A novel Bayesian K-PD model for synergy: Challenges and opportunities for sequential knowledge integration

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1. Objective

The purpose of this work is to highlight and overcome some of the challenges arising from the Bayesian sequential integration of a number of small trials in a PK-PD modeling framework.

2. Case Study

Context: Pre-clinical safety evaluation of a novel compound meant to be co-administered with a marketed compound.
Safety biomarker: Body temperature (assessed up to 4 hours after oral administration).
Data sources: 11 trials conducted sequentially; in each of them, *one specific dose combination is assessed* (**Table 1**).
Design: 4 treatment groups for each trial: *Vehicle*, *Marketed*, *Novel*, *Combination*.

Trial	1	2	3	4	5	6	7	8	9	10	11
Marketed compound (mg/kg)	10	2.5	10	0.63	10	0.16	2.5	0.63	0.16	0.04	0.04
Novel compound (mg/kg)	40	40	10	40	2.5	40	10	10	10	10	40

Table 1: Dose levels assessed in 11 synergy trials

3. K-PD Model for Synergy

We use an **indirect response model** [1]:

$$\frac{d\bar{R}_{it}}{dt} = k_{in}\left(1 - \frac{I_{max}C_{it}}{IC_{50} + C_{it}}\right) - k_{out}\bar{R}_{it}.$$

where a **virtual one-compartment first order absorption PK profile** of the marketed compound [2] inhibits the production of body heat (R_{it}).
The novel compound **increases the potency** of the marketed compound:

$$IC_{50} = \exp\left(\alpha D_{N,i} + \beta D_{M,i} D_{N,i}\right),$$

where $D_{N,i}$ and $D_{M,i}$ are the doses of novel and marketed compounds, α represents the main effect attributed to the novel compound and β is the interaction coefficient.

6. Results: Sequential Pooling

The posterior predictions using Methods 1 to 3 are biased downward. However, a noticeable improvement can be observed for Method 4, where five optimally designed trials are pooled (**Figure 4**).

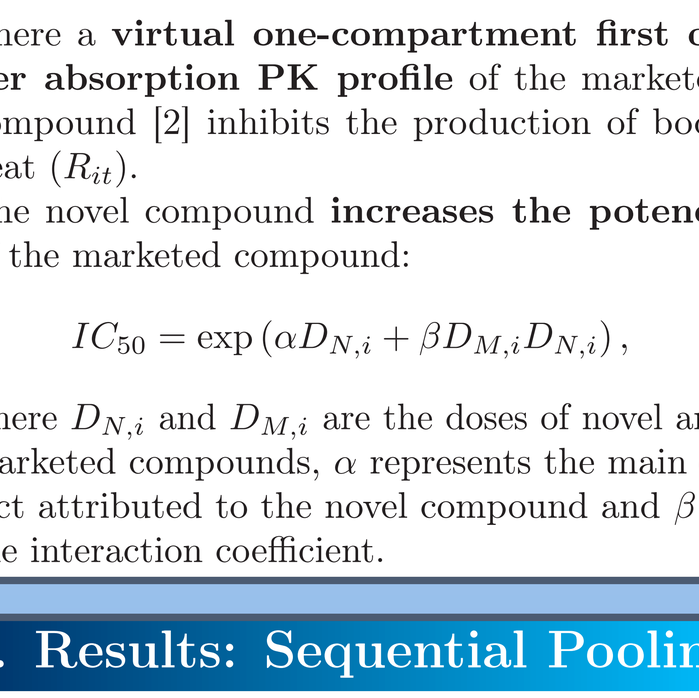

Figure 4: Posterior predictions, trial 1: Sequential pooling comparison (methods 1 to 4 and simple pooling)

4. Bayesian Integration and Modeling Aspects

A **Bayesian estimation** of the model is considered, taking into account prior knowledge from a historical dose-response trial of the marketed compound, using Stan. The following modeling aspects are assessed:

- **Impact of prior specification**.
- **Choice of random effect**.
- **Impact of Bayesian sequential integration**:
  - **Reference model**: Trials 1-11 are pooled together;
  - **Sequential pooling**: Different strategies are considered (**Table 2**, **Figure 1**).

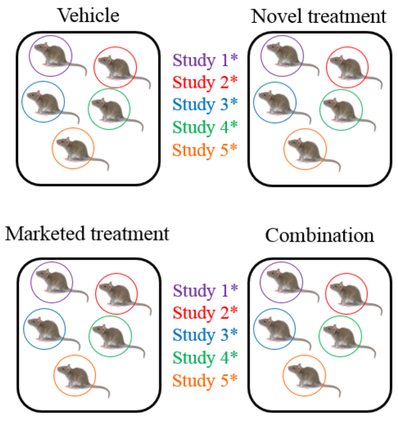

Figure 1: Sequential pooling, method 4: 5 optimal trials

Method	Trial integration sequence
1: Original trial order	$1 \to 2 \to 3 \to 4 \to 5 \to 6 \to 7 \to 8 \to 9 \to 10 \to 11$
2: Random order permutation	$5 \to 3 \to 8 \to 11 \to 6 \to 1 \to 2 \to 9 \to 7 \to 4 \to 10$
3: Three trials at a time	$1,2,3 \to 4,5,6 \to 7,8,9 \to 10,11$
4: Five "optimal" trials	$1^* \to 2^* \to 3^* \to 4^* \to 5^*$

Table 2: Different Bayesian integration strategies evaluated

5. Results: Impact of prior choice and random effect position

- **Impact of prior elicitation**: Different priors for I_{max} are assessed (**Figure 2**). When a highly informative prior is chosen (Prior 1, $SD = 0.02$), the parameters are nearly uncorrelated; when the prior standard deviation is doubled (Prior 2, $SD = 0.04$) the correlations become stronger, and they enhance even further when a uniform prior (Prior 3, $SD = 0.29$) is elicited.

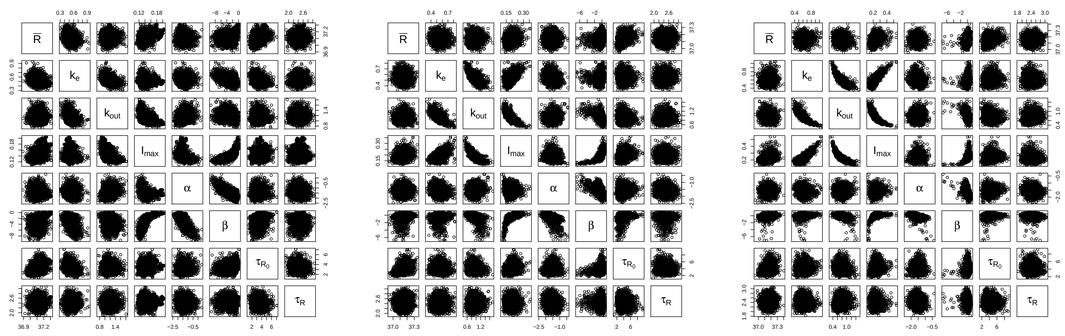

Figure 2: Parameter correlation matrix. Impact of eliciting Prior 1 (left); Prior 2 (center); Prior 3 (right)

- **Position of random effect**: When a random k_{out} model is performed (**Figure 3**), a downward bias is observed in the prediction of time profiles belonging to the combination group. In such group, the posterior means of subject-specific random effects are completely separated from the other treatment groups, due to an overcompensation between k_{out} and β.

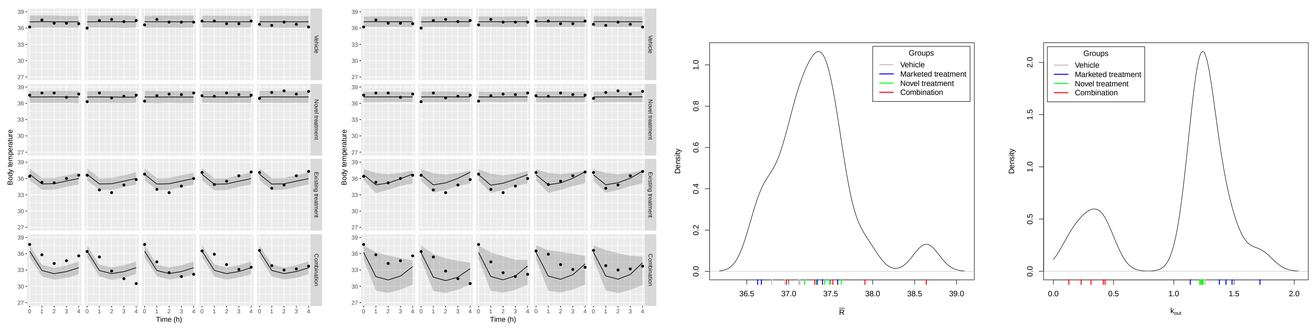

Figure 3: Posterior predictions and predictive intervals (left) and distribution of the posterior mean of subject-specific random effects (right) using random baseline and random k_{out} models respectively, trial 1

7. Discussion

- The novel K-PD model for synergy worked well with **informative priors** and **random baseline**, pooling the trials **together**.
- Careful attention should be devoted when weakly informative priors are elicited and a random effect is allocated to a parameter which is part of a highly correlated parameter space.
- A **well designed** integration of trials (optimal doses, sampling times, replicates) is crucial for an accurate estimation process, as it prevents the risk of parameter identifiability issues.

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[2] Jacqmin P, Snoeck E, van Schaick EA, et al. Modelling Response Time Profiles in the Absence of Drug Concentrations: Definition and Performance Evaluation of the KPD Model. J Pharmacokinet Pharmacodyn 2007;34(1):57-85

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