A comparative analysis of Phase I dose-finding designs incorporating pharmacokinetics information

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Introduction

- "First-in-human" (FiH) studies for promising therapies aim at evaluating the safety of a candidate drug, along with pharmacokinetics (PK), in humans, and typically include a small sample of healthy volunteers or patients.
- Conventional randomized designs can be unsafe and inaccurate with low sample size. Adaptive approaches use Bayesian experimental designs to perform dose-finding trial, leveraging pre-existing data to make prior guesses on the parameters, thereby compensating for small population sizes.
- In most Phase I and Phase I/II studies in patients, dose-finding and pharmacokinetics/pharmacodynamics (PK/PD) are still analyzed separately [1]. Various dose-finding methods using PK data have been proposed in recent literature based on different approaches to integrate PK data in the toxicity estimation.

Objective

Explore how PK information is used in existing prospective Bayesian dose-finding designs and assess via extensive simulations the performance and the robustness to model misspecification/deviation of these methods for accurate toxicity estimation and MTD identification.

Methods

We conducted an extensive narrative review to identify dose-finding designs using PK data and classified separatly the different selected approaches for PK integration: PK logistic (PKLOGIT) model [2]; Exposure Driven Escalation with Overdose Control (ED-EWOC) method [3]; Time-To-Event PK (TITE-PK) design [4]. We also implemented an alternative design to ED-EWOC, called Exposure Driven (ED), without the EWOC dose allocation rule. Finally, the Bayesian Logistic Regression Method (BLRM), that does not use PK data, was chosen as a benchmark for the simulation study.

Notation: p_T represents the probability of toxicity. Let d_k be the dose—level k and λ the target probability of toxicity. Drug concentrations in patients are sampled at times $\boldsymbol{t} = (t_1, \dots, t_j, \dots, t_J)$, with $C_i(t_j)$ and c_{ij} respectively the actual concentration and the measured concentration of the drug in the i-th patient at time t_j. Let z_i be the logarithm of the AUC of the i-th patient, $z_i = \log(\mathrm{AUC_i})$, and z^* be the reference $\log(\mathrm{AUC})$ computed on the reference dose d^*.

Name	Model
BLRM	**Logistic regression** $\mathrm{logit}\big(p_\mathrm{T}(d_\mathrm{k}, \boldsymbol{\beta})\big) = \log(\beta_1) + \beta_2\big(\log(d_\mathrm{k}) - \log(d^*)\big)$
PKLOGIT	**Normal approximation of AUC** $z_i \vert \boldsymbol{\beta}, v \sim \mathcal{N}(\beta_0 + \beta_1 \log(d_i), v^2)$ **Logistic regression** $\mathrm{logit}\big(p_\mathrm{T}(\mathrm{z}, \boldsymbol{\beta'})\big) = \beta_2 + \beta_3(\mathrm{z} - \mathrm{z}^*)$
ED-EWOC/ED	**PopPK model** $C(t_j \vert d_i, \beta_{1i}) = c(d_i, t_j, \beta_{1i}) \times (1 + \epsilon_{ij}), \quad \epsilon_{ij} \sim \mathcal{N}(0, \sigma_\epsilon^2)$ **Logistic regression** $\mathrm{logit}\big(p_\mathrm{T}(z_i \vert \beta_2, \beta_3)\big) = \beta_2 + \beta_3(\mathrm{z_i} - \mathrm{z}^*)$
Informed and naive TITE-PK	**K-PD: One-compartment model with IV bolus** $\begin{cases} \frac{dC(t)}{dt} = -k_e C(t) \\ \frac{dC_{\mathrm{eff}}(t)}{dt} = k_{\mathrm{eff}}\big(C(t) - C_{\mathrm{eff}}(t)\big) \end{cases}$ **Complementary log-log regression** $\mathrm{cloglog}\big(P(T \le t^* \vert C_{\mathrm{eff}}(t^* \vert d))\big) = \log(\beta) + \log\big(\mathrm{AUC}_E(t^* \vert C_{\mathrm{eff}}(t^* \vert d))\big)$

Table 1: Bayesian inference – Modelling of dose-finding designs using PK data for toxicity assessment.

Simulation settings

All methods were evaluated for a Phase I dose-finding trial based on the development of the TGF-β inhibitor LY2157299 [5], in a simulation study consisting of…

- 1000 clinical trials,
- 30 patients per trial,
- 4 doses (30.6 mg, 50.69 mg, 93.69 mg, and 150.37 mg) with dose-level 3 as the reference,
- cohorts of size 2,
- and a targeted probability of toxicity $\lambda = 25\%$.

Scenarios

- 26 scenarios were implemented exploring different settings with deviation on the position of the MTD and/or misspecification of PK measures of exposure or PK model.
- In total, 6 sets of scenarios are created with the last one containing only one scenario, named respectively set A, B, C, D, E or F. In each set, each of the 5 scenarios corresponds to a location of the MTD among the four doses, except the last scenario, which models the case where all doses are too toxic.

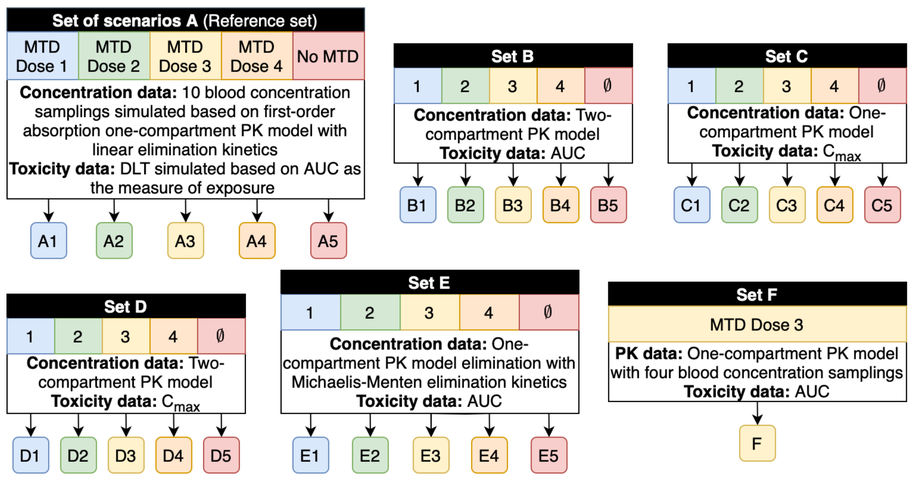

Figure 1: Construction of the sets of scenarios with their respective simulation framework to obtain drug concentration and toxicity data.

Results

- **Set A:** The designs performed well in terms of correct MTD selection for scenario A1, except both TITE-PK methods, displaying a tendency to overdose for the lowest doses. PKLOGIT performed on average marginally worse than the most effective PK methods. When comparing the two PK dose-finding methods using a popPK model, ED-EWOC outperformed substantially ED, demonstrating effective overdose control for lower-dose MTD. However, in scenarios A3 and A4, the results were reversed.
- **Set B**: Similar results to set A.
- For scenarios C1, C5, D1, and D5, ED-EWOC and ED were outperformed by informed and naive TITE-PK methods respectively.
- **Set E:** Compared with set A, all dose-finding methods displayed on average better performance in terms of correct MTD selection.
- BLRM struggled to recommend the appropriate dose as MTD in scenarios with intermediate-dose MTDs.
- PK dose-finding methods were better than BLRM in estimating the probabilities of toxicity for all doses, especially in the case of low-dose MTD, as in scenario A1 for example.

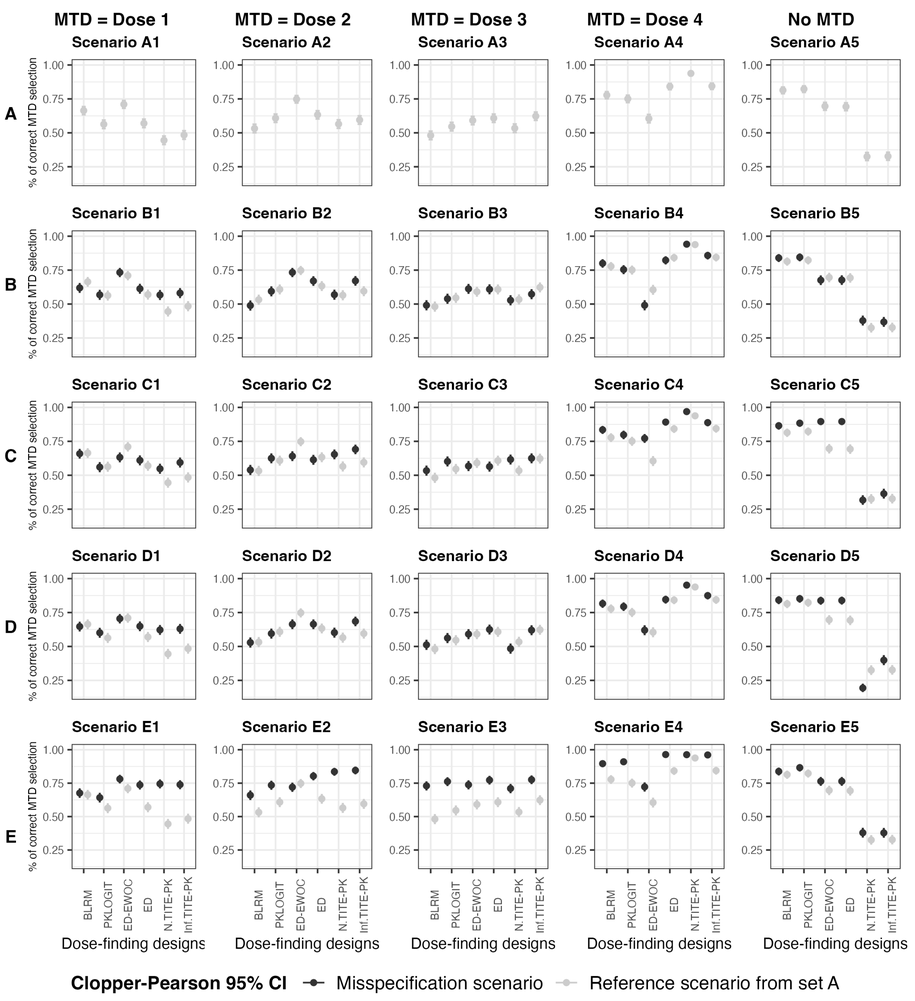

Figure 2: Percentage of correct MTD selection with Clopper-Pearson 95% confidence intervals for reference set of scenarios A (A1-A5) and for deviation/misspecification scenarios (B1-E5) compared with MTD-associated scenarios from set A.

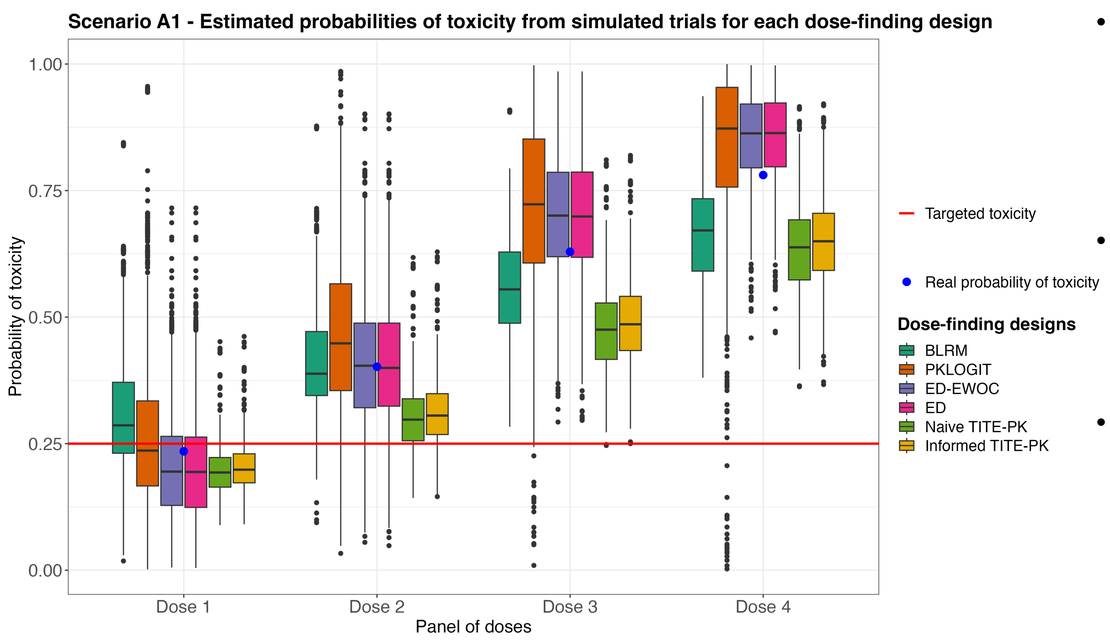

Figure 3: Scenario A1 - Estimated probabilities of toxicity at all doses for all dose-finding methods where the MTD is on dose-level 1.

Assessment of PK methods

- PKLOGIT, like BLRM, struggles with lower-dose MTD selection, stopping more often for safety reasons than other PK dose-finding methods.
- ED-EWOC and ED show potential, especially under misspecification, but are generally inferior to TITE-PK for MTD selection.
- TITE-PK performs consistently well, barring low-dose MTDs and misspecification scenarios, but unlike ED-EWOC and ED, fails to estimate properly the probabilities of toxicity.

Discussion

- Incorporating PK information into model-based approaches as a covariate or using a PK latent model for Phase I dose-finding trial is likely to achieve safer dose-escalation and to recommend, at least as much as the BLRM, the accurate MTD for further investigation.
- Additionally, PK dose-finding methods can evaluate the full dose-toxicity curve for the drug and provide plausible estimates of the probability of toxicity for each dose with limited sample size.

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