A Bayesian PK/PD model for synergy: a case study

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1. INTRODUCTION & OBJECTIVE

Studies on pharmacodynamic (PD) drug-drug interactions are usually performed in an in-vitro setting, but are rarely undertaken in an **in-vivo** framework.

In this work, a novel Bayesian population PK/PD model for the estimation of PD synergy is described based on a pool of in-vivo studies.

- An **indirect response model** with a **latent pharmacokinetic** (PK) profile is used, with a **PD interaction** on the potency, extending the in-vitro methodology for synergy to an in-vivo framework.
- **Random effects** are incorporated to allow for differences in animals.
- **Bayesian estimation** is investigated, allowing for the incorporation of knowledge from a historical dose-response study on the existing treatment.

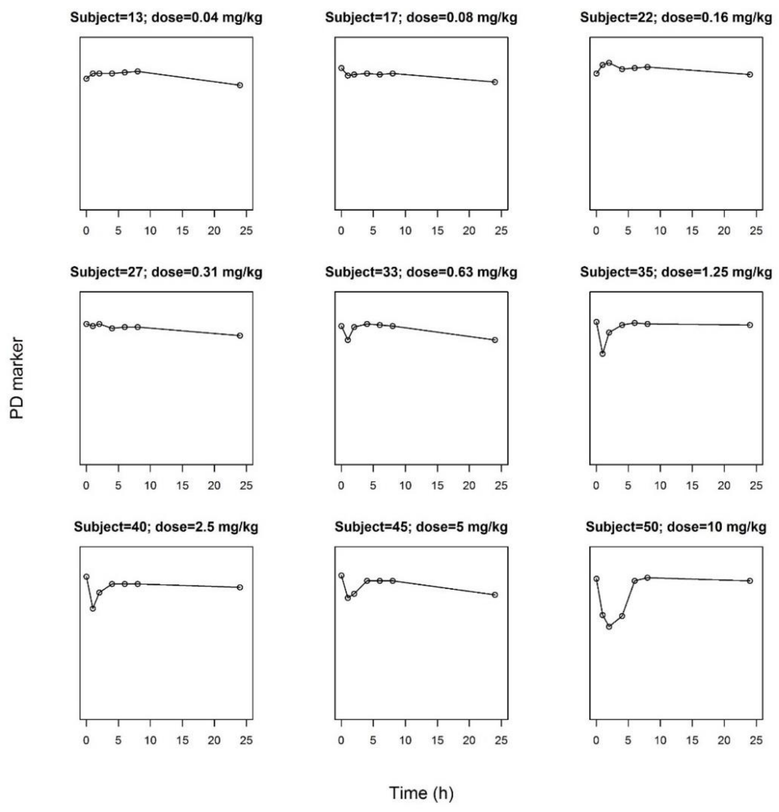
2. CASE STUDY

This study was part of the pre-clinical safety evaluations of a **new compound** with the intent to develop it for co-administration with an **existing treatment**.

2.1. Historical data

- Only existing treatment was administered.
- A dose range was investigated in 55 rats (each of them receiving a single dose).
- Continuous safety biomarker was assessed up to 24 hours after oral administration (Figure 1).

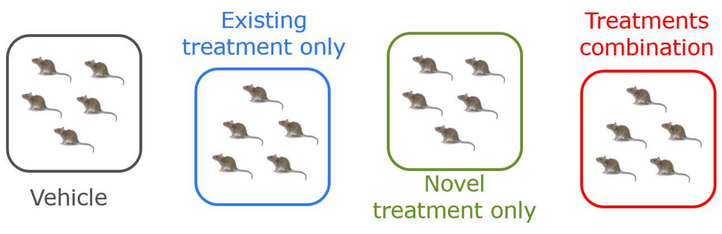
Figure 1. Observed time profiles of the biomarker for 10 selected individuals form the historical study



2.2. Synergy data

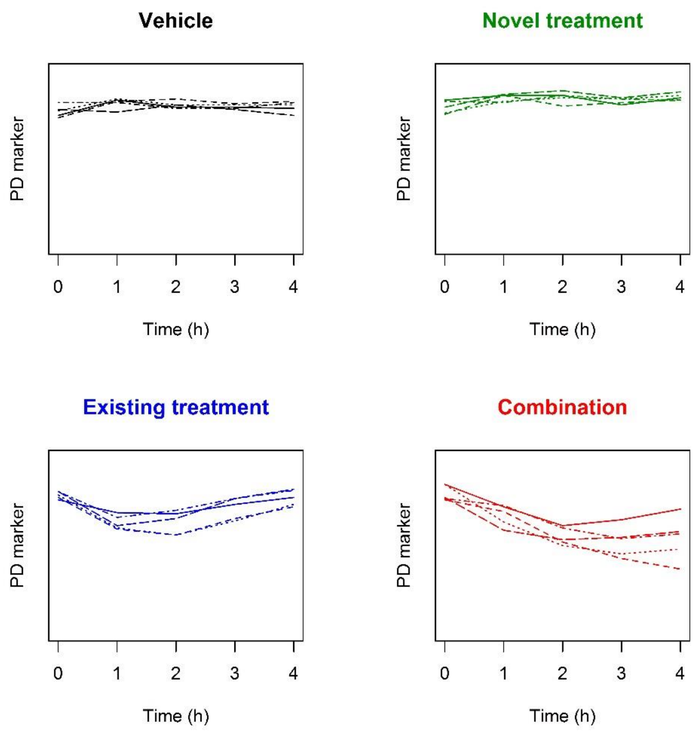
- Both existing and novel treatments were assessed: the marketed treatment was administered with the highest dose used in the historical study (10 mpk); a dose of 40 mpk was set for the novel treatment.
- 20 rats in total, 5 per treatment group (Figure 2).
- Safety biomarker was assessed up to 4 hours after oral administration.
- Absence of PK interaction was already confirmed in a previous study.

Figure 2. Synergy study design



As depicted in Figure 3, the **combination** group showed unexpectedly a **more pronounced** change of the biomarker compared to the group with marketed compound only.

Figure 3. Time profiles, synergy study 1



To understand this synergetic behavior, the study was repeated another 10 times, each with a different dose level combination (Table 1).

Table 1. Dose levels used in synergy studies

Study	1	2	3	4	5	6	7	8	9	10	11
Existing treatment dose (mpk)	10	2.5	10	0.63	10	0.16	2.5	0.63	0.16	0.04	0.04
Novel treatment dose (mpk)	40	40	10	40	2.5	40	10	10	10	10	40

3. METHODS

4.1. Latent PK/PD model

A **turnover model**,[1,2] which assumes that a **latent one-compartment PK** profile with oral absorption of the marketed treatment[3] (C_{it}) inhibits the production of the biomarker (R_{it}), copes with the observed profiles described in Figure 1:

$$R_{it} \sim N(\bar{R}_{it}, 1/\tau_R) \qquad \frac{d\bar{R}_{it}}{dt} = k_{in}\left(1 - \frac{I_{max}C_{it}}{IC_{50} + C_{it}}\right) - k_{out}\bar{R}_{it}$$

At time $t = 0$, $R_{i0} = k_{in}/k_{out}$ corresponds to the fact that, for each individual i, the biomarker is in a steady state condition prior to administration of the compound. To allow for heterogeneity amongst animals, the PK/PD model is extended via the inclusion of a **random effect** for R_{i0}.

4.2. Synergy

It is assumed that the presence of the novel compound **increases the potency** (IC_{50}) of the marketed compound for the safety biomarker:

$$IC_{50} = exp(\beta M_i N_i)$$

where M_i and N_i represent respectively the doses of marketed and novel treatments, and β is the interaction coefficient.
The model presented can be considered as an **extension of** the in-vitro **Loewe definition of synergy**[4] to an in-vivo framework, in the situation where one of the two treatments is inactive if administered as a monotherapy. In case of synergy, $IC_{50} < 1$, as a lower exposure of the marketed compound is required to gain a certain effect, in the presence of the novel treatment. Thus, $\beta < 0$.

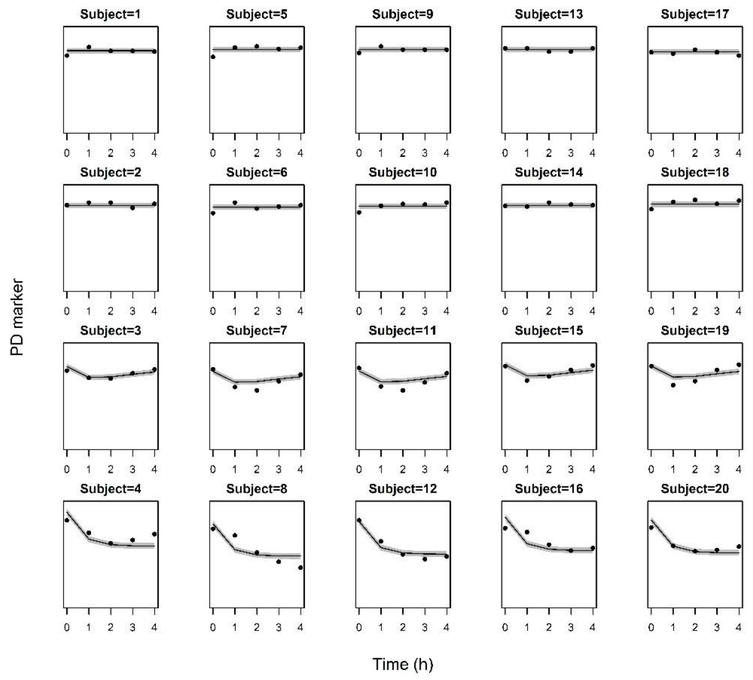
4.3. Bayesian data integration

A Bayesian estimation of the model was considered, taking into account prior knowledge from the historical study. Prior distributions for all parameters were chosen by setting the expected values equal to the point estimates obtained for the historical data, while standard errors were doubled. The Bayesian modeling was conducted using Stan (RStan version 2.12.1).

4. RESULTS

The Bayesian model showed good fit to the data. Individual predictions of the biomarker for data of study 1 are shown in Figure 4.

Figure 4. Individual predictions for study 1



The posterior mean of β resulted negative, and its credible interval did not include 0, confirming the presence of a pharmacodynamic synergy between the study treatments.

Figure 5. Predicted biomarker change from baseline depending on marketed and novel treatment doses

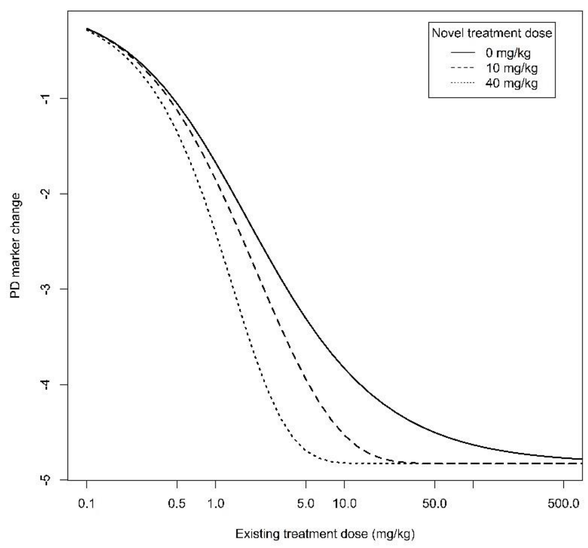


Figure 5 illustrates how the predicted biomarker changes as a function of both the existing and the novel treatment. The synergistic behavior affects the biomarker level only for extremely high doses of the existing treatment, whereas **clinically relevant doses remain unaffected**.

5. DISCUSSION

- The novel PK/PD model for synergy presented has proven to work well in a Bayesian framework, where 11 studies conducted at different time periods were pooled.
- Further work is being devoted at keeping the sequential nature of the studies, i.e., fitting a Bayesian model so that the posteriors resulting from a study are used to determine the priors of the study which follows.
- Allocation of random effect and prior elicitation represented the major challenges in fitting the model. These aspects will be more deeply explored in a further work.

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