

Novel integrated population PD modeling framework to inform decision making during Oncology phase I dose-escalation

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Background

- Phase I trials in oncology often enroll small cohorts of 3-6 patients at a time to increasing doses of an experimental drug step-wise while controlling safety.
- Once the primary safety follow-up period (usually 1 cycle of treatment) for a cohort is complete, a dose escalation meeting (DEM) takes place to decide on the dose for the next cohort.
- By design, data accrues over time and at early stages is very sparse and can be incomplete for some patients, i.e., the most recent cohort may have safety data, but no drug concentration data recorded.
- Here we introduce a novel integrated population pharmacodynamic (popPD) approach to support decision making throughout the trial.

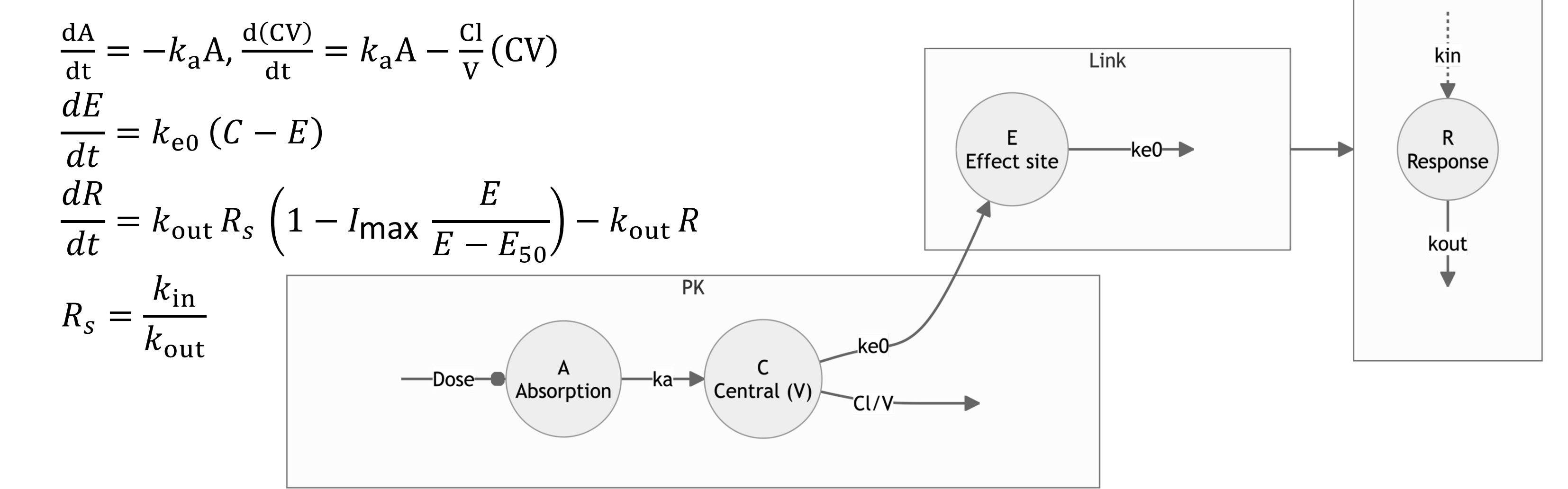
Conclusions

- The use of Bayesian modeling for pharmacodynamic responses of key interest to a program allows to integrate prior knowledge (disease models, prior distributions on parameters) and trial data. This facilitates decision making at early stages of a trial.
- At the core of the proposed integrated popPD approach we introduce a simplified pharmacokinetic (PK) model which is used to construct a longitudinal exposure measure in the context of the pharmacodynamic model.
- We compare using either the same PK model for all patients (K-PD), patient specific non-compartmental analysis estimates of PK per patient (NK-PD) or a full joint PK-PD approach (with a simplified PK model). We find that the K-PD approach works best at very early stages, but is outperformed by the NK-PD and PK-PD approach at the middle of the example trial. The NK-PD approach being more robust and significantly easier to implement.

Objectives: (1) Inform DEMs in due time by prediction of outcomes for future cohorts at planned doses/regimens; (2) avoid overconfident predictions by accounting for uncertainty in key inputs; (3) integrate incomplete data (e.g., patients from the latest cohort which often only have safety data but no concentration data reported)

Methods

- Data from trial NCT02375958 studying PCA062 given as infusion (in mg/kg) every 2 weeks (q2w) to patients with pCAD+ tumors [2, 3].
- DEM data was emulated with the cut-off date for each DEM, with the PK data of the last two patients enrolled in each cohort set to missing. Three different popPD models implemented using the brms R package [4] are fit with Stan [5] at each cut-off date dataset and evaluated on the data before and after the cut-off date, respectively.
- For the exposure models NK-PD and PK-PD, the patient specific PK data is summarized in the form of a model fit from which an approximate posterior is used in the context of the platelet count PD model.
- A simplified structural model of platelet counts and priors are aligned with models published prior to the trial [6].



A: drug amount in absorption compartment; where dosing happens, Ka: absorption rate, C: drug concentration in central compartment; what is measured, V: volume of central compartment, Cl: clearance from central compartment, defines elimination rate $k = Cl/V$, E: drug concentration in the effect compartment, k_{e0} : transfer rate

Integrated popPD modeling

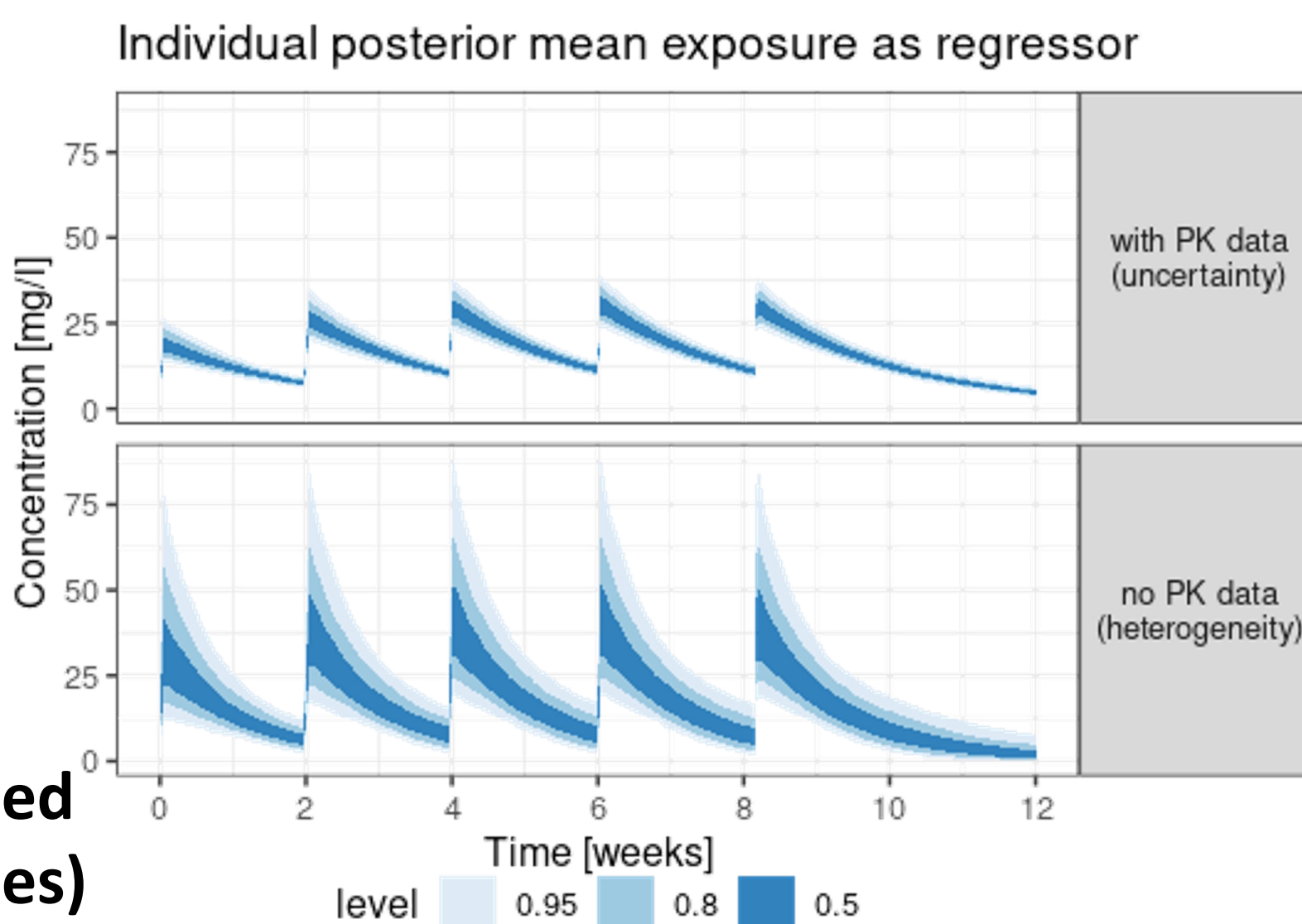
- Focus on modelling PD** - including data of patients with missing PK data
- Longitudinal population models **leveraging prior knowledge** (e.g. model structure and/or parameters from literature or pre-clinical)
- Time-varying exposure** using one model of
 - K-PD: Actual dosing history, average PK parameters for all patients
 - NK-PD: adds non-compartmental analysis (NCA) estimates of CL & V per patient
 - PK-PD: adds Cmin measurements
- Assess benefit & risk for future patients** using simulations

When to use: Early stages of dose escalation

- Quick turnaround** tailored to the program needs
- To be used when **popPKPD is not yet established**
- Model assumptions for time-varying exposure must be **reasonably met given analysis goals** (in agreement with known drug pharmacology)

Time-varying exposure

- Available PK data leads to precise exposure
- Lack of PK data leads to substantial uncertainty due to between-patient heterogeneity
 - Needed for modelling PD data of patients in **absence of PK data**
 - Used for simulation of future patients as **needed for dosing recommendations**
- => **Integrated modeling approach with PD needed to propagate uncertainty (avoids shrinkage issues)**



Results

- All models reasonably capture the dynamics of the endpoint.
- The NPDE residuals over time suggest for all models a reasonable fit to the data.
- The K-PD model has less flexibility due to fewer patient specific parameters. This can be seen from patient B in figure 1 for whom the model performs worse than the NK-PD and PK-PD models.
- The model performance is scored here using the continuous ranked probability score (CRPS), see [7]. The CRPS has a higher score for lower bias and for lower variance predictions.
- The training row shows the scores for each model per DEM cut-off. The future row shows the scores on the complementary data set of the respective future.
- The NK-PD model appears best overall.

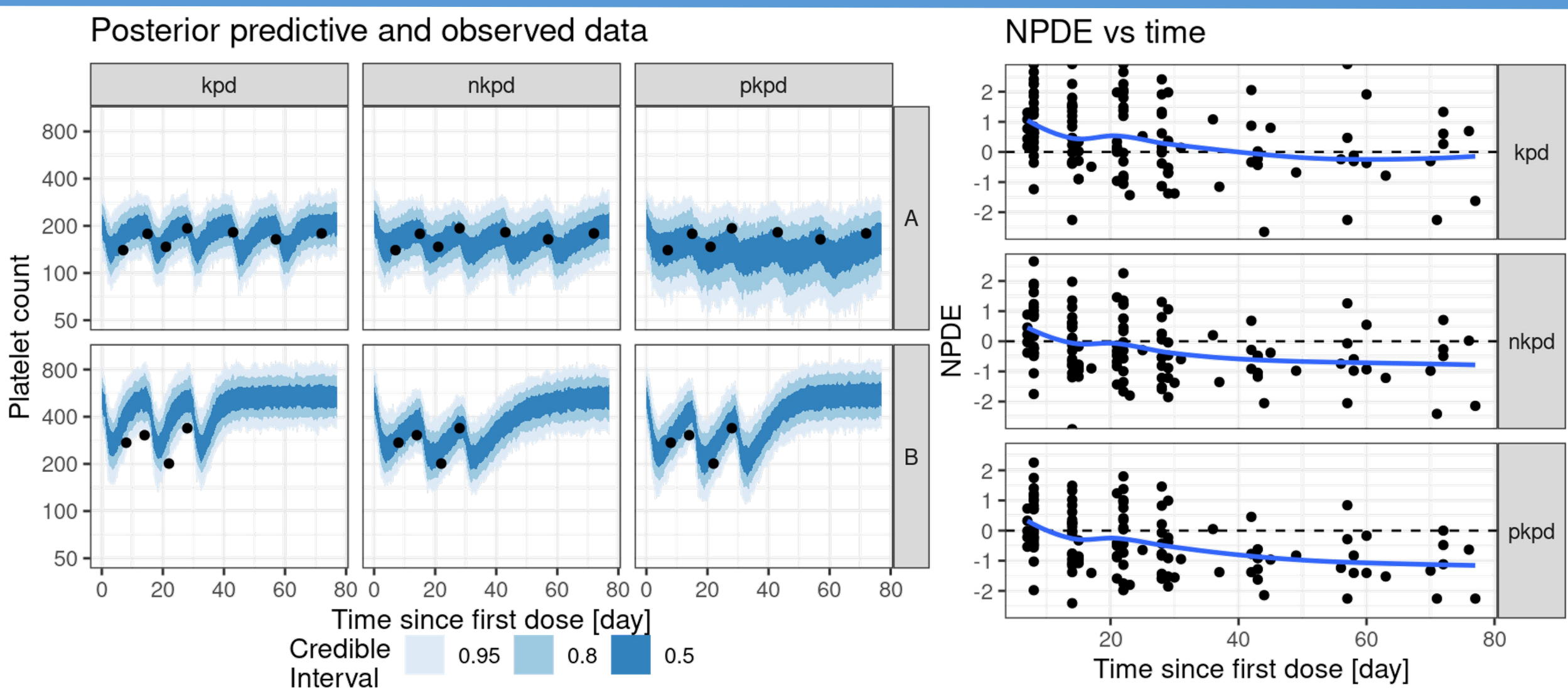
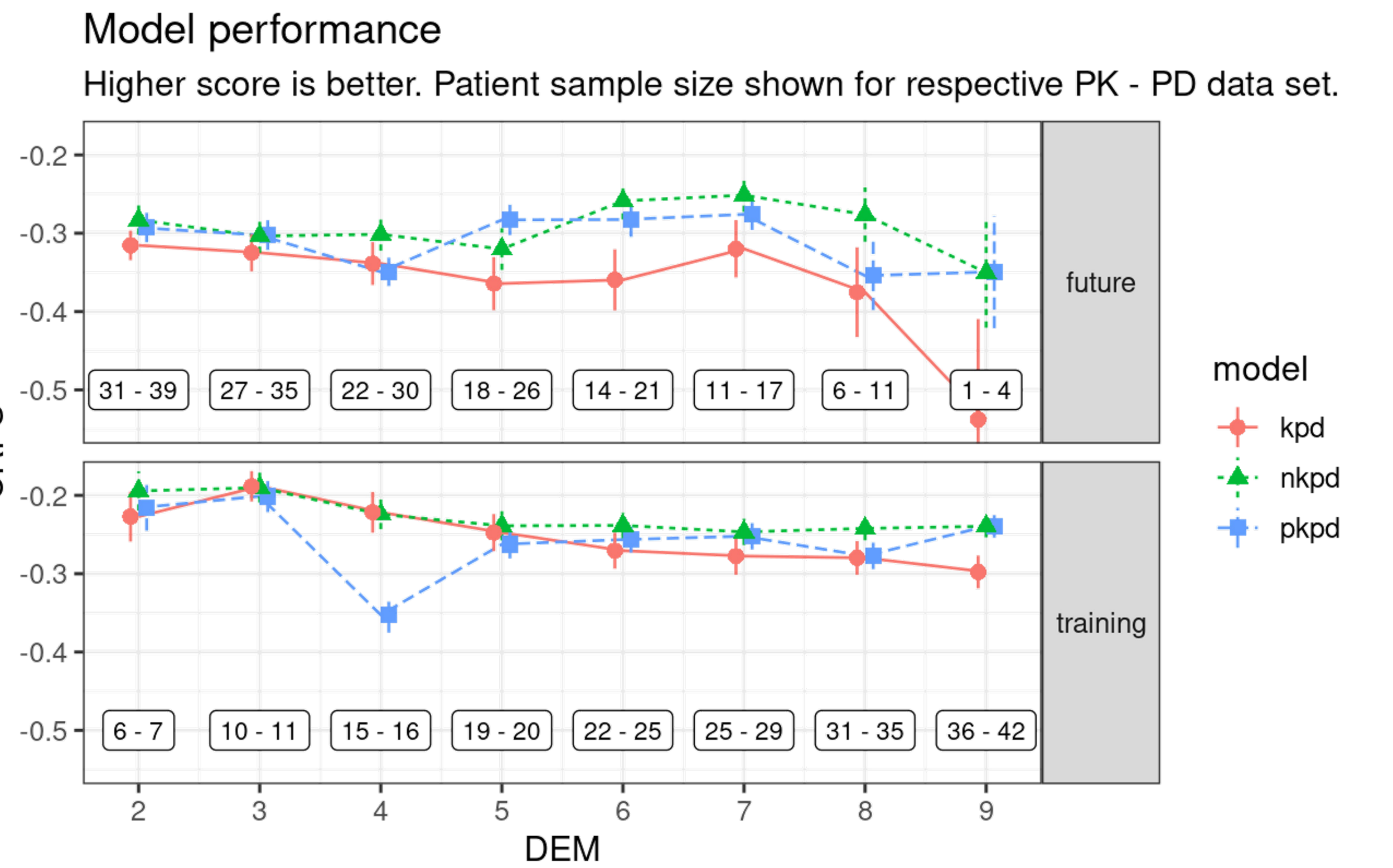


Figure 1 (above): Model checks at DEM 7 data cut-off for all three models.
Figure 2 (below): Benchmark of candidate models throughout trial.



Parameter	Units	Definition	Distribution	Prior 95% CrI	Note
Cl	L/hr	Clearance of central compartment	Log-normal	0.0006, 0.16	
ω_{CL}	None	Patient random effect standard deviation log(Cl)	Log-normal	0.04, 1.05	0 for K-PD
V	L	Volume of central compartment	Log-normal	0.64, 156.71	5L for K-PD
ω_V	None	Patient random effect standard deviation log(V)	Log-normal	0.12, 0.32	0 for K-PD
k_a	1/hr	Absorption rate	Constant	$\log(2)/(1/6)$	
F_r	None	overall scaling factor (applied to dose)	Log-normal	0.62, 1.62	1 for K-PD & NK-PD
ω_{F_r}	None	Patient random effect standard deviation log(F_r)	Log-normal	0.04, 1.05	0 for K-PD & NK-PD
κ	None	Transfer rate to effect compartment relative to Cl/V	Log-normal	0.14, 7.10	
ω_κ	None	Patient random effect standard deviation log(κ)	Half-Normal	0.02, 1.12	
ω_{R_s}	None	Measurement error of observed log(R_s)	Half-normal	0.003, 0.22	
k_{out}^{-1}	hr	first order elimination time-scale of response	Log-normal	15.1, 79.3	
I_{max}	None	Maximal inhibition proportion	Uniform	0.025, 0.975	
$\omega_{I_{max}}$	None	Patient random effect standard deviation logit(I_{max})	Half-Normal	0.02, 1.12	
E_{50}	mg/L	Half effect concentration in effect compartment	Log-normal	0.13, 31.3	

Table 1. Prior distribution for model parameters

References

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