Bayesian sequential integration within a preclinical PK/PD modeling framework using rstan package

Lessons learned

Drouville, *Dragonfish*
Drouville is a patient, graphic designer and artist from Argentina who has survived Multiple Myeloma and a relapse.

Fabiola La Gamba,
Tom Jacobs, Jan Serroyen, Helena Geys, Christel Faes

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Case Study and Aim

A novel **PK/PD model** has been developed to assess the **synergy** resulting from the co-administration of 2 compounds.

$$\frac{d\bar{R}_{it}}{dt} = k_{in}\left(1 - \frac{I_{max}C_{it}}{IC_{50} + C_{it}}\right) - k_{out}\bar{R}_{it}, \qquad IC_{50,comb} = IC_{50}\ e^{\alpha D_{n,i} + \beta D_{e,i} D_{n,i}}$$

11 trials are integrated **sequentially**: the posteriors from one trial are used to determine the priors of the next trial.

Trial 1 → **Trial 2** → … → **Trial 11**

Challenge: Performing a complex nonlinear hierarchical model on small data during the first integration steps may cause **practical identifiability issues**.

Aim: To study the **factors** influencing the results using **`rstan`**

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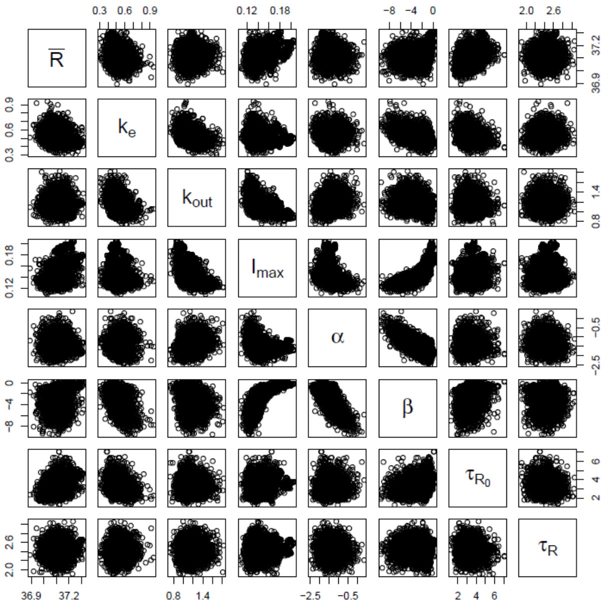
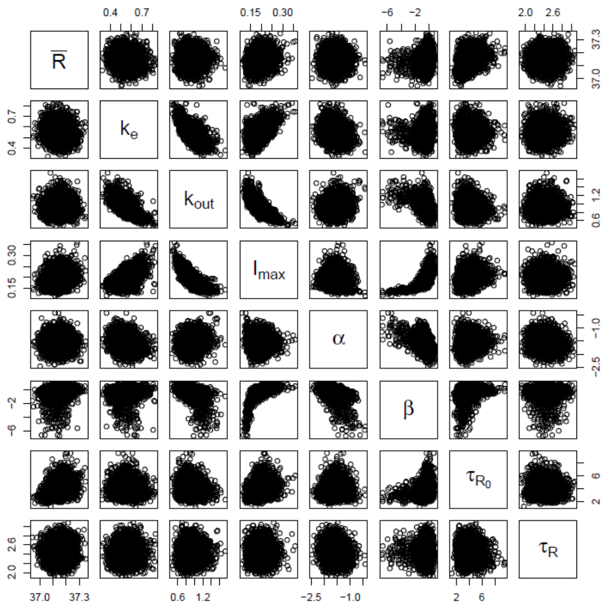
Prior Specification

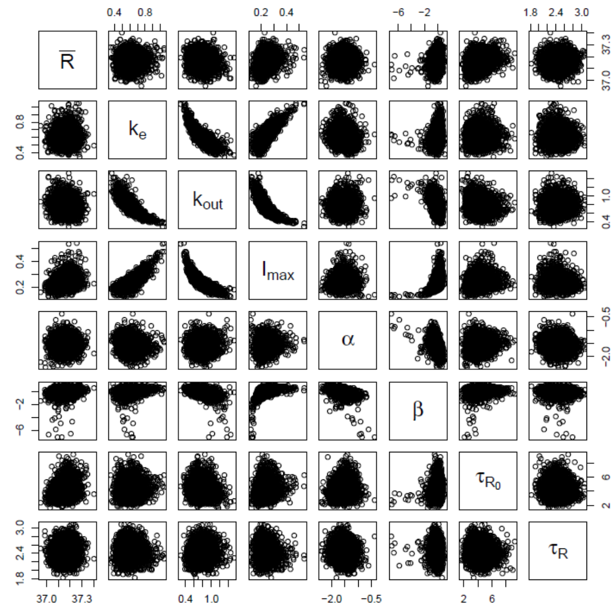
Prior for I_{max}, SD=0.02



Prior for I_{max}, SD=0.04



Prior for I_{max}, SD=0.29



Parameter correlation increases with decreasing prior precision.
The correlated parameters compensate each other → biased estimates

Take home message n.1 It is better to use informative priors, whenever possible

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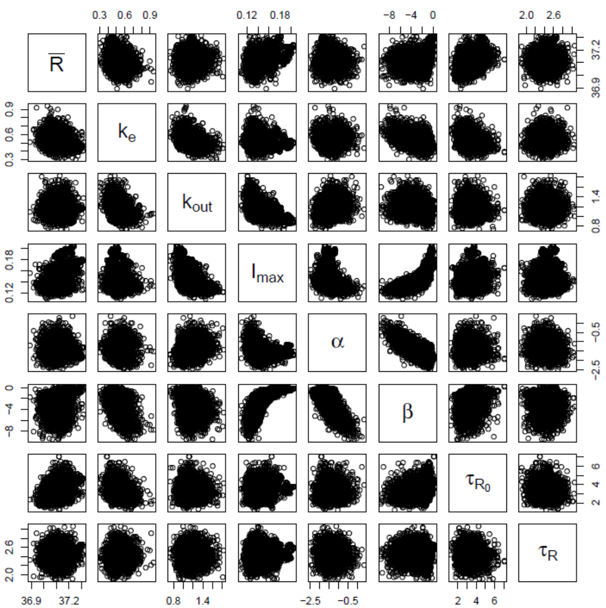

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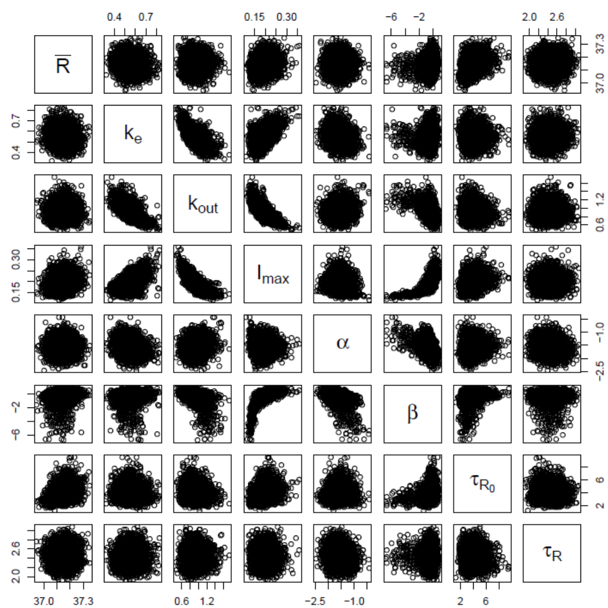

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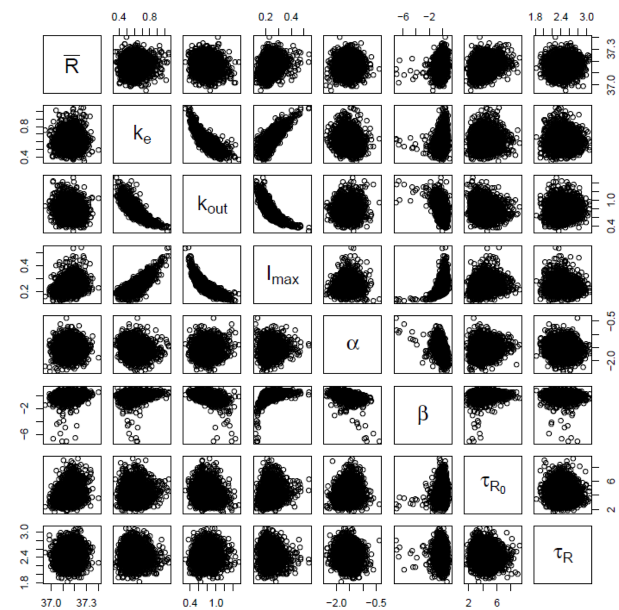

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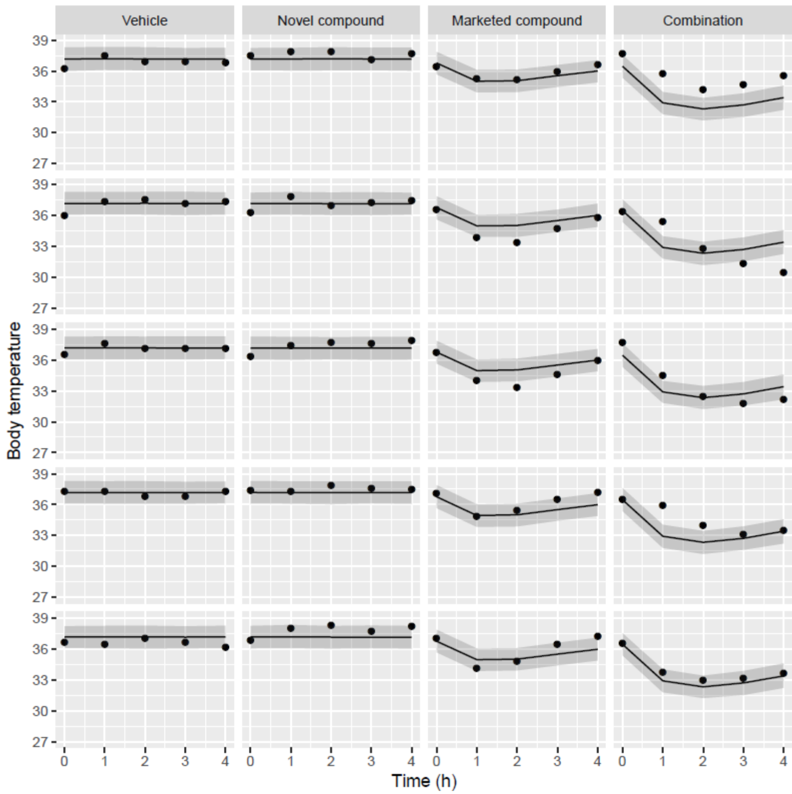
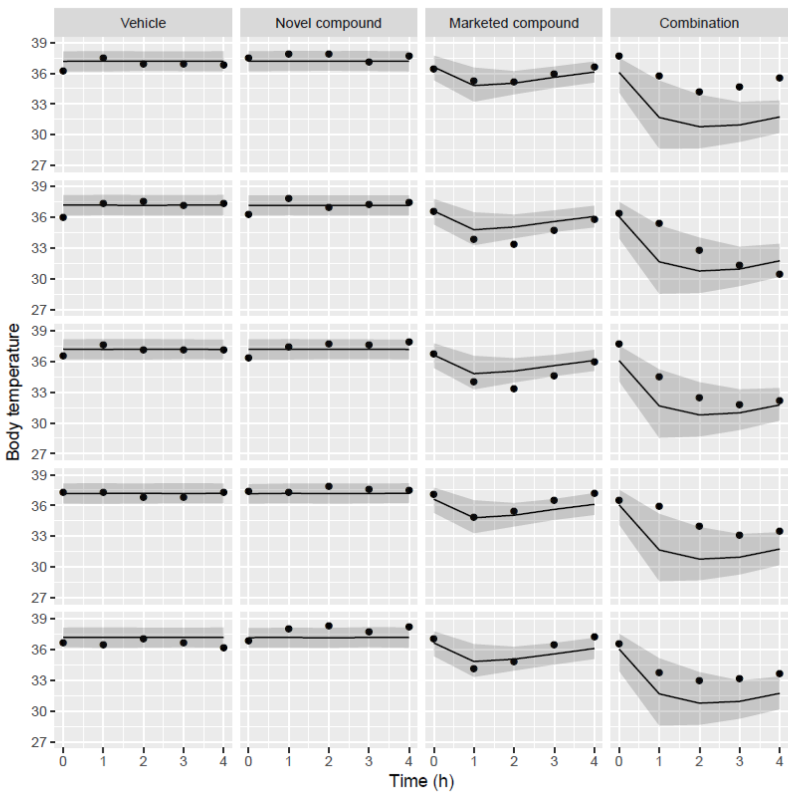
Choice of Random Effect

Posterior predictions and predictive intervals, trial 1

Random baseline model



Random k_{out} model



Take home message n.2 Better to allocate the random effect on a parameter that is not highly correlated with others, to avoid overcompensations

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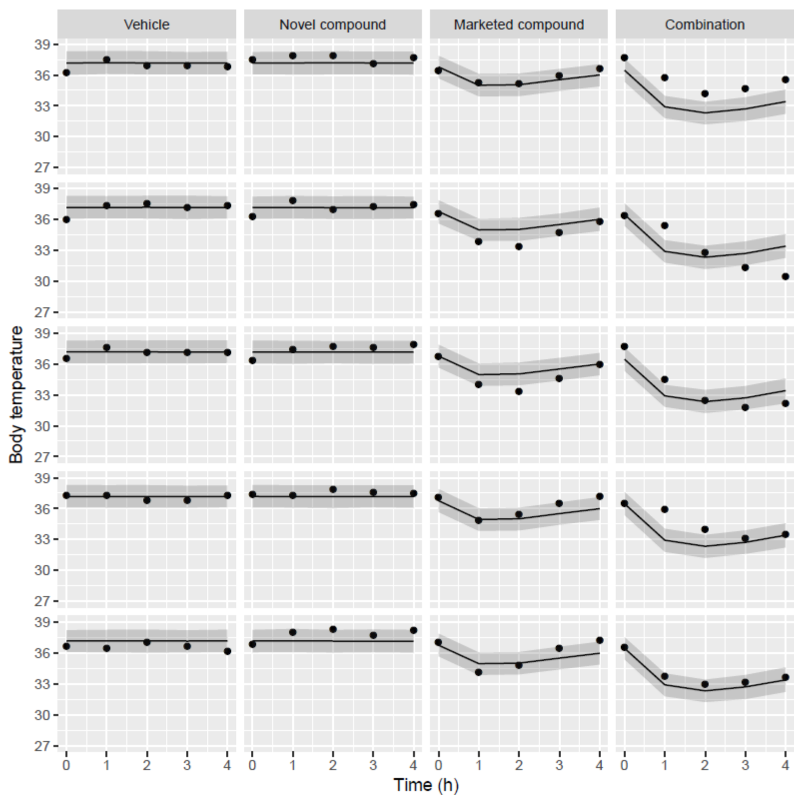

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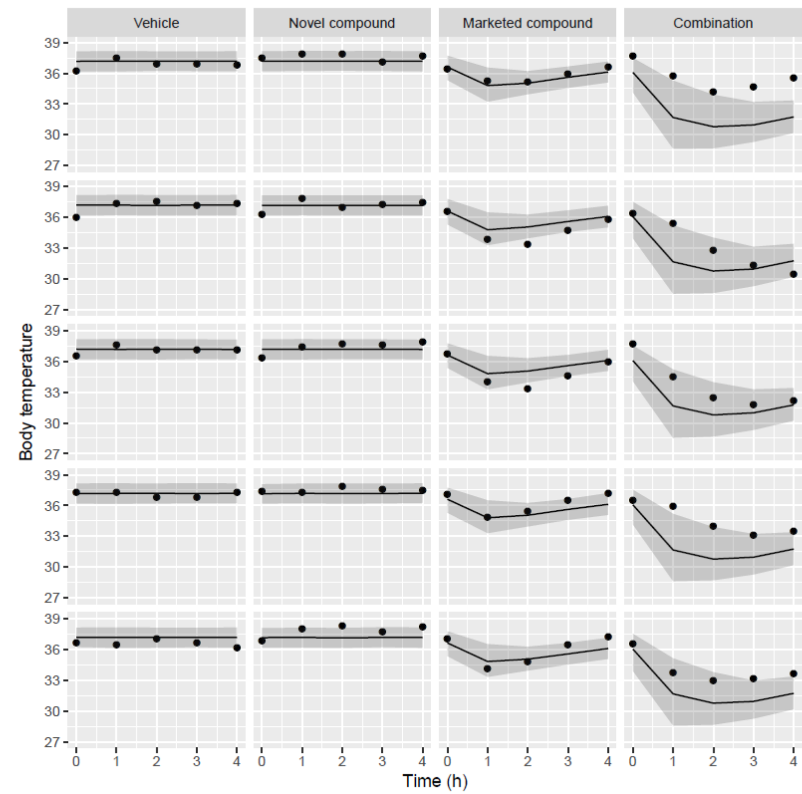

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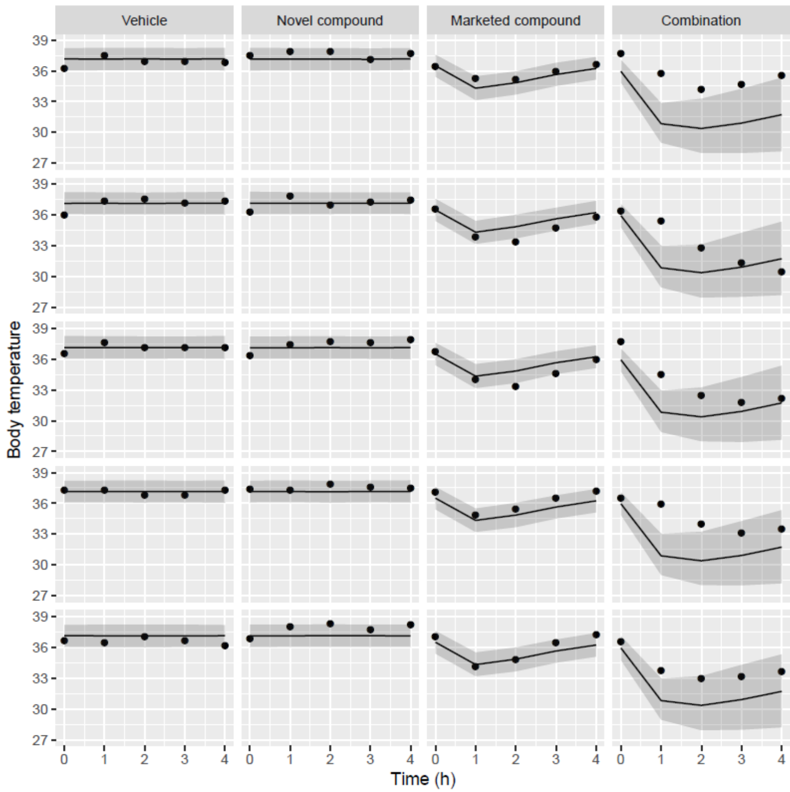
Design of sequential integration

Posterior predictions and predictive intervals, trial 1

One single dose assessed in each trial



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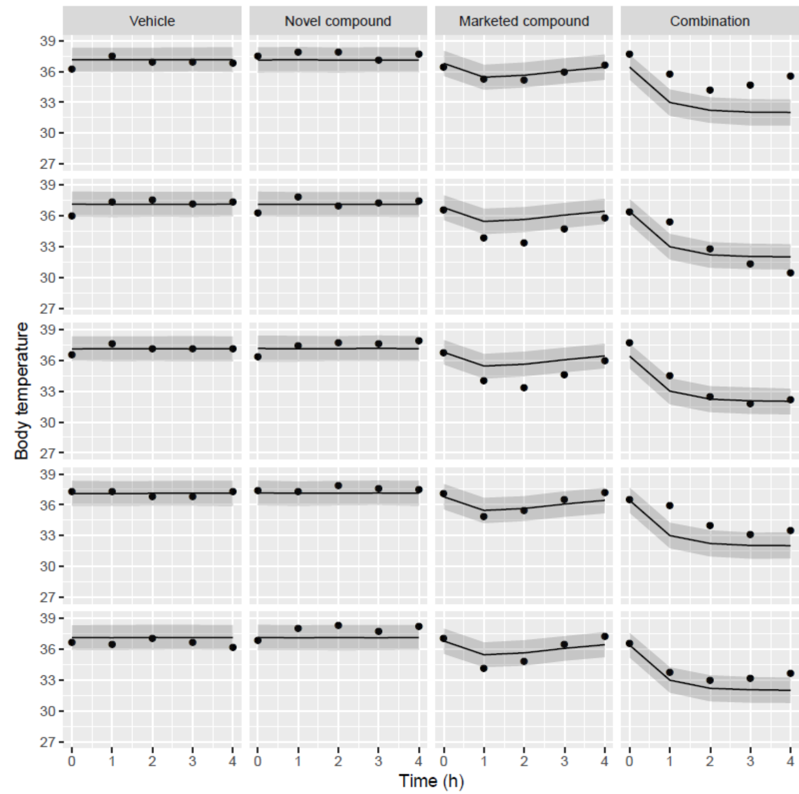

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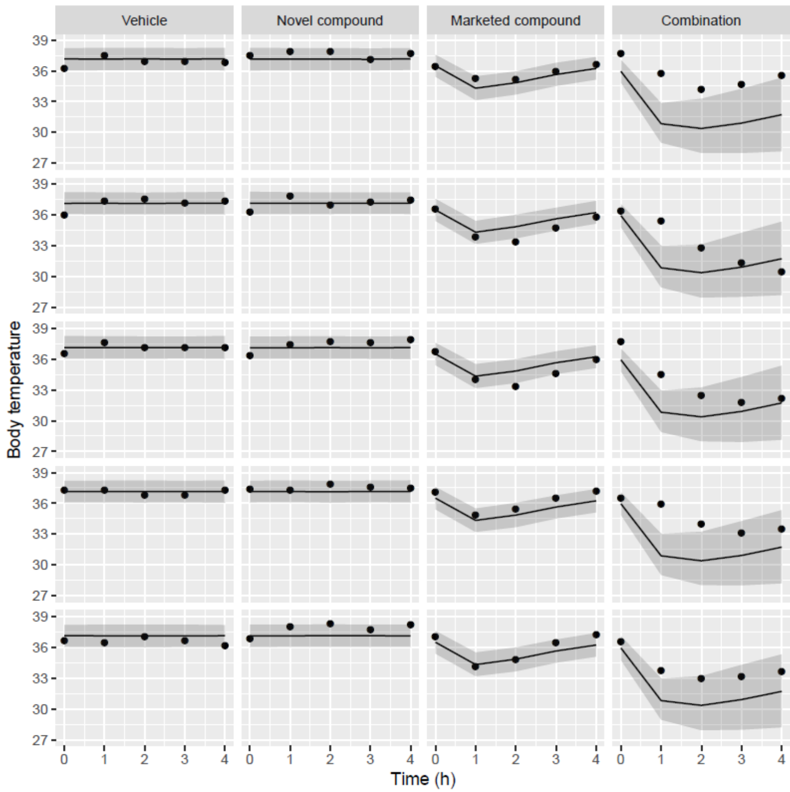

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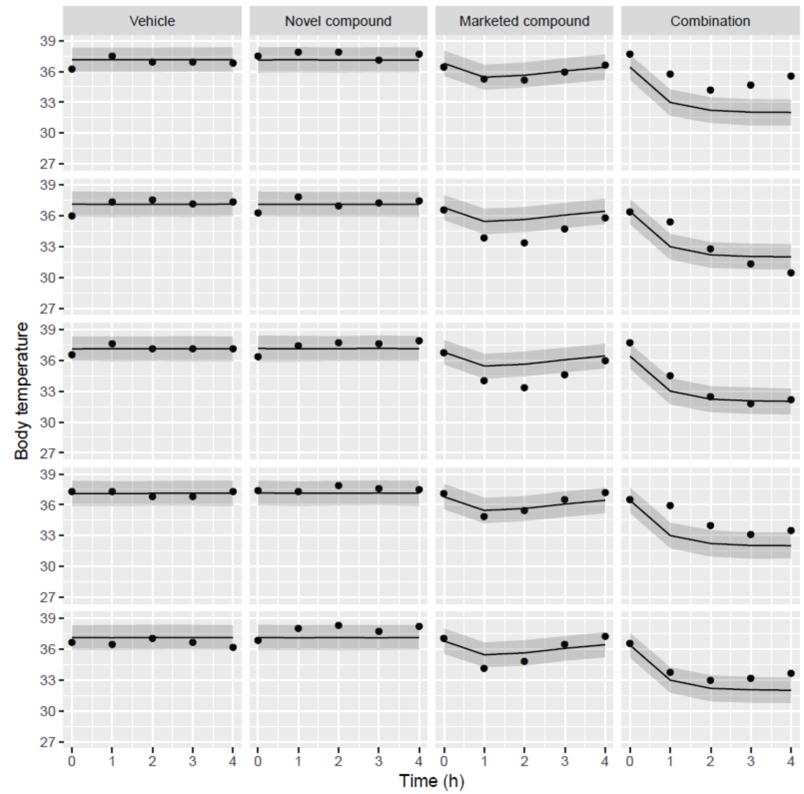

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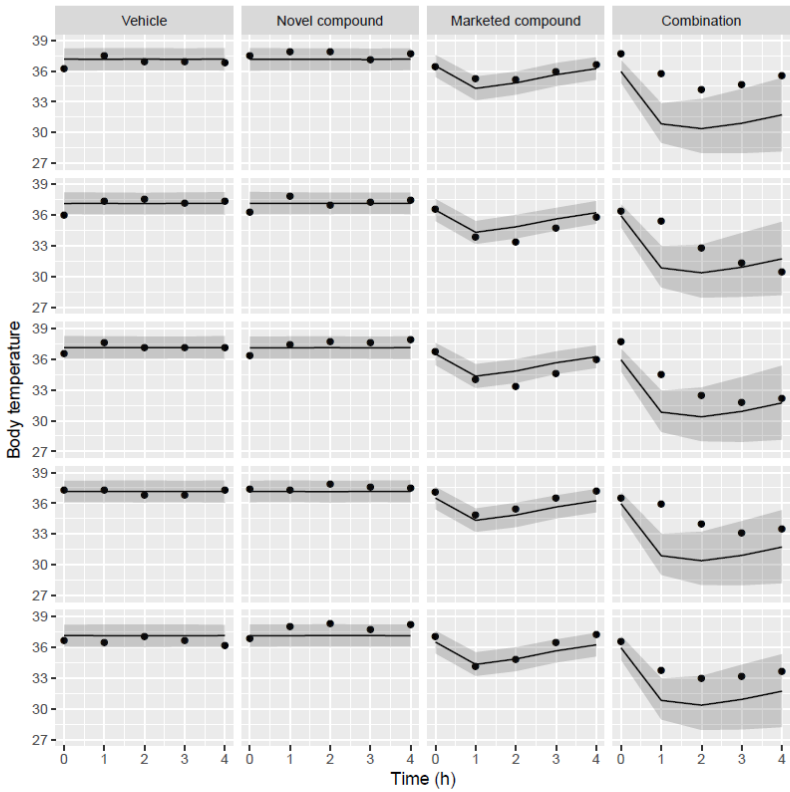

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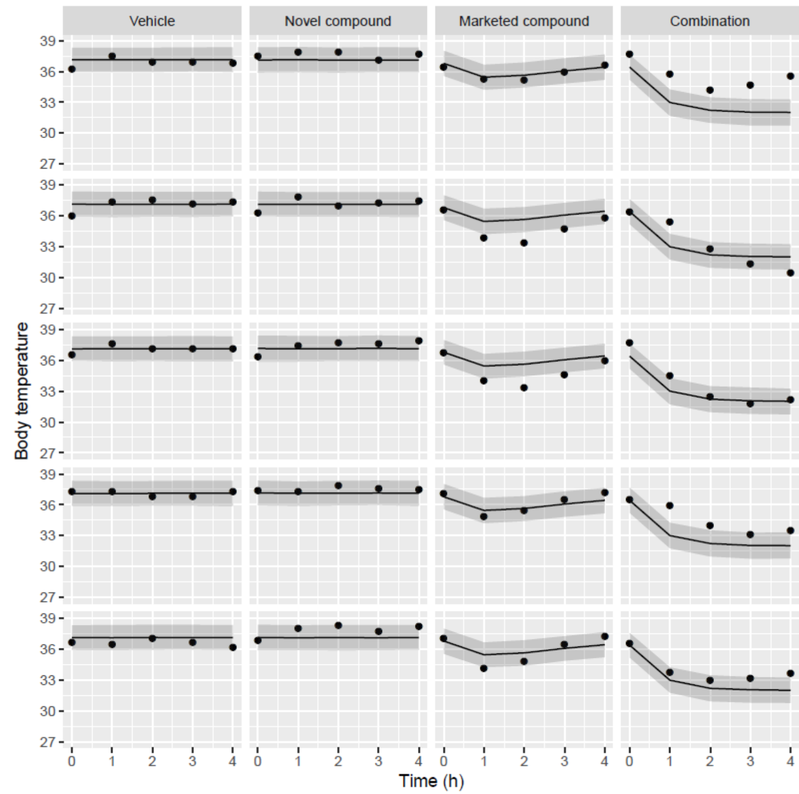

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Simulation study

Aim: To assess to what extent of model complexity the sequential integration deviates from the simple pooling

		Non-hierarchical	Hierarchical
Linear model	Informative	✓	✓
	Uninformative	✓	✓
1-comp PK model*	Informative	✓	✓
	Uninformative	✓	!
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* Linear kinetics, non-linear over time, sequential integration over doses

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