prior for $\boldsymbol{\theta}$ can be approximated based on an optimiser to agree with those exact summaries.

- **A Bayesian decision-theoretic approach** $\rightarrow \omega_k$

We relate the commensurability with how accurate preclinical information can predict human responses.

Prior predictive distributions can be derived based on preclinical information. Optimal predictions for whether incoming patients will experience DLT or not are made by maximising the expected utility, which is featured with a utility function assigning a reward or penalty for predictions: specifically, a utility of 1 to correct predictions, 0 to incorrect predictions of no-DLT, and c ($0<c<1$) to incorrect predictions of DLT. At each interim analysis, these prior predictions are compared with accumulated actual outcomes.

		Observation		Count	
		No-DLT	DLT		
Prediction	No-DLT	u_{00}	u_{10}	n_{00}	n_{10}
	DLT	u_{01}	u_{11}	n_{01}	n_{11}

Table 1: Cross-tabulation of utilities, and frequencies of predicted versus actual human DLTs and no-DLTs.

Commensurability between preclinical information and human data is described by taking average of predictive accuracy across all doses that have been administered so far $\bar{a} = \frac{1}{T}\sum_{t=1}^{T} \frac{\sum_{l=0}^{1}\sum_{m=0}^{1} u_{lm} n_{lm}}{\sum_{l=0}^{1}\sum_{m=0}^{1} n_{lm}}$, $T \leq J$. The mixture weight ω_k is therefore determined by $\bar{a}$.

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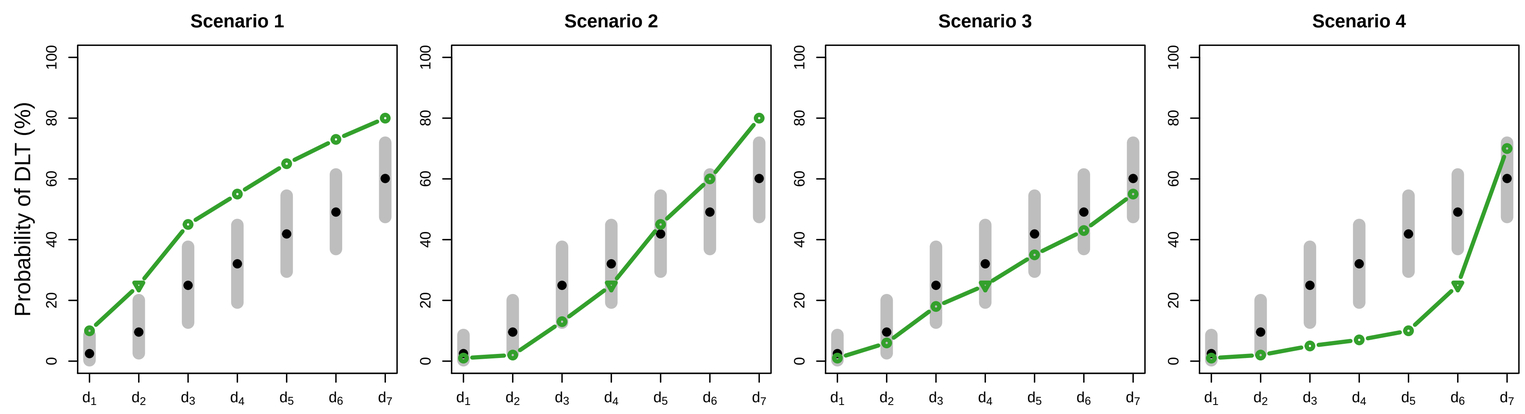
Simulation study

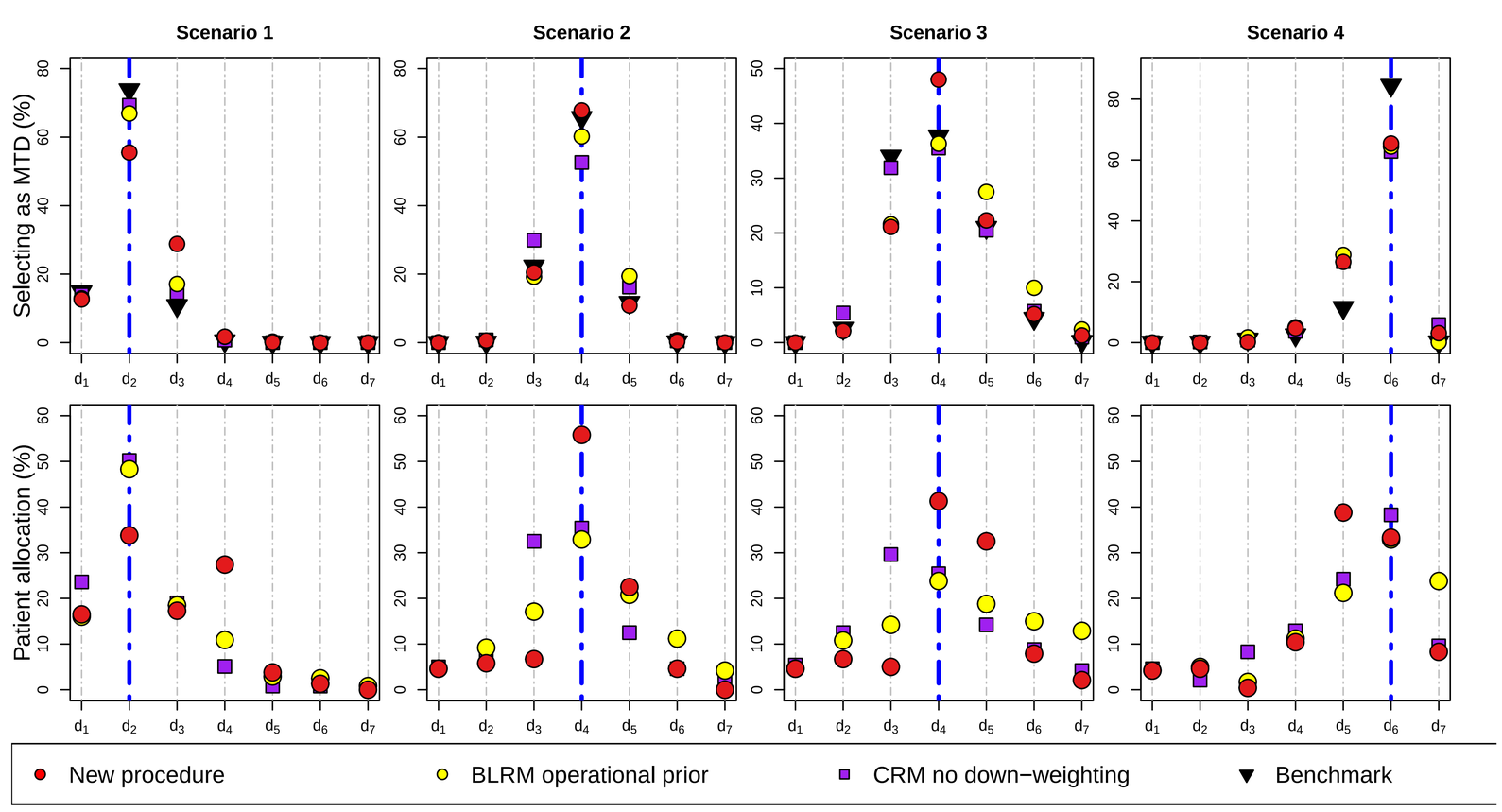
Probabilities of DLT at the lowest and highest dose are respectively thought to be 0.03 and 0.60, based on preclinical studies with 60 subjects for each. Such information is used to formulate the informative prior component $g(\theta)$ for a phase I dose-escalation study, of which the maximum sample size is 24 and the cohort size is 1. The objective is to estimate the maximum tolerated dose, defined as the dose at which the underlying probability of DLT is 0.25. Patient gain criterion is used for interim dose recommendations, for which the probability of excessive toxicity at the recommended dose is controlled at at pre-defined level, say, $\Pr(\tilde{p}_j \geq 0.45) \leq 0.25$. We compare the proposed procedure with

(I) Bayesian logistic regression model (BLRM) with an operational prior
(II) CRM with non-downweighted preclinical information, for which prior medians $\rightarrow$ skeletons
(III) Non-parametric optimal benchmark design

Investigated human toxicity scenarios (green) and priors determined by preclinical information, represented by median (black) and 95% credible intervals (grey), are shown in the graphs below.



Results



Results are presented based upon 5000 simulated trials per scenario. The optimal benchmark design provides a bound that results from traditional model-based methods adopting uninformative prior cannot exceed. In contrast, the proposed BDTA does better in *Scenarios 2 & 3*, where for almost all doses the true probability of DLT fall into the 95% credible intervals of the prior distribution determined by preclinical information. In *Scenario 1* where preclinical information underestimates the true probabilities in humans for all doses and in *Scenario 4* where true target dose is far away from the one suggested by preclinical information, the proposed procedure works satisfactorily.

Discussion

- The proposed procedure is very robust and competitive
  - When preclinical information is commensurate to some extent with human data $\rightarrow$ patients have enhanced possibility to receive the target dose & greater estimation precision achieved
  - When prior-data conflict emerges $\rightarrow$ sensible down-weighting & safe dose escalations
- Many topics for future development may be interesting to explore, for example, extending the procedure to accommodate the incorporation of both efficacy and toxicity preclinical information

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