Bayesian sequential integration within a preclinical PK-PD modeling framework

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

Bayes 2019, 22 May, Lyon

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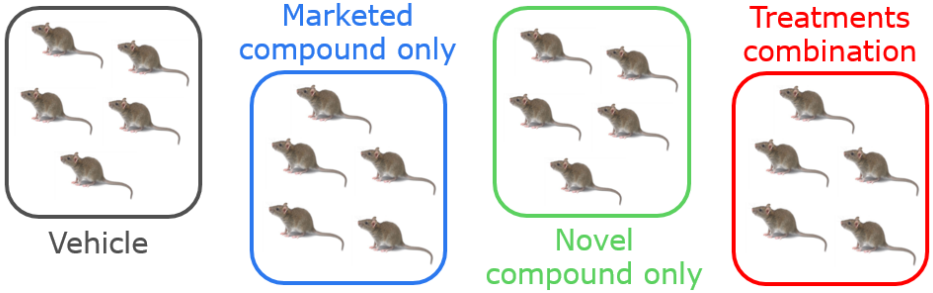
Outline

- Case Study & Proposed (P)K-PD model for synergy
- Bayesian Sequential Integration: Modeling Aspects
  1. Prior specification
  2. Choice of random effect
  3. Design of experiments
- Simulation study
- Discussion

Case Study & Proposed (P)K-PD model for synergy

Case study

Aim: To assess the safety (decrease of body temperature) resulting from the co-administration of marketed and novel compounds using 11 in-vivo trials



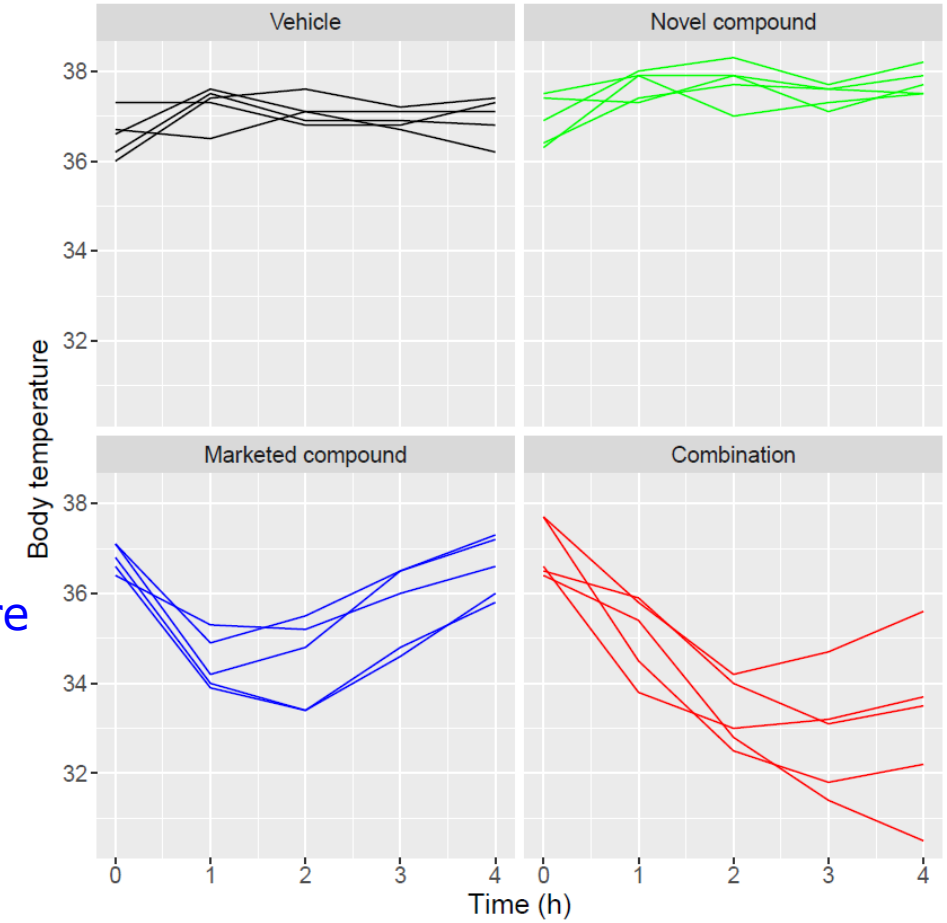
One specific dose combination for each trial, collected over **different time points**

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

Case study – Example from trial 1

No change

Body temperature decrease



No change

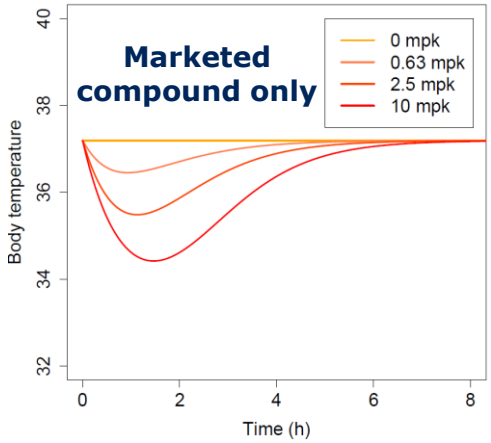
More pronounced decrease, later maximal effect

Proposed (P)K-PD model for synergy

Turnover model assuming that a **virtual** concentration of the marketed compound inhibits the production of body heat

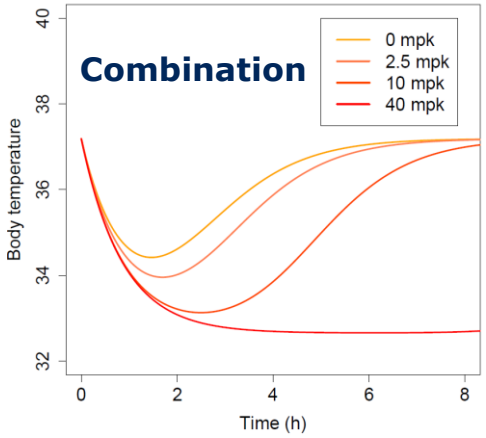
$$\frac{d\bar{R}_{it}}{dt} = k_{in}\left(1 - \frac{I_{max}C_{it}}{IC_{50} + C_{it}}\right) - k_{out}\bar{R}_{it} \qquad R_{i0} = k_{in}/k_{out}$$

The novel compound **increases the potency** of the marketed compound



$$IC_{50,comb} = IC_{50}\ e^{\alpha D_{n,i} + \beta D_{e,i} D_{n,i}}$$

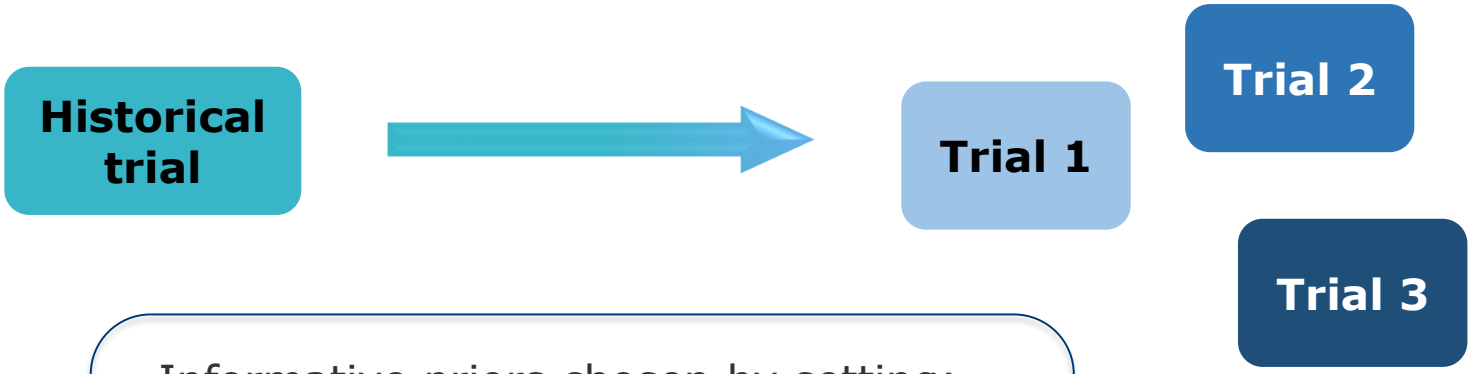
$D_{e,i}$=Marketed compound dose
$D_{n,i}$=Novel compound dose



Initial analysis: Bayesian pooling

Frequentist analysis (NONMEM)

Trial 1-11: Bayesian analysis (Stan)



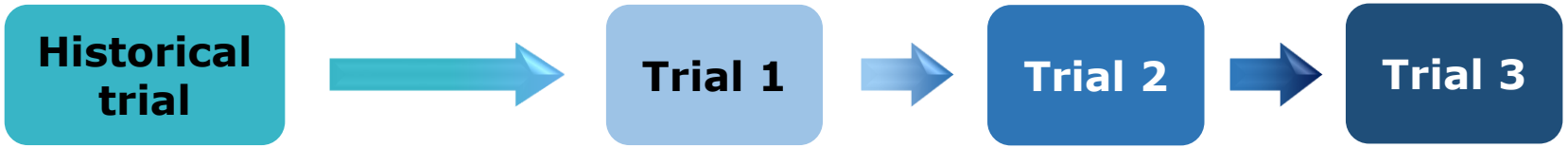
Informative priors chosen by setting:

- Expected values → point estimates
- Standard deviations → double of s.e.

from the analysis of historical data

Bayesian sequential integration

The posteriors from one trial are used to determine the hyperparameters of the priors of the next trial.



Benefits:

- Analyze the data from every **single** trial **immediately**, instead of waiting for the end of data collection
- The parameter estimates resulting from each integration step may be used for the **design** of the next trials

Challenge:

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

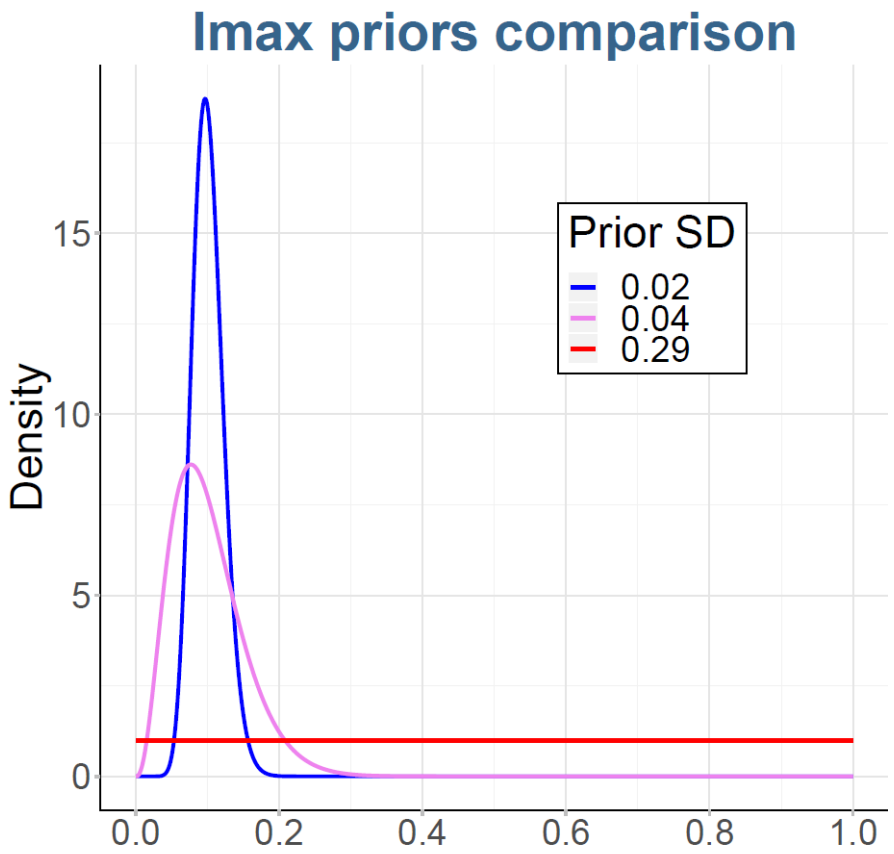
Bayesian Sequential Integration: Modeling Aspects
1. Prior Specification

Prior specification – Methods

Different priors chosen for I_{max}:

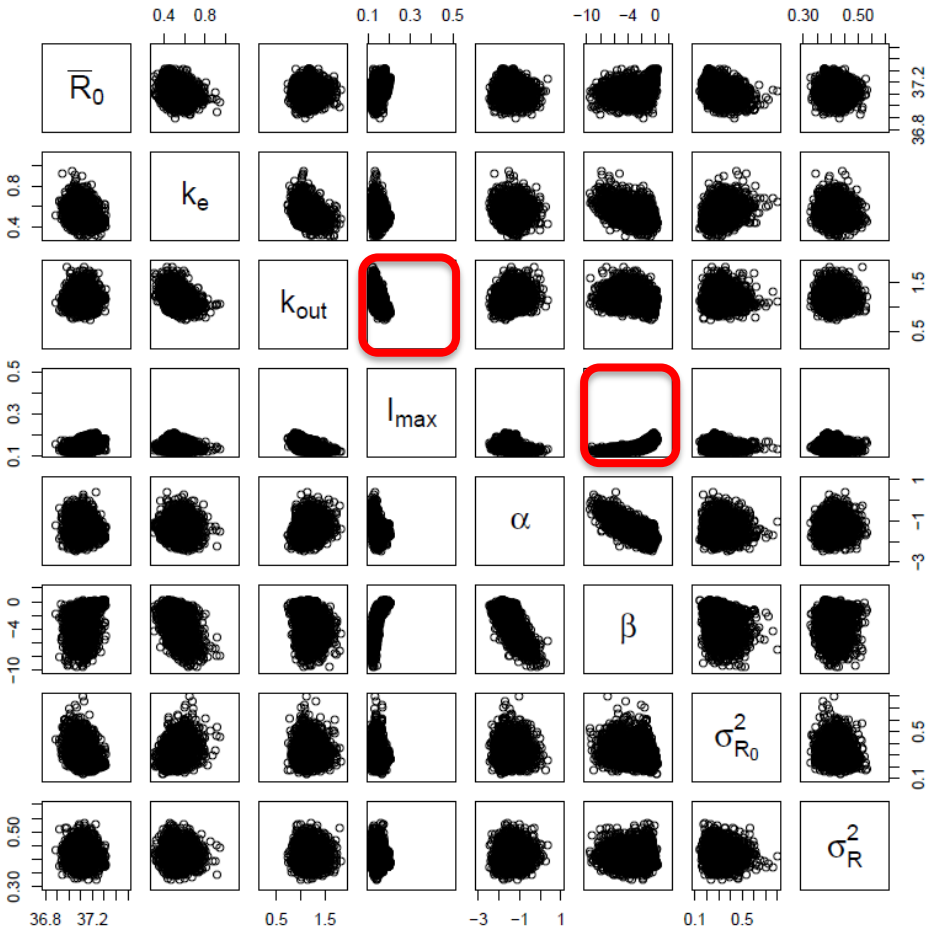
- Prior used for the initial analysis (SD=0.02)
- Prior with doubled SD (SD=0.04)
- Uniform distribution (SD=0.29)

Analysis run on trials 1, 2, 3 pooled together (to allow for identifiability of parameter β)



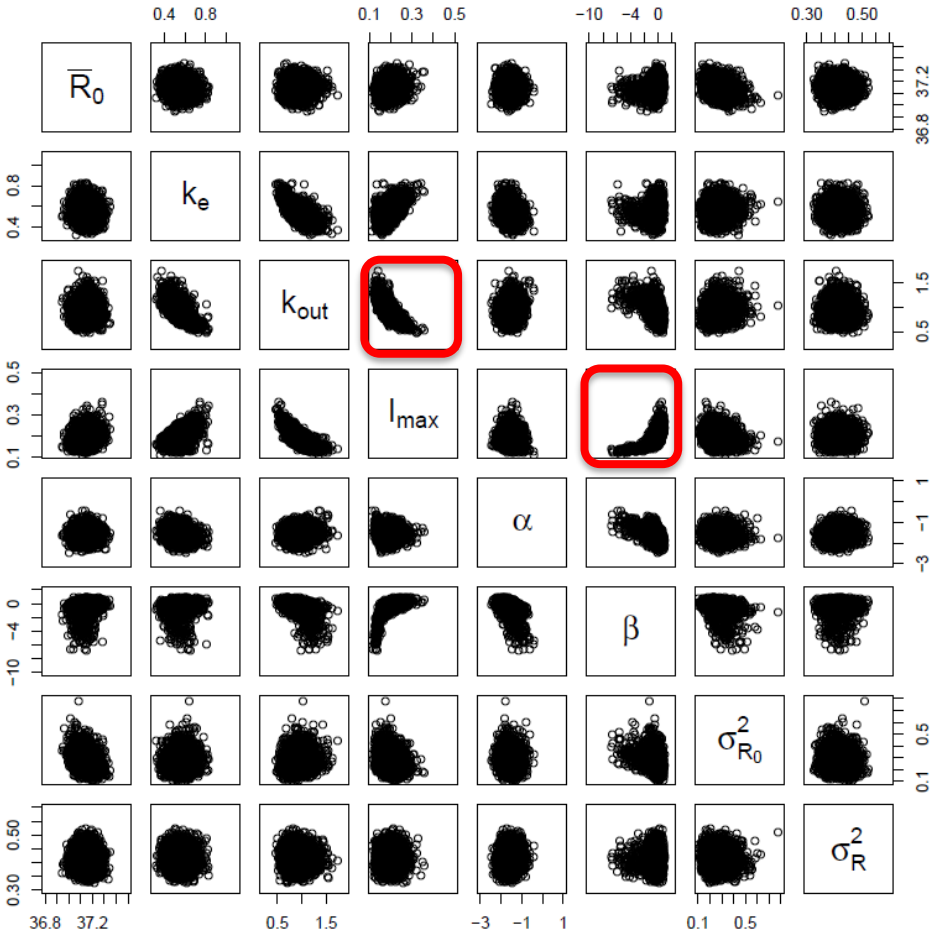
Prior specification – Results

Prior for I_{max}: SD=0.02



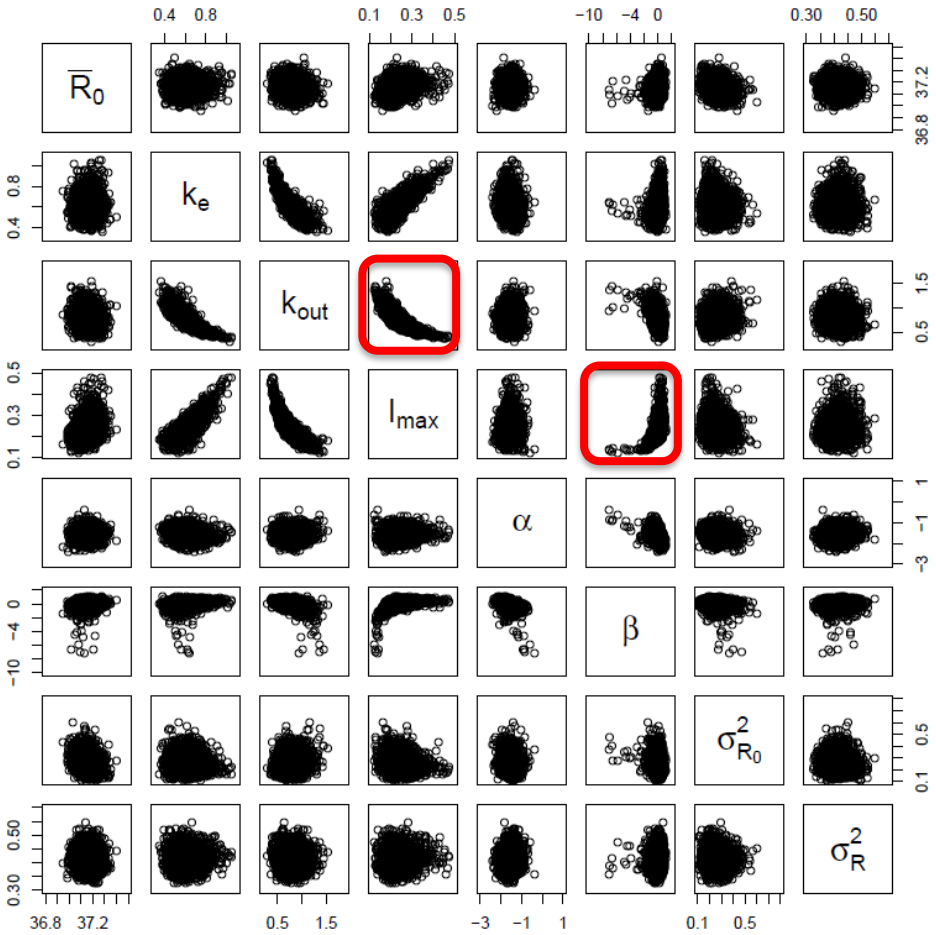
Prior specification – Results

Prior for I_{max}: SD=0.04



Prior specification – Results

Prior for I_{max}: SD=0.29



Prior specification – Results

Parameter	I_{max} SD=0.02	I_{max} SD=0.04	I_{max} SD=0.29
k_e	0.53 (0.39; 0.71)	0.55 (0.41; 0.71)	0.61 (0.44; 0.82)
k_{out}	1.15 (0.88; 1.52)	0.91 (0.63; 1.29)	0.78 (0.48; 1.12)
I_{max}	0.15 (0.12; 0.19)	0.20 (0.14; 0.27)	0.24 (0.17; 0.34)
$\bar{R}_0$	37.12 (36.99; 37.26)	37.15 (37.03; 37.27)	37.16 (37.04; 37.28)
α	-1.42 (-2.09; -0.51)	-1.58 (-2.08; -1.00)	-1.55 (-2.04; -1.09)
β	-2.85 (-7.34; -0.15)	-0.51 (-3.29; 0.48)	-0.13 (-1.17; 0.67)
$\sigma^2_{R_0}$	0.31 (0.19; 0.51)	0.26 (0.15; 0.44)	0.25 (0.15; 0.41)
σ^2_R	0.41 (0.36; 0.48)	0.41 (0.36; 0.48)	0.41 (0.36; 0.48)

The less informative the prior is specified, the larger the bias is observed.
The correlated parameters compensate each other

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

Bayesian Sequential Integration: Modeling Aspects
2. Choice of random effect

Choice of random effect – Methods

Different random effect choices considered:

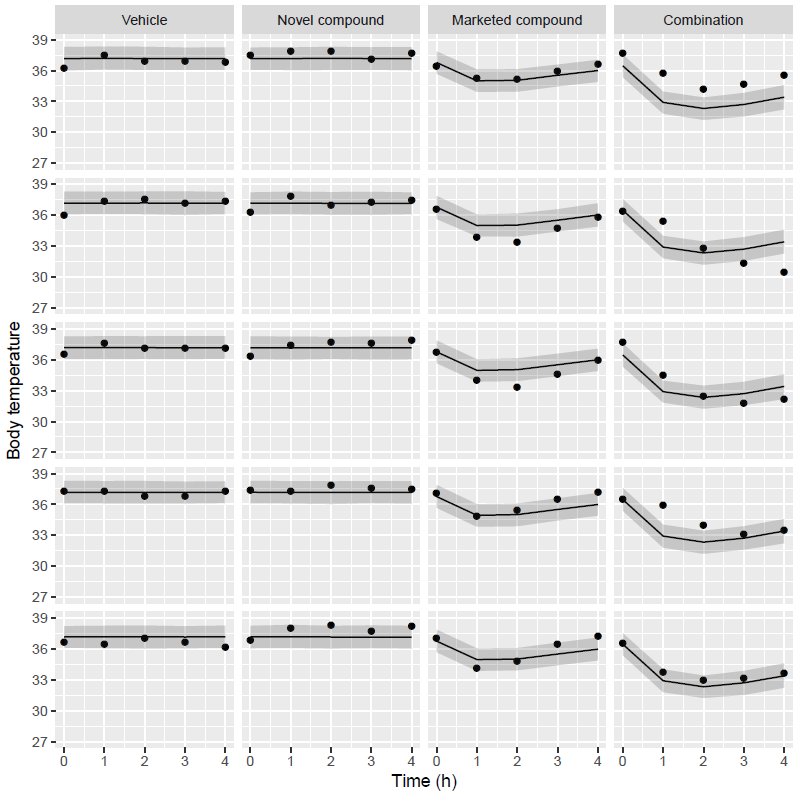
- Random baseline
- Random k_{out}
- Random k_{in} → convergence issues

Model run on all trials pooled together

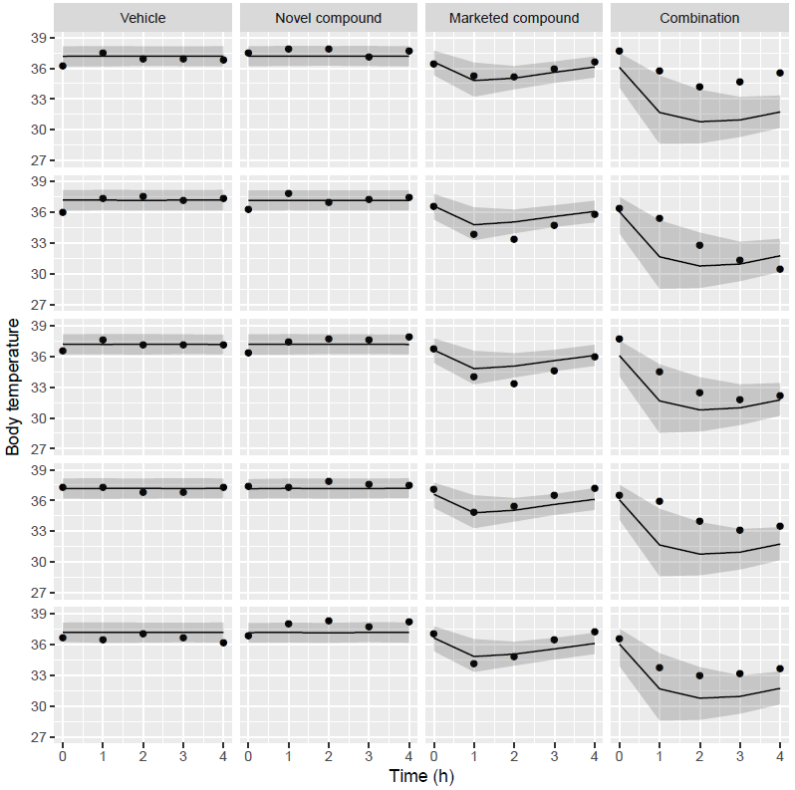
Choice of random effect – Results

Posterior predictions and predictive intervals, trial 1

Random baseline model



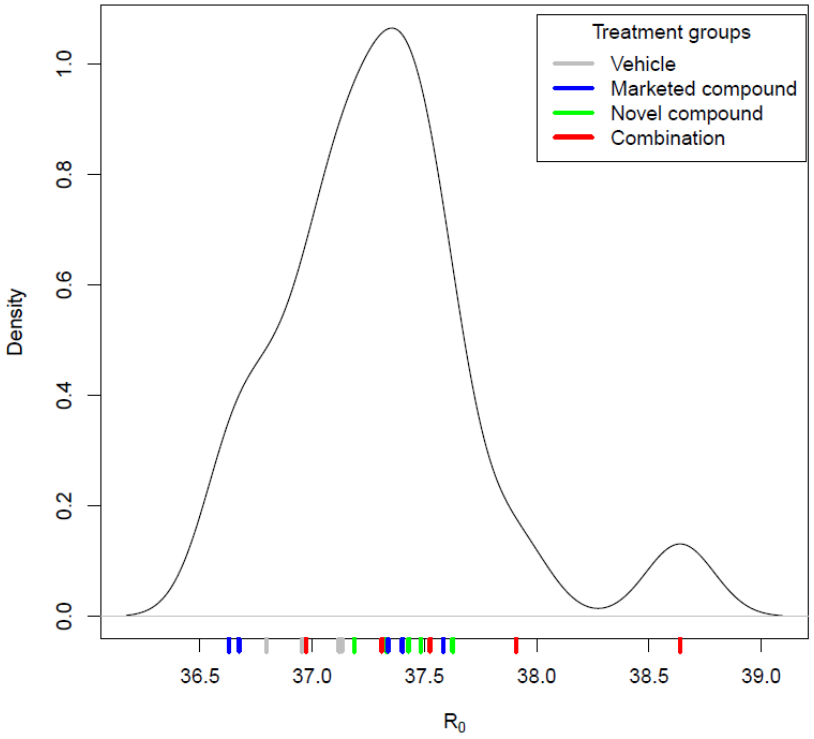
Random k_{out} model



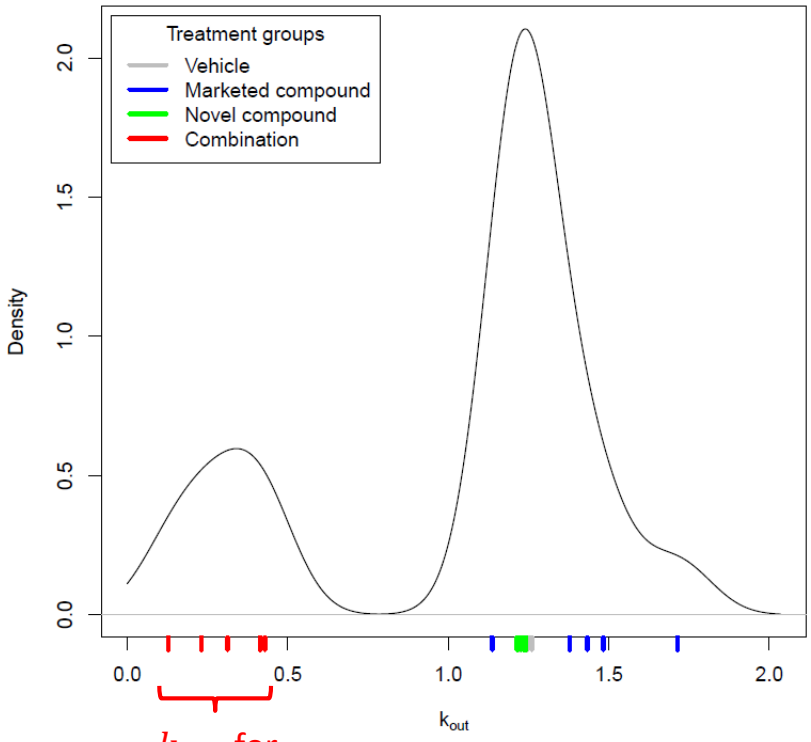
Choice of random effect – Results

Distributions of the posterior means of subject-specific random effects

Random baseline model



Random k_{out} model

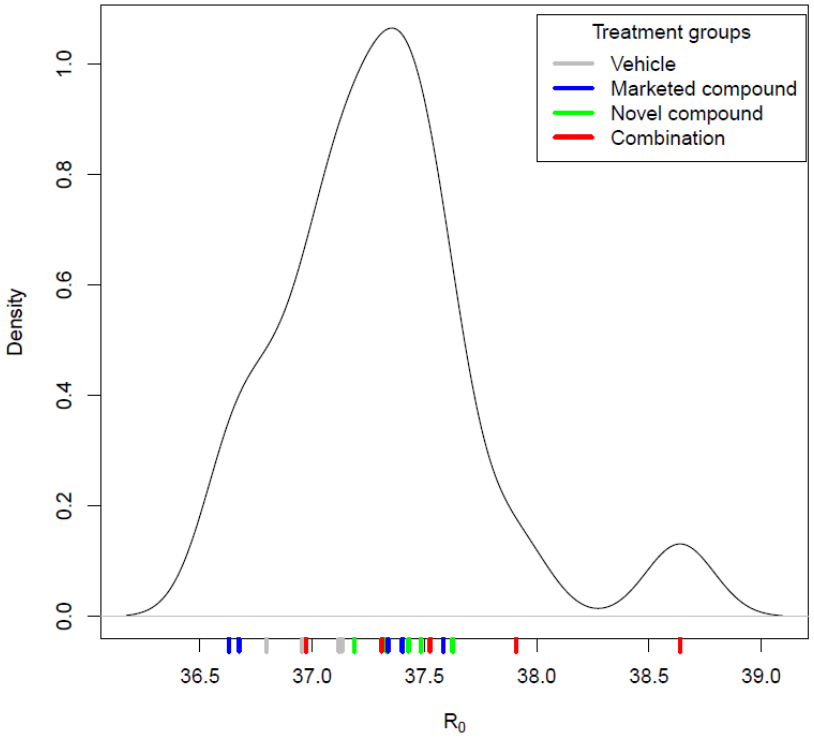


k_{out} for combination group

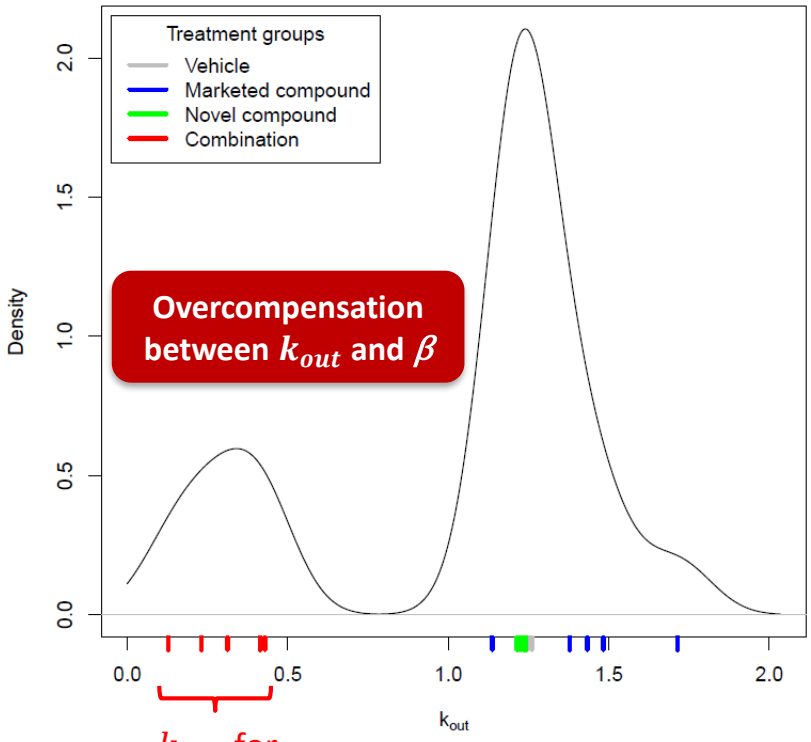
Choice of random effect – Results

Distributions of the posterior means of subject-specific random effects

Random baseline model



Random k_{out} model

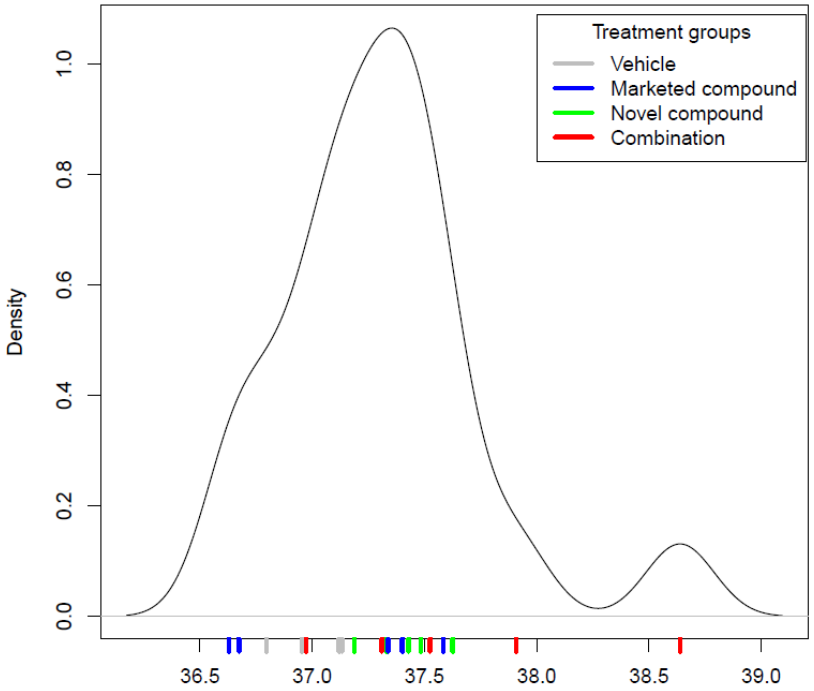


k_{out} for combination group

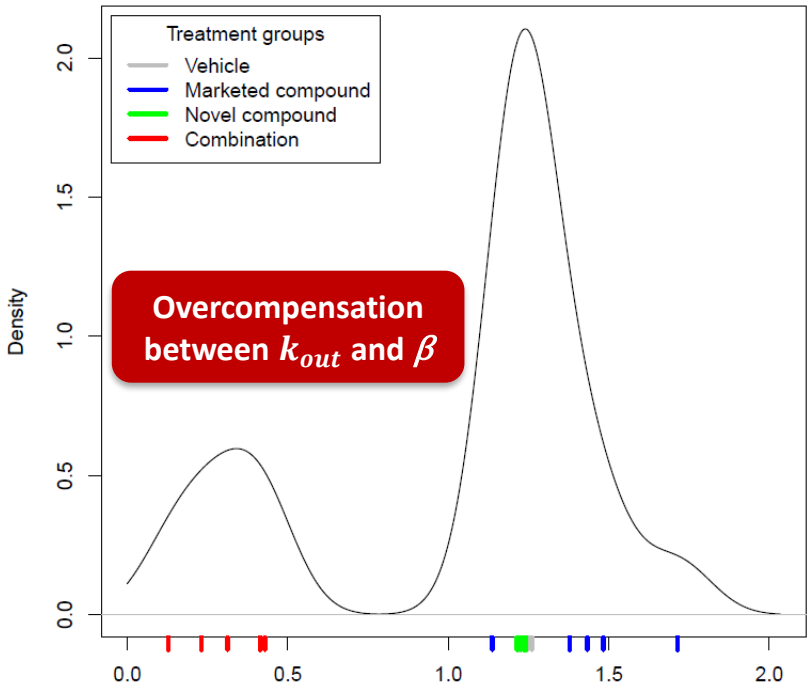
Choice of random effect – Results

Distributions of the posterior means of subject-specific random effects

Random baseline model



Random k_{out} model



Take home message n.2 Better to allocate the random effect on a parameter that is easier to estimate, to avoid overcompensations

Bayesian Sequential Integration: Modeling Aspects
3. Design of experiments

Design of experiments – Methods

Different types of sequential integrations compared with simple pooling:

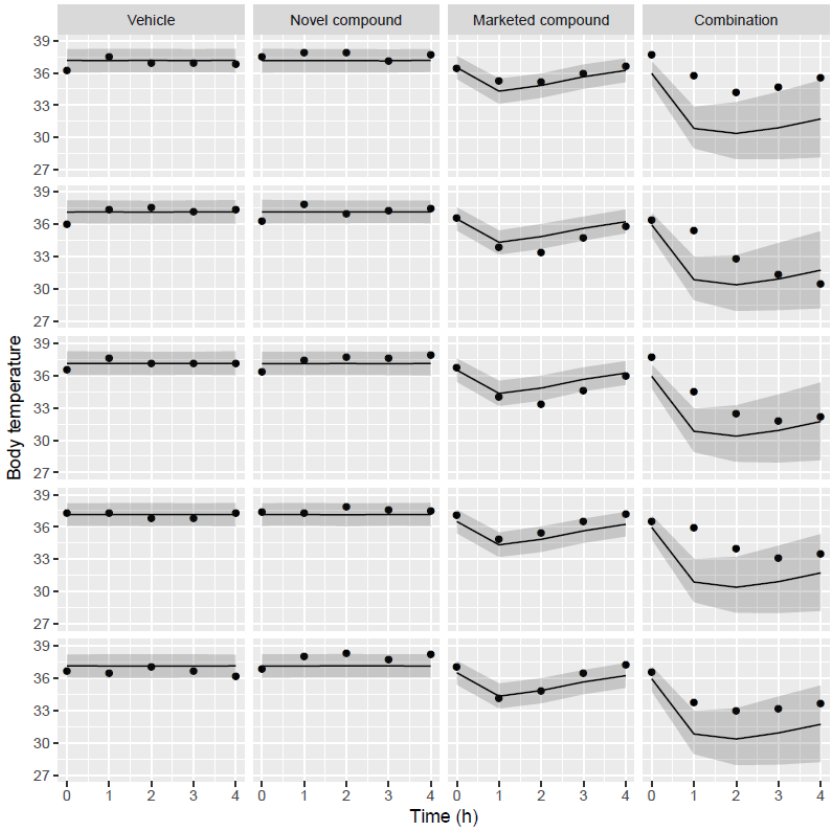
1. Pooling of 1 trial at a time*, keeping the original trial order
2. Pooling of 1 trial at a time*, order permutation
3. Pooling of 3 trials at a time, keeping the original trial order
4. Sequentially pooling 5 "optimal" trials: sampled from the existing data so that each of them contains all possible dose combinations

*The first three trials were pooled together to guarantee the identifiability of β.

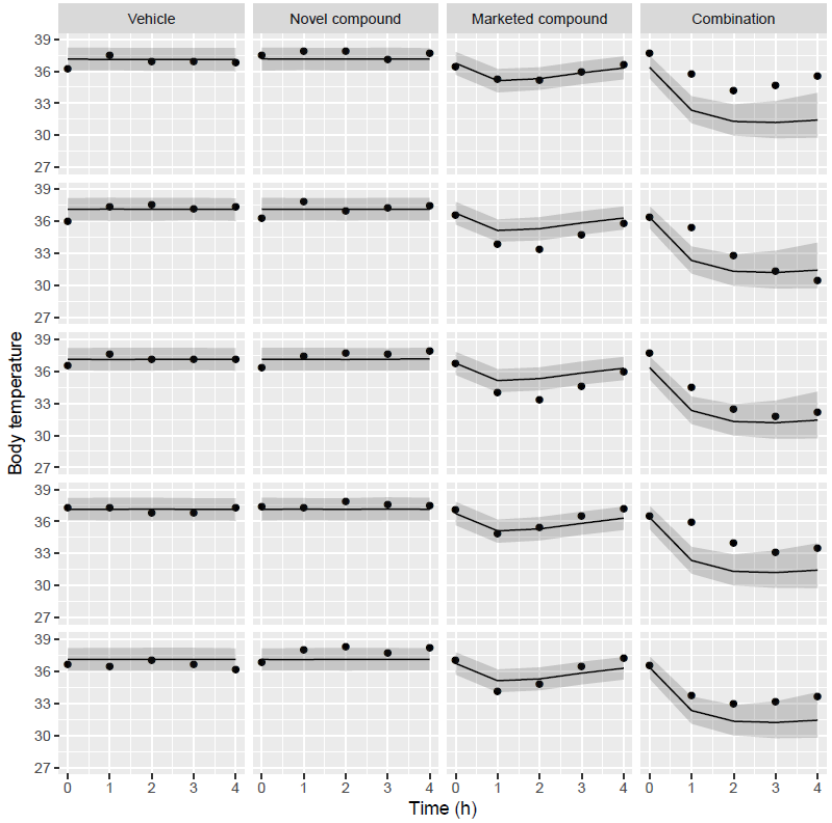
Design of experiments – Results

Posterior predictions and predictive intervals, trial 1

1. Sequential integration, 1 trial at a time



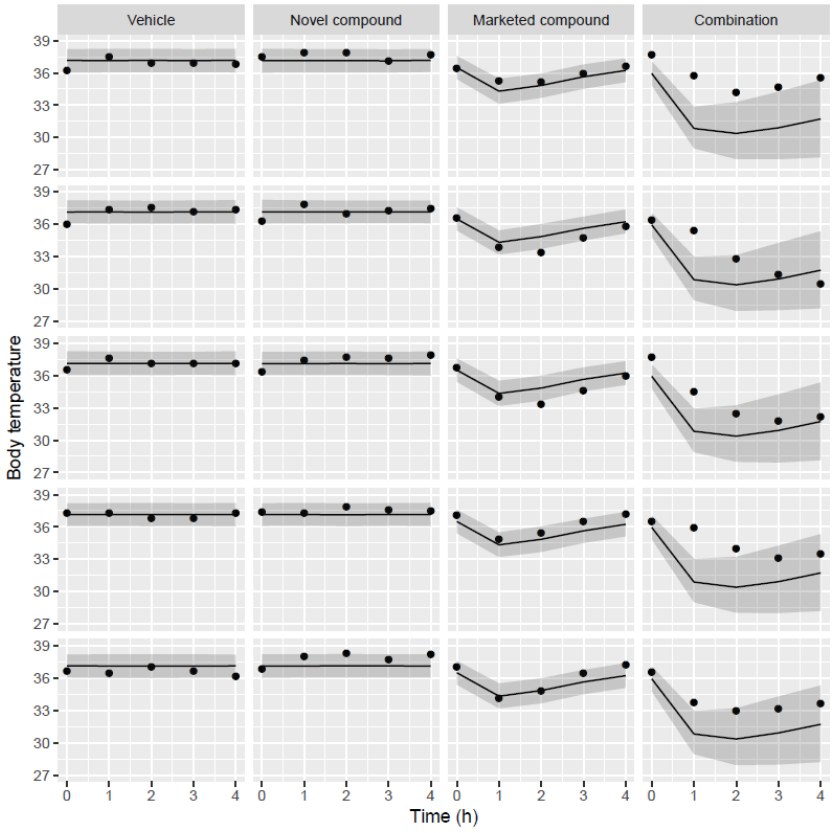
2. Sequential integration, permuted order



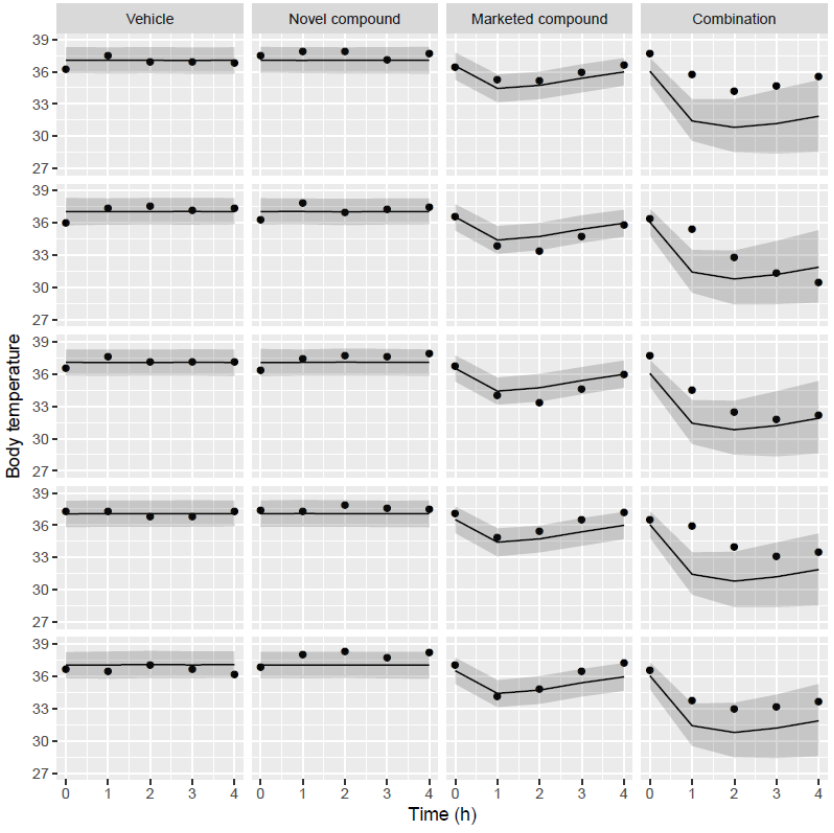
Design of experiments – Results

Posterior predictions and predictive intervals, trial 1

1. Sequential integration, 1 trial at a time



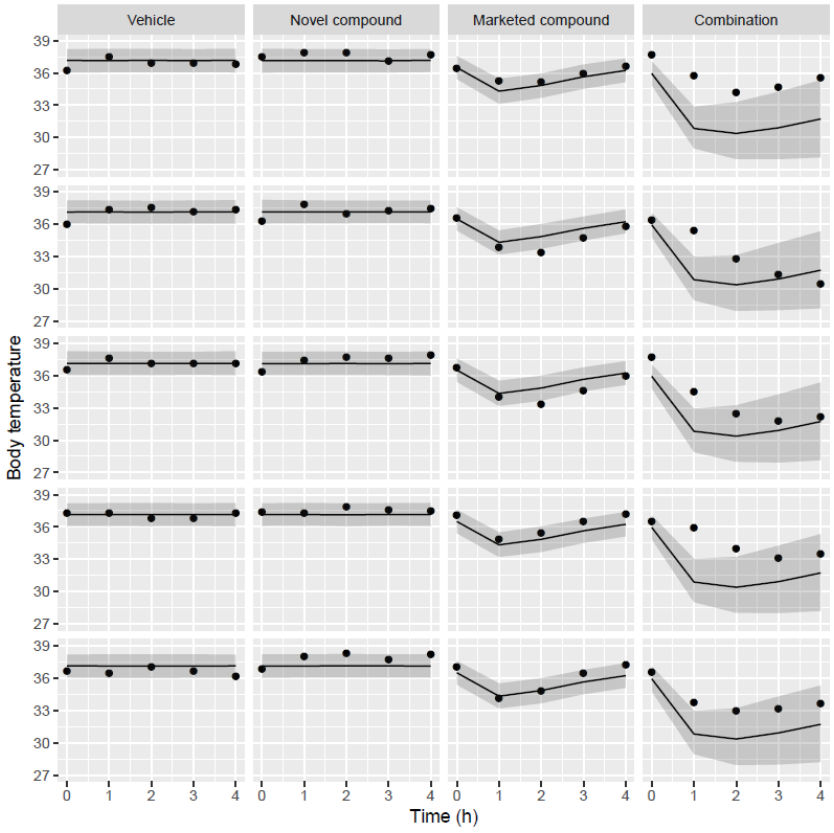
3. Sequential integration, 3 trials at a time



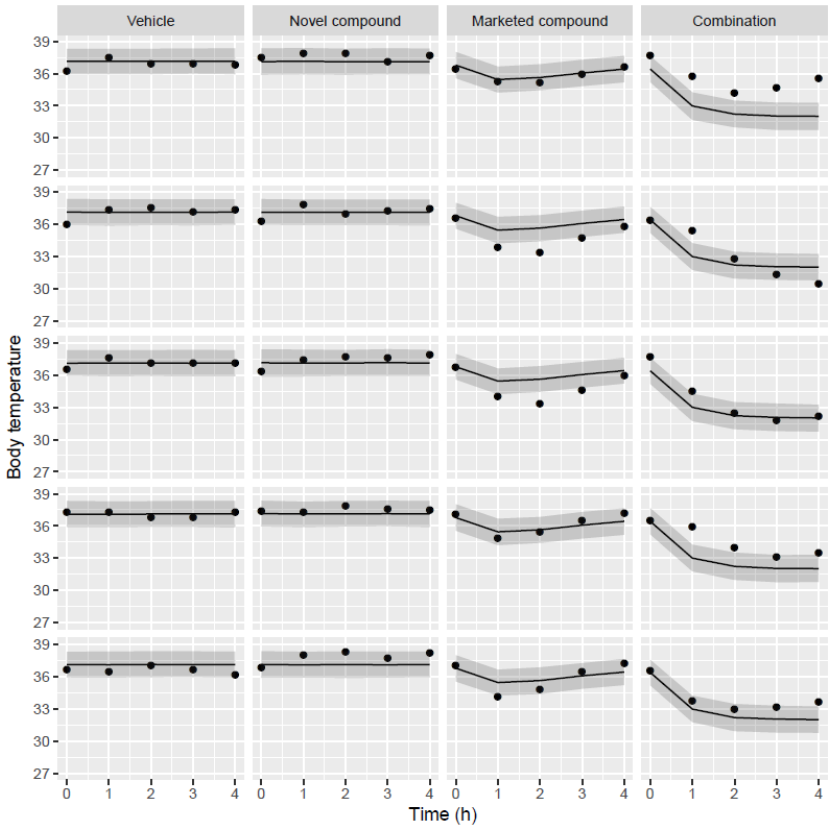
Design of experiments – Results

Posterior predictions and predictive intervals, trial 1

1. Sequential integration, 1 trial at a time

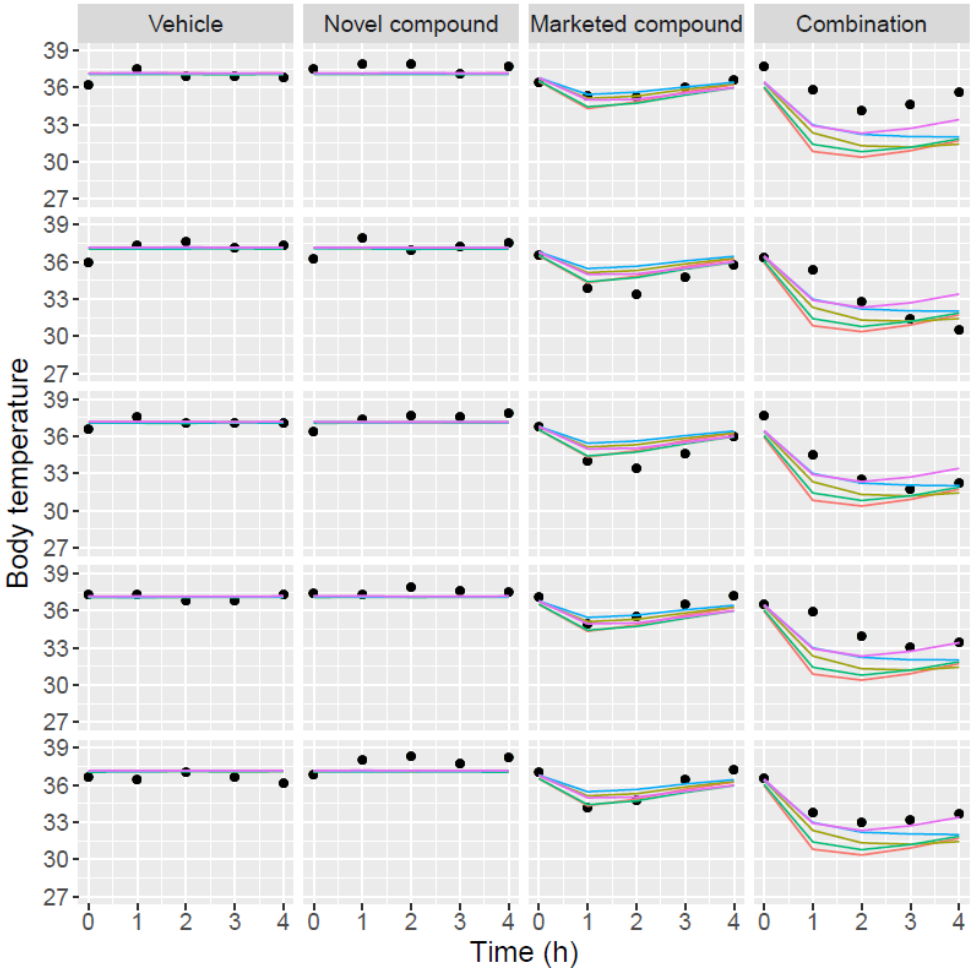


4. Sequential integration, optimal trials



Design of experiments – Results

Posterior predictions, trial 1



Practical identifiability issues at first integration steps when trials are **poorly designed**

Take home message n.3
Trial design plays a crucial role in the performance of Bayesian sequential integration

Simulation study

Aim

To compare Bayesian pooling with sequential integration using linear and nonlinear models (1000 simulation runs):

1. Linear model
2. One-compartment PK model
3. Sigmoidal Emax model

- For each model, both absence and presence of inter-individual variability (IIV) is assessed → **different scenarios**

- For each scenario, informative and uninformative prior distributions are considered → **different sub-scenarios**

All scenarios reflect the setting of **pre-clinical trials** (small sample size, one or few doses per trial).

Results

		Non-hierarchical	Hierarchical
Linear model	Informative	✓	✓
	Uninformative	✓	✓
1-comp PK model*	Informative	✓	✓
	Uninformative	✓	!
Sigmoidal Emax model	Informative	✓	✓
	Uninformative	✓	✗

* Linear kinetics, non-linear over time, sequential integration over doses

Discussion

Discussion

- The Bayesian sequential integration is an appealing approach, as it allows to analyze every single trial immediately without reanalyzing the data up to the current study

- If a **linear** model is performed and the parameters are **not correlated**, this technique produces **unbiased** and **precise** estimates

- Mitigating the risk of **bias** when a **nonlinear** model is performed can be achieved via:
  - Carefully designed integration of studies, to avoid the risk of practical identifiability issues
  - The specification of informative prior distributions
  - The allocation of random effects on parameters that are easier to estimate

Thank you!

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.

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