

Incorporating pharmacokinetic information in phase I studies in small populations

M. Ursino^a, E. Comets^{b,c}, F. Lentz^d, C. Alberti^e, T. Friede^f, N. Stallard^g, S. Zohar^a

a) INSERM, UMRS 1138, team 22, CRC, University Paris 5, University Paris 6, Paris, France; b) INSERM, CIC 1414, University Rennes-1, Rennes, France; c) INSERM, IAME, UMR 1137, University Paris Diderot, Paris, France; d) Federal Institute for Drugs and Medical Devices, Bonn, Germany; e) INSERM, UMR 1123, Hôpital Robert-Debré, APHP, University Paris 7, Paris, France; f) Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany; g) Statistics and Epidemiology, Division of Health Sciences, Warwick Medical School, The University of Warwick, UK.

Clinical setting

Phase I dose-finding studies in oncology aim at determining the maximum tolerated dose (MTD) while limiting the number of patients exposed to high toxicity. In small populations, when one could not conduct several or separate trials to have a good estimation of the MTD and the PK parameters, it would be important to reach these two goals within the same clinical trial. In this work we modify and propose several Bayesian adaptive designs for sequential dose-finding designs including PK measures as covariate or dependent variables. We have assumed toxicity to be related to PK measure of exposure.

Simulation setting

We chose an example in drug development to build a realistic simulation study based on a PK/PD model describing toxicity and efficacy for a TGF- β inhibitor LY2157299 in patients with glioma [4]. TGF- β signalling is an important regulator growth in advanced cancer, and its inhibition could simultaneously inhibit tumour spread and neo-angiogenesis thus improve the patient's antitumor immune response. In [4], toxicity was found to be related to the area under the curve (AUC), and preclinical data was used to determine a threshold for future clinical development.

In the present work, we consider a simplified one-compartment model with first-order absorption as in [5]. The absorption rate constant k_a was assumed to be fixed, and log-normal distributions were used to account for interindividual variability in clearance (CL) and volume (V), with means respectively $CL_{pop}=10$ L/h and $V_{pop}=100$ L and IIV of 70%. Figure 1 shows the PK profiles simulated with the population parameters for different doses. We also introduced patient variability in the PK-toxicity relationship by defining $s(AUC)=\alpha AUC$, where α was assumed to come from a lognormal distribution with zero mean and standard deviation ω_α , and we considered toxicity occurred when $s(AUC)$ was over a given threshold τ_T . The probability of toxicity, p_T , is then given by

$$p_T(D) = \Phi\left(\frac{\log(D) - \log(\tau_T) - \log(CL_{pop})}{\sqrt{\omega_{CL}^2 + \omega_\alpha^2}}\right)$$

Figure 2 shows the changes in the probabilities of toxicity in response to changes in ω_α . Here we show the results for two scenarios where $\tau_T=10.96$ mg l^{-1} h and $\omega_\alpha = 0$ or 1.18. We simulated 1000 trials for each scenario, assuming 30 patients per trial. We simulated the same subjects for all methods, by using the same parameters and toxicity events, to improve consistency. We have considered 6 possible dose levels (12.6, 34.65, 44.69, 60.8, 83.69 and 100.37 mg), that are the doses with probability of toxicity of, respectively, 0.001, 0.05, 0.1, 0.2, 0.35, 0.45 in scenario 1.

Estimation procedure

We used the package `rjags` in R to implement the dose-finding methods and simulate clinical trials based on the real-life example. Estimates of the AUC were obtained by individual non-linear regression with the `nls` function in R. 10 sampling time points were used, 6 around the peak and 4 in the tail, in order to have a quite precise estimation.

Notations :

- P_T = probability of tox
- D_k = k-th dose level
- $Z = \log AUC$
- $\Delta Z = \log AUC_{pop} - \log AUC_{patient}$
- β = set of parameters

Dose-finding methods :

- * PKCOV [1]

$$P_T = \frac{1}{1 + \exp(\beta_0 - \beta_1 \log D_k - \beta_2 \Delta Z)}$$
 β_0 fixed
- * CRMPK_L
 - CRN (Continuous reassessment method) with power working model
 - + PKLIM [2]

$$Z | \beta, u \sim N(\beta_0 + \beta_1 \log D_k, u^2)$$

$$P_T = P(Z > L | \hat{\beta}, \hat{u})$$
 $\hat{\beta}$ fixed threshold
- * PKLOG [2]

$$P_T(D) = \frac{1}{1 + \exp(\beta_3 - \beta_4 \Delta Z)}$$

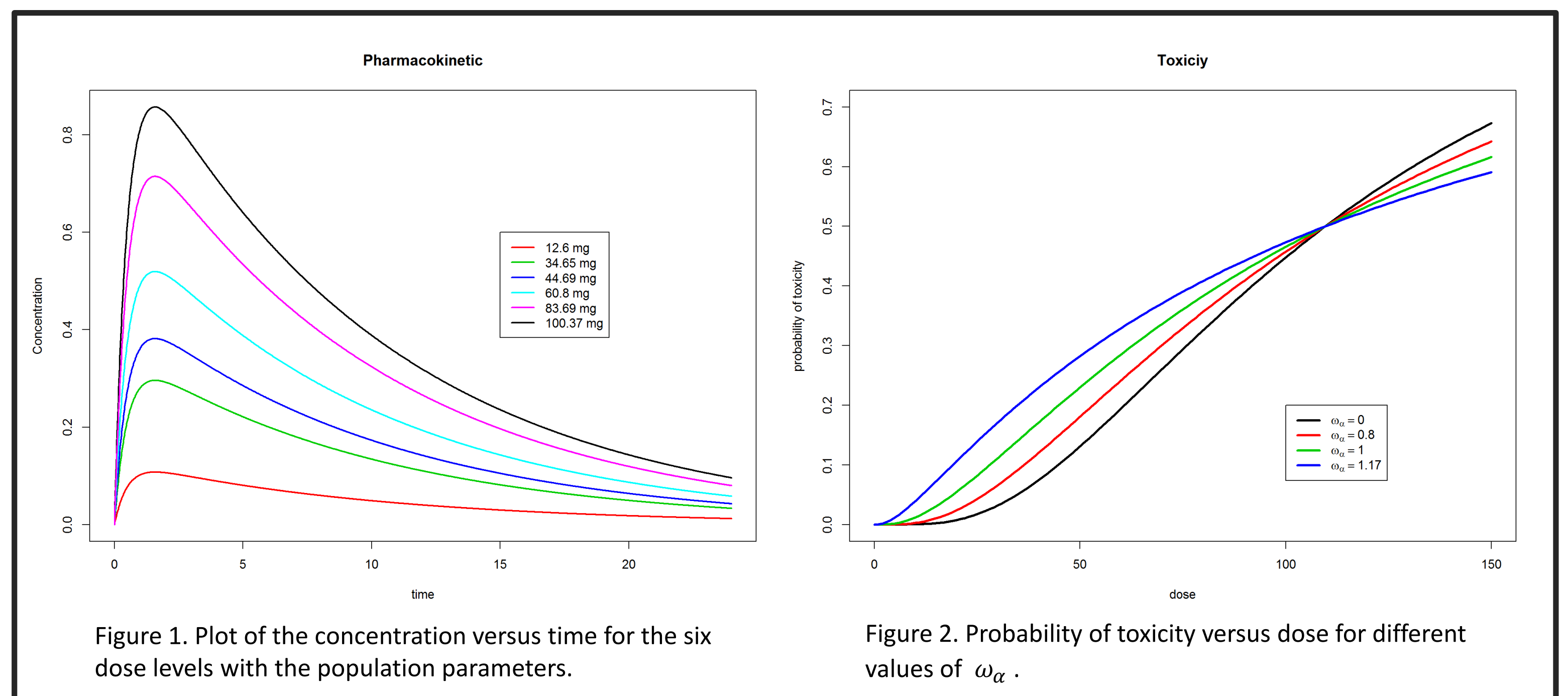
$$P_T(D) = \int P_T(z) g(z) dz$$
 $\downarrow$
 posterior distribution given by PKLIM
- * PKPOP

$$P_T(D) = \frac{1}{1 + \exp(\beta_3 - \beta_4 \Delta Z)}$$
 value predicted by PKLIM

STEPS :

- Bayesian parameter estimation with available data
- dose suggested for the next patient:

$$D_{k+1} = \arg \min_{D_k} |P_T(D_k) - \theta|$$
 target probability



Scenario 1

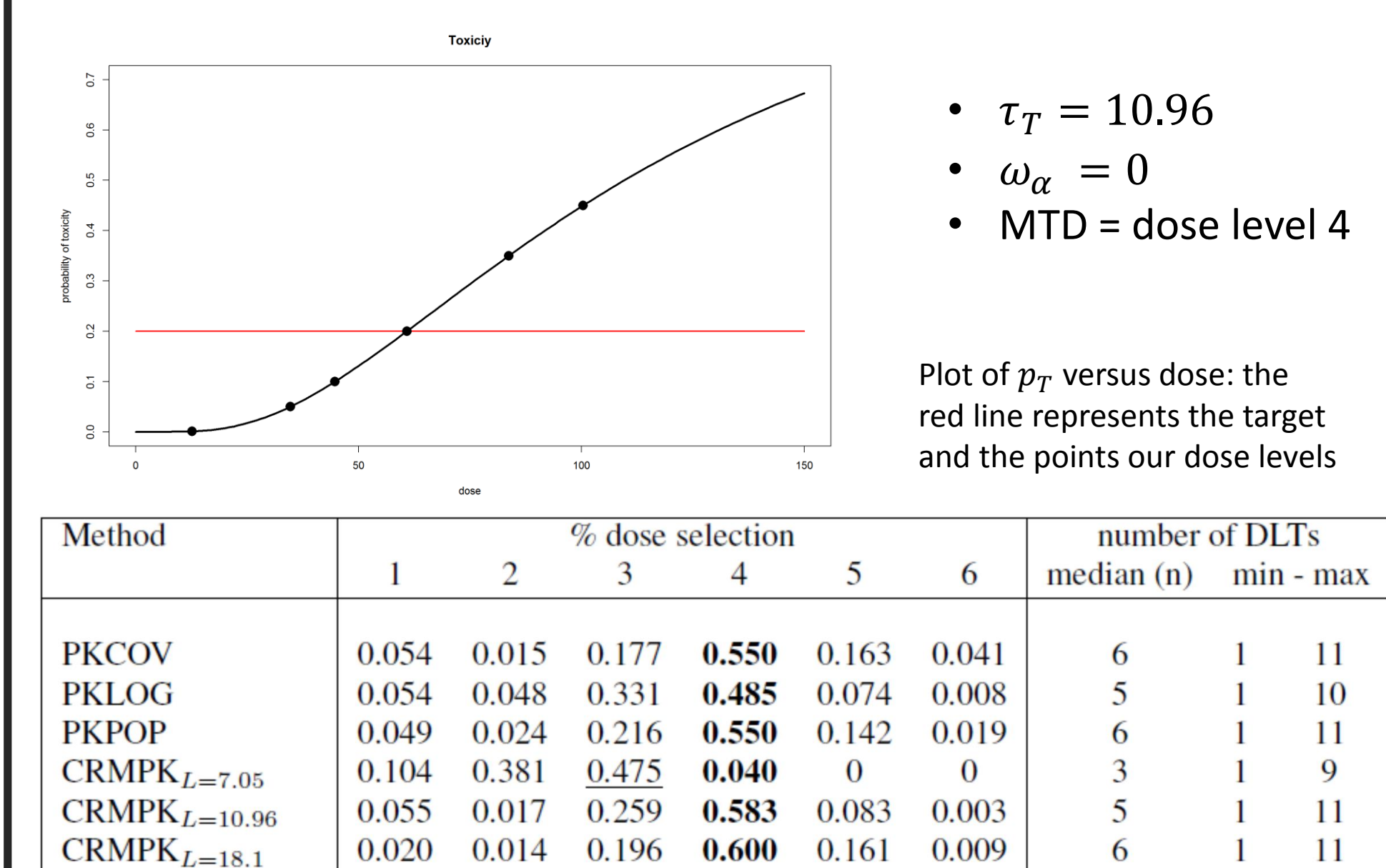
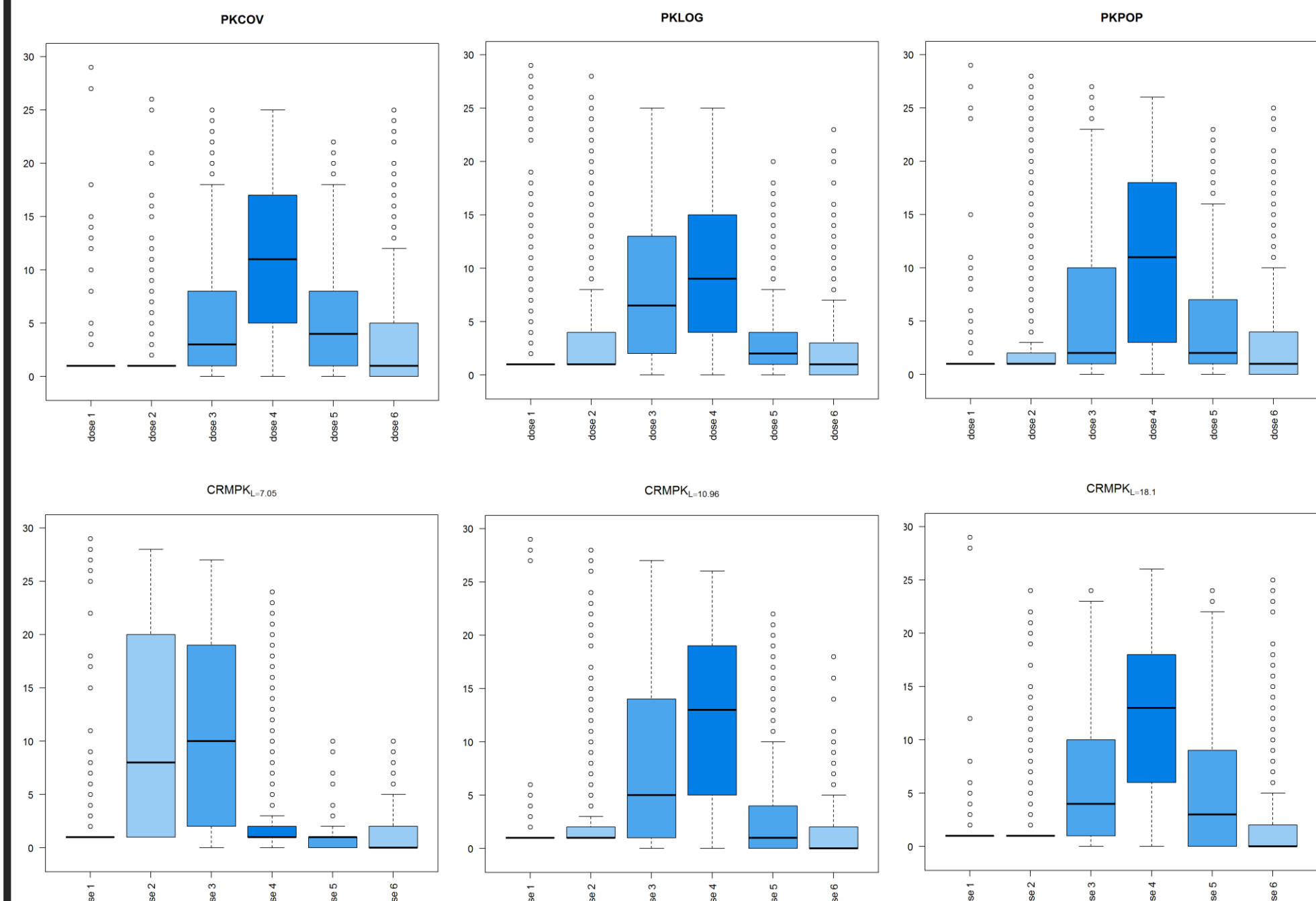


Figure 3: dose allocation. The boxplot represents the median percentage of the 30 subjects allocated to each dose, and the whiskers show the variability across the 1000 simulated trials.



Nearly all methods targeted the correct MTD with a percentage between 50% and 60%. PKLOG was slightly less effective in selecting the MTD, but explored much more doses below the MTD, and was thus more safe with less DLT. CRMPK was very sensitive to assumptions, as dose selection is strongly biased with a low threshold ($L=7.05$).

Scenario 2

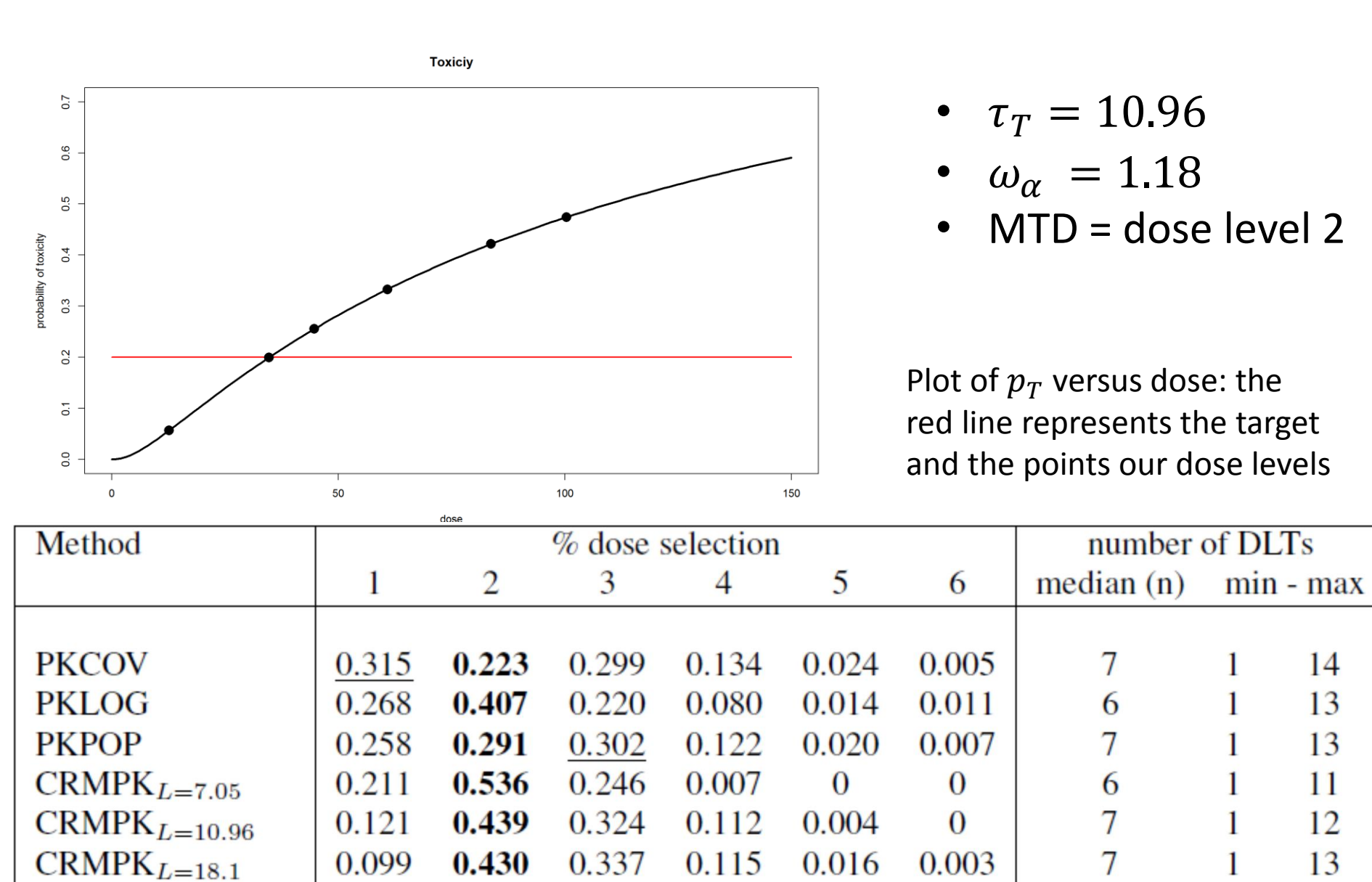
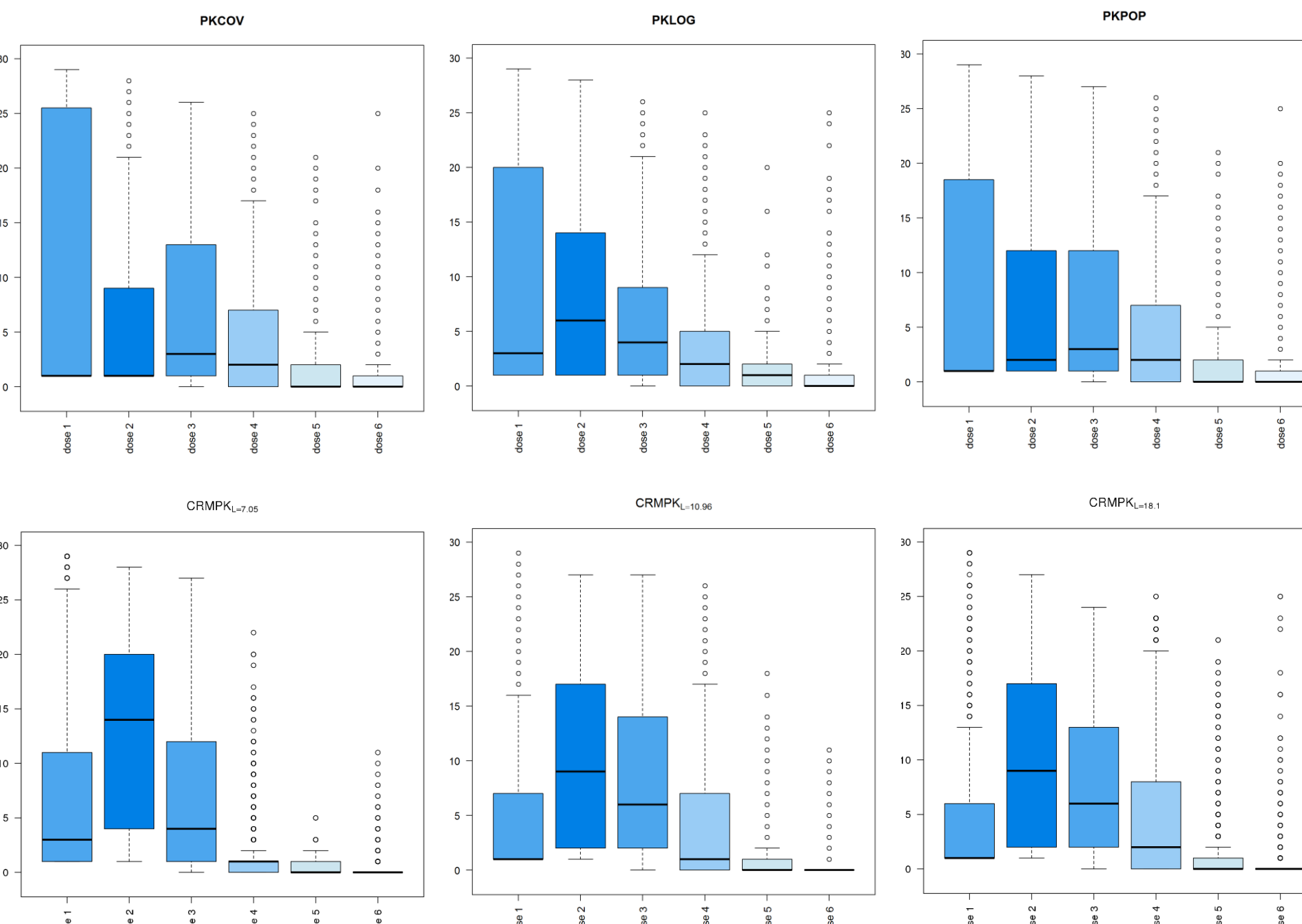


Figure 4: dose allocation. The boxplot represents the median percentage of the 30 subjects allocated to each dose, and the whiskers show the variability across the 1000 simulated trials.



All methods explored not only the MTD and the doses nearer to it but also the other doses. Adjacent dose levels to the MTD were suggested more often with PKCOV. PKLOG was not able to distinguish between dose level 2 and dose level 3.

Results

Methods incorporating PK measurements had good performance when informative prior knowledge was available in terms of Bayesian prior distribution on parameters. Some methods were however very sensitive to correct assumptions on the PK-toxicity relationship. The pattern of dose allocations was quite varied across the different methods.

Discussion

In this work, we considered dose-finding methods where PK data is included as a covariate or as a dependent variable in the toxicity model. We applied them to dose-finding with a binary outcome for toxicity, in a realistic setting with an underlying PK model.

PKCOV can be seen as a "continuous" CRM with a PK covariate added. In scenario 2, the wrong MTD was chosen in 77% of cases. On the other hand, it explores more adjacent doses to MTD, leading to richer PK data for the estimation of PK parameters at the end of the trial.

In CRMPK, PKLIM takes the role of a second constraint on AUC and the choice of L is crucial. When L is equal to the real toxicity threshold τ_T , CRMPK maintained the performance of CRM while reducing the number of overdosing. Increasing L relaxes the constraint on PK and CRMPK then behaves more like the CRM. However, when L is too low, CRMPK was not able to reach the real MTD, due to the PK constraint.

PKLOG, combining the results of two models, can lead to error spreads when computing p_T . Its toxicity-AUC underline model does not fit the real relationship between toxicity and AUC in scenario 1. However, it has good performance in scenario 2 while having a good exploration of the different doses. We add a more simple step to compute p_T in PKPOP: it reduces errors spread in case of $\omega_\alpha = 0$, but not in scenario 2.

- Future steps: assess the impact on the estimation of the dose-concentration-toxicity curve for the different approaches
- add the efficacy outcome
- explore the introduction of fully model-based PK/PD in dose allocation rules

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