Bayesian pooling and sequential integration of small trials: A comparison within linear and nonlinear modelling frameworks

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Outline

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  2. One-compartment PK model
  3. Sigmoidal Emax model
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Background: Bayesian sequential integration using a novel K-PD model for synergy

Background

Bayesian sequential integration recursively updates the posterior distributions whenever new information becomes available.

Given a number of trials conducted sequentially, the posteriors from one trial are used to determine the hyperparameters of the priors of the following trial.

Benefits:

- It allows to analyze the data from each new trial **immediately**, respecting the **sequential nature** of data collection.
- The parameter estimates resulting from each integration steps may be used for the **design** of the next trials.

Background

In previous work, small trials were sequentially integrated using a **K-PD model**:

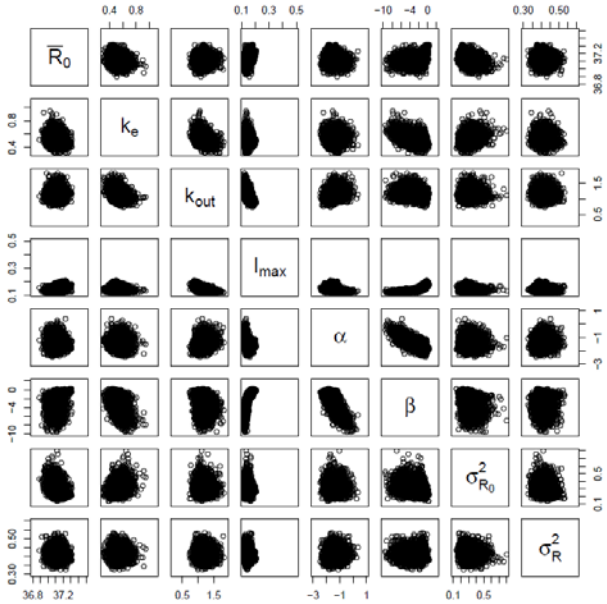
$$\frac{d\bar{R}_{it}}{dt} = k_{in}\left(1 - \frac{I_{max}C_{it}}{IC_{50} + C_{it}}\right) - k_{out}\bar{R}_{it}$$

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

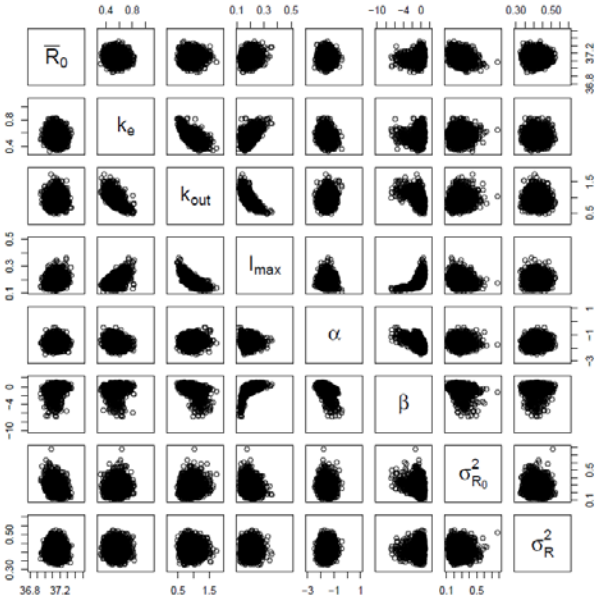
In a **pre-clinical** PK-PD modelling framework, however, several **precautions** should be undertaken to ensure an accurate sequential integration.

Prior Specification

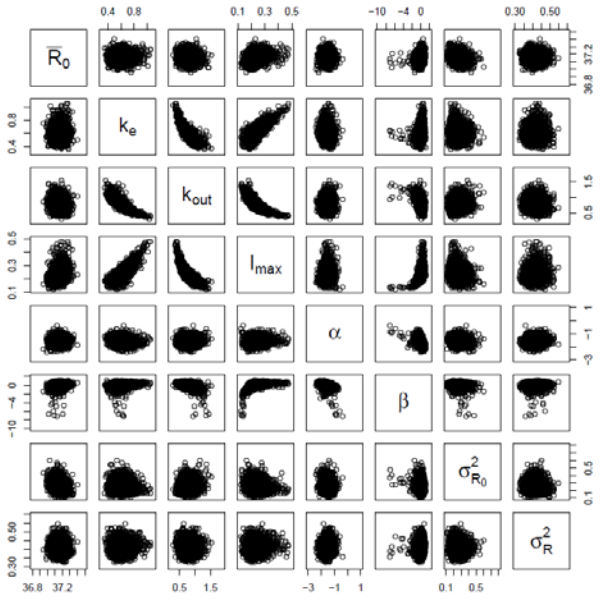
Prior for I_{max}, SD=0.02



Prior for I_{max}, SD=0.04



Prior for I_{max}, SD=0.29

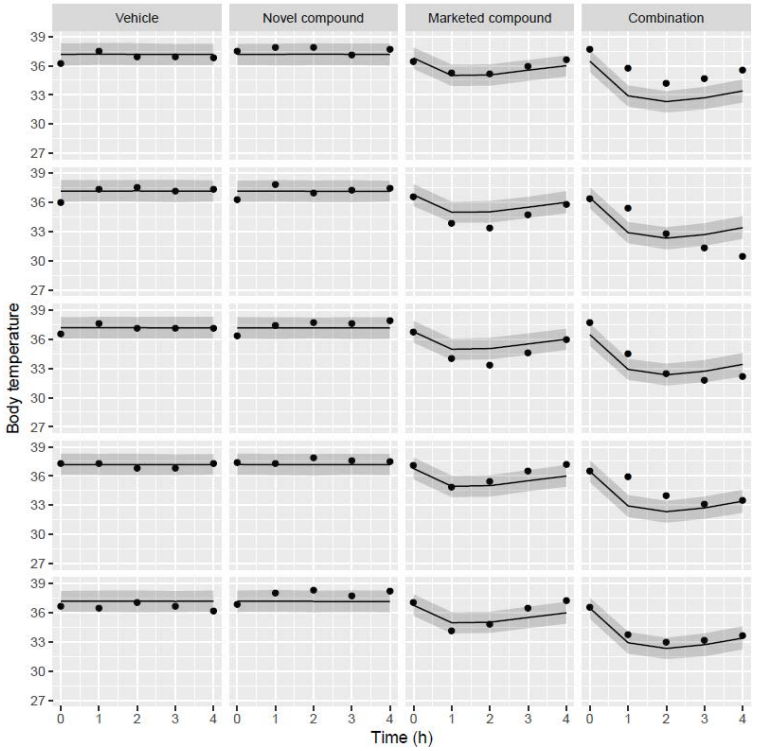


Parameter correlation increases with a decreasing prior precision.

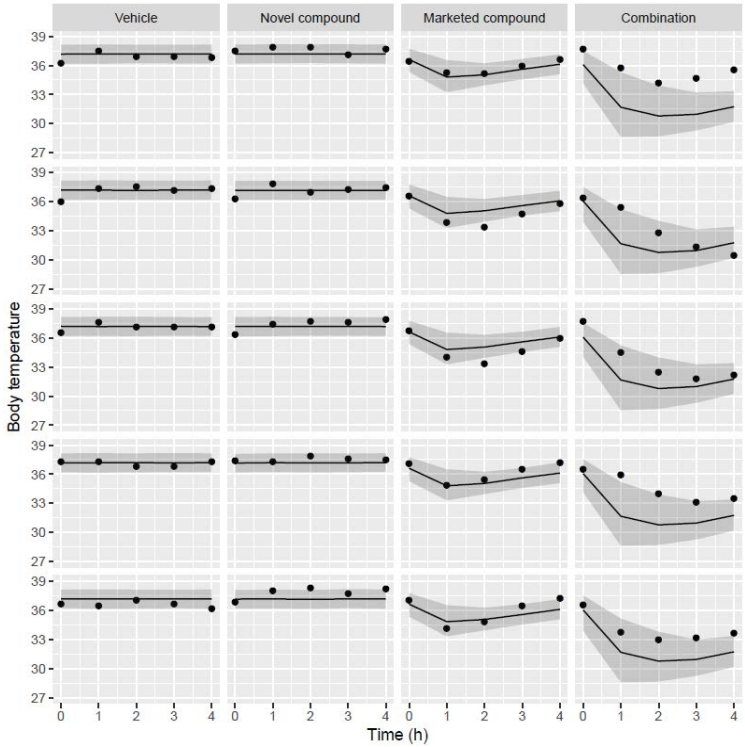
Choice of Random Effect

Posterior predictions, trial 1

Random baseline



Random k_{out}

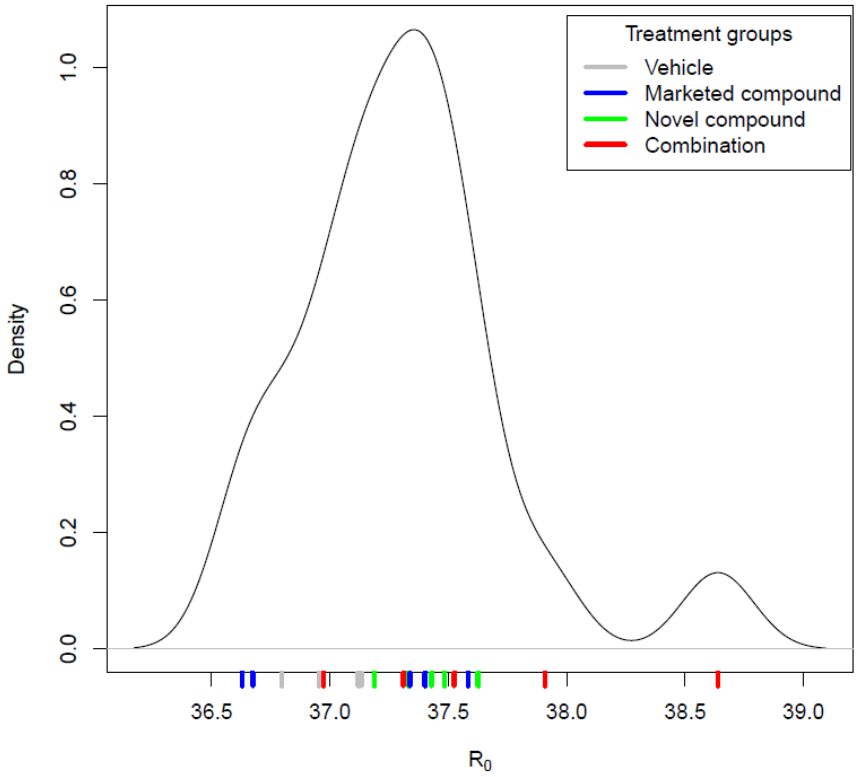


Worse posterior predictions when the random effect is allocated on a parameter which is highly correlated with other parameters

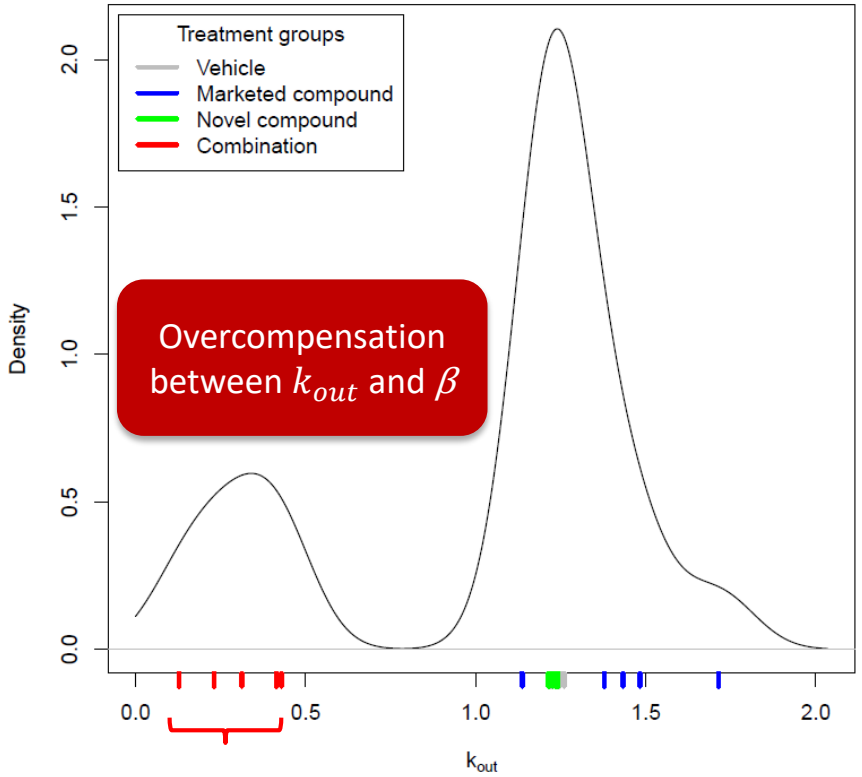
Choice of Random Effect

Distributions of the posterior means of subject-specific random effects

Random baseline



Random k_{out}



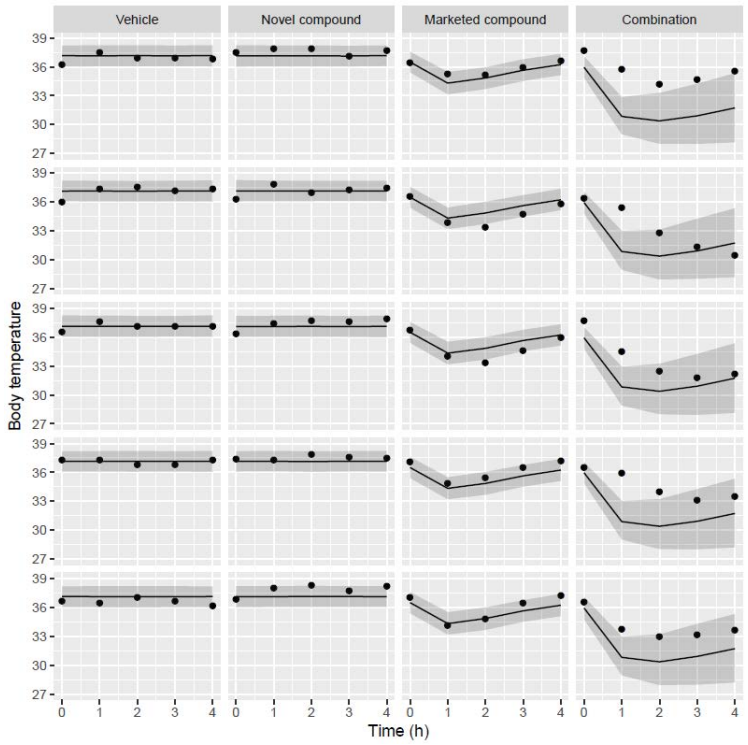
Overcompensation between k_{out} and β

k_{out} for combination group

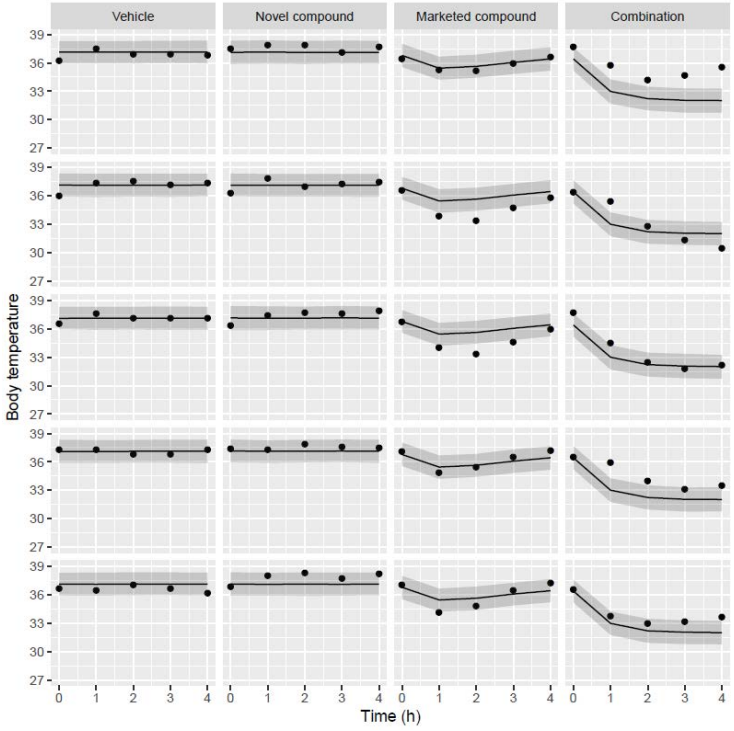
Design of experiments

Posterior predictions, trial 1

Integration of original trials



Integration of well designed trials



Worse posterior predictions when trials are poorly designed. Identifiability issues may arise during the first integration steps.

Bayesian pooling vs 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. Emax model

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

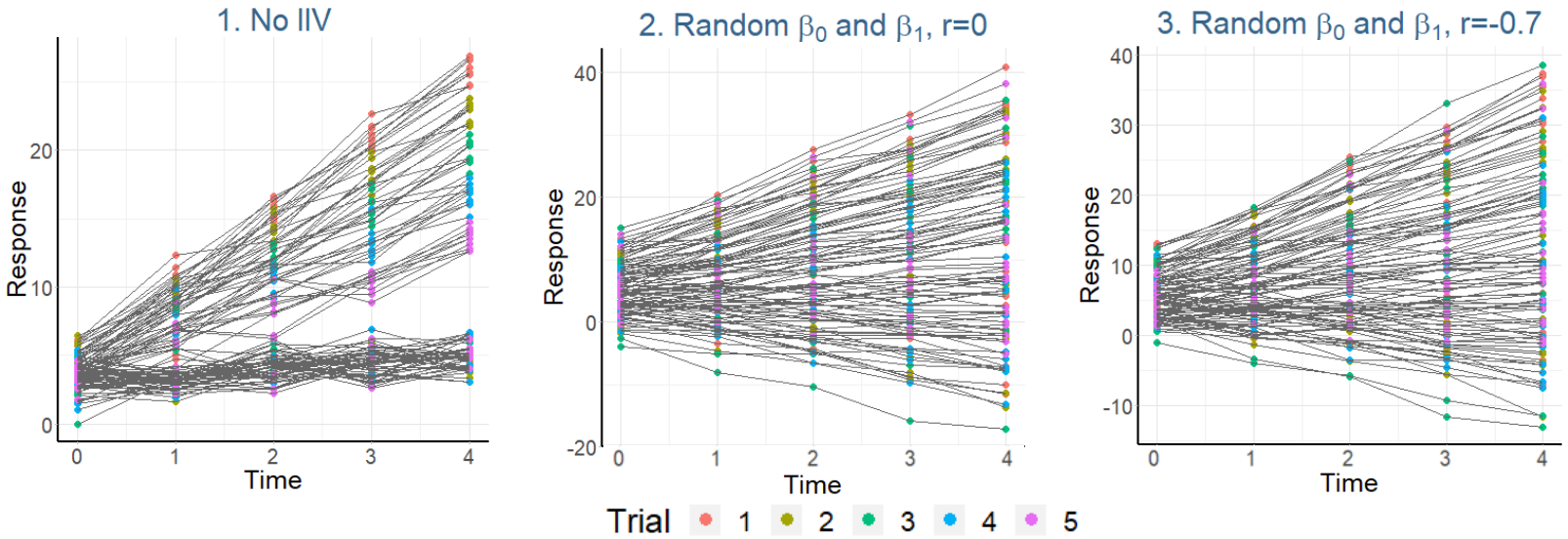
- For each scenario, informative and uninformative prior distributions are considered → **different sub-scenarios**

All scenarios reflect the setting of **pre-clinical trials** (often characterized by small sample size).

Simulated data – linear model

- 5 trials: 1 specific dose assessed in each of them (100, 50, 25, 12.5, 6.25)
- In each trial: 10 subjects assigned to compound, 10 subjects to placebo
- Longitudinal data: 5 time points (0 to 4 hours)

$$R_{ij} \sim N(\beta_0 + \beta_1 t_j + \beta_2 \log(d_i) + \beta_3 t_j \log(d_i), \sigma^2)$$
$$\beta_0 = 3, \quad \beta_1, \beta_2 = 0.5, \quad \beta_3 = 1, \quad \sigma^2 = 1$$



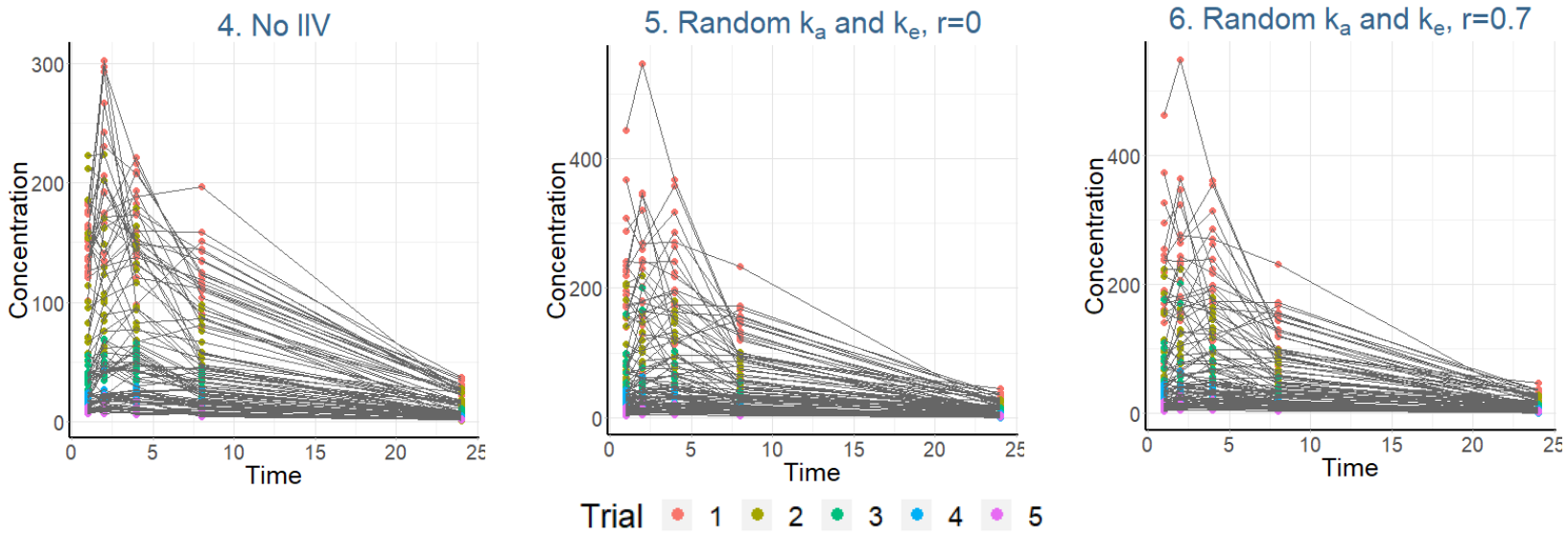
Simulated data – One-compartment PK model

- 5 trials of 20 subjects: 1 specific dose assessed in each trial
- Longitudinal data: 5 time points (1, 2, 4, 8, 24 h after oral administration)

$$\log(C_{ij}) \sim N(\log(\bar{C}_{ij}), \sigma^2)$$

$$\bar{C}_{ij} = \frac{d_i k_e k_a}{Cl(k_a - k_e)}\left[\exp(-k_e t_j) - \exp(-k_a t_j)\right]$$

$$k_a = 1.17, \quad k_e = 0.09, \quad Cl = 0.04, \quad \sigma^2 = 0.06$$

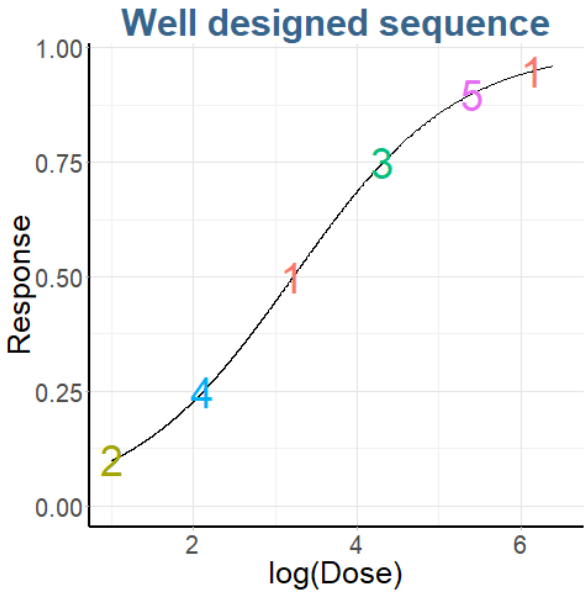


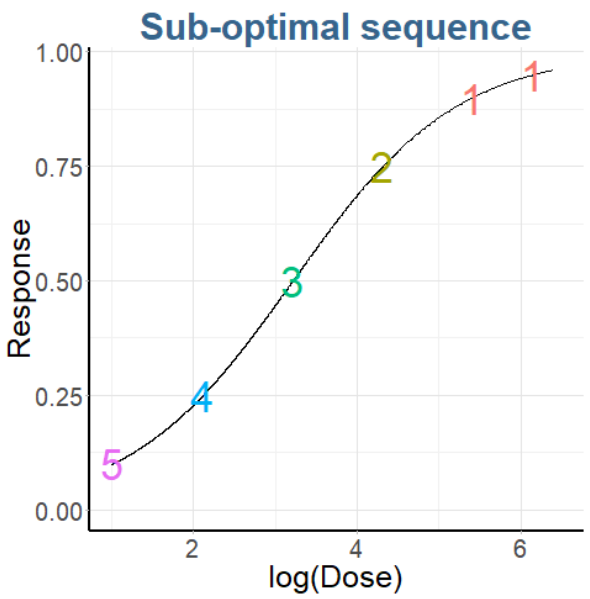
Simulated data – Sigmoidal Emax model

5 trials; units clustered in 7 groups per trial.

- First trial: 3 units for each group → 2 active doses, 1 placebo
- Subsequent trials: 2 units for each group → 1 active dose, 1 placebo

Different sequences of dose level integration:



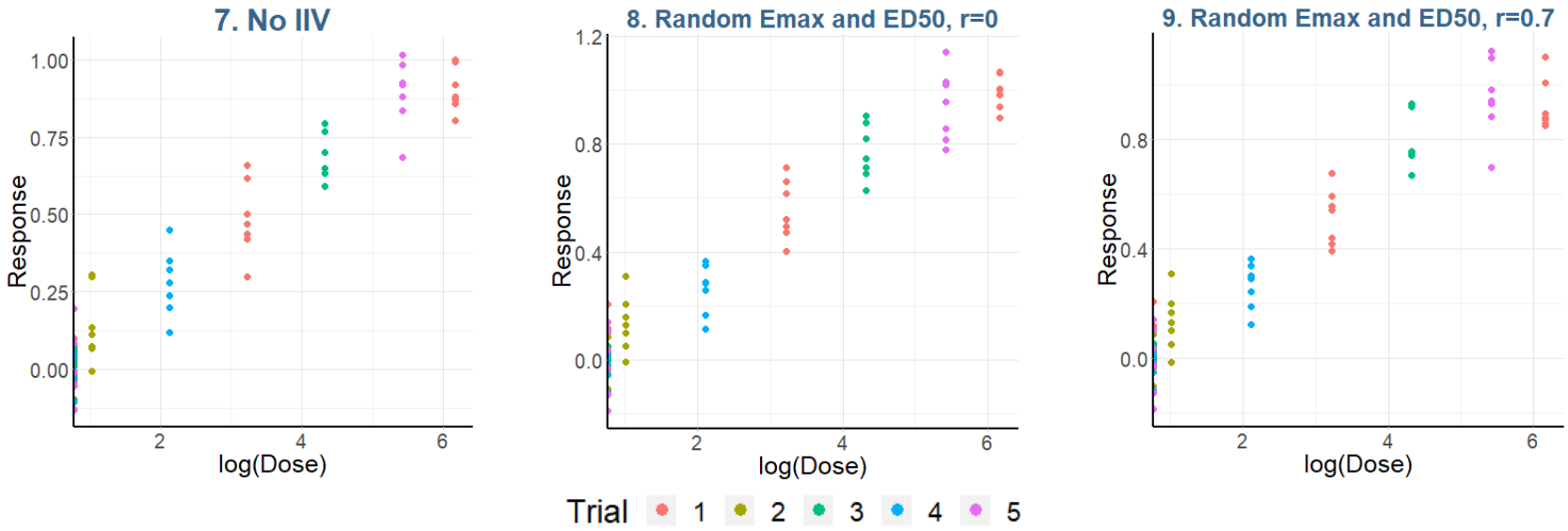


Simulated data – Emax model, well designed sequence

Trial	1	2	3	4	5
Dose	475, 25	2.78	75	8.33	225

$$R_{ij} \sim N(\bar{R}_{ij}, \sigma^2), \quad \bar{R}_{ij} = E_0 + \frac{d_{ij}^H E_{max}}{d_{ij}^H + ED_{50}^H}$$

$$E_0 = 0, \quad ED_{50} = 25, \quad H, E_{max} = 1, \quad \sigma^2 = 0.01$$

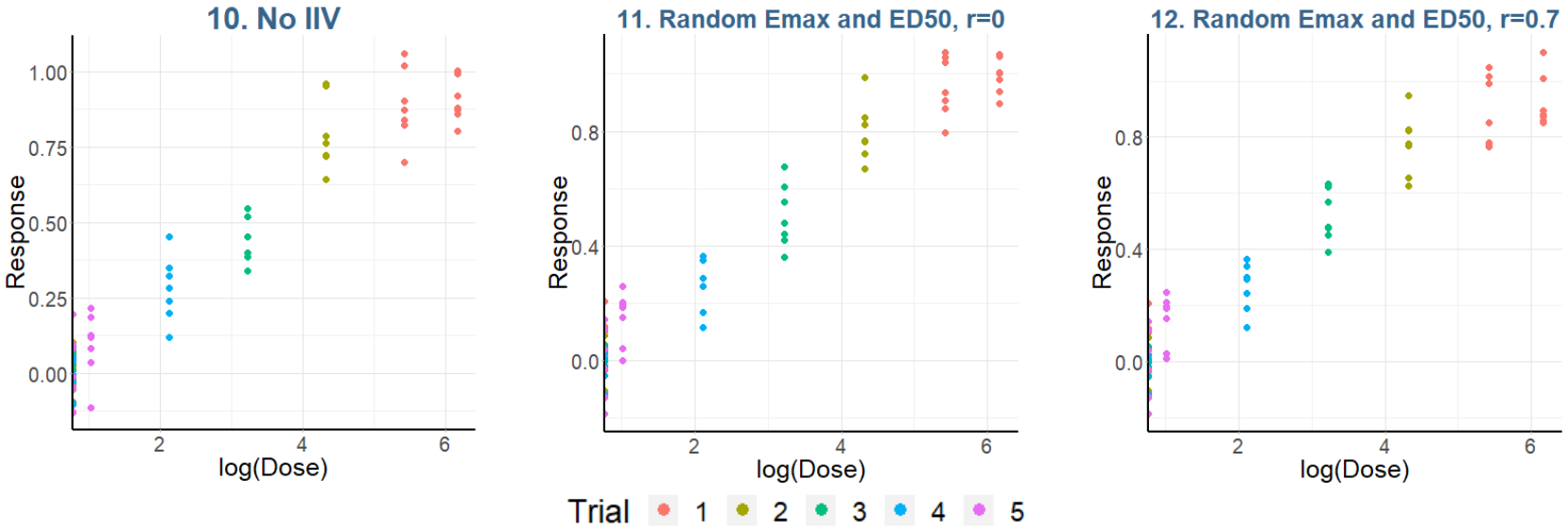


Simulated data – Emax model, sub-optimal sequence

Trial	1	2	3	4	5
Dose	475, 225	75	25	8.33	2.78

$$R_{ij} \sim N(\bar{R}_{ij}, \sigma^2), \quad \bar{R}_{ij} = E_0 + \frac{d_{ij}^H E_{max}}{d_{ij}^H + ED_{50}^H}$$

$$E_0 = 0, \quad ED_{50} = 25, \quad H, E_{max} = 1, \quad \sigma^2 = 0.01$$



Results

Results

		Non-hierarchical	Hierarchical (2 uncorrelated R.E.)	Hierarchical (2 correlated R.E.)
Linear model	Informative	✓	✓	✓
	Uninformative	✓	✓	✓
1-comp PK model	Informative	✓	✓	✓
	Uninformative	✓	!	!

Although the PK model is non-linear over time, it assumes linear kinetics. Therefore the estimates from the first integration step are highly informative for subsequent steps.

When a hierarchical PK model is performed using uninformative priors, few simulation runs produced anomalous estimates for IIV of k_a. Two sampling times for the absorption phase may be not enough to guarantee a precise estimation of such parameter.

Results

		Non-hierarchical	Hierarchical (2 uncorrelated R.E.)	Hierarchical (2 correlated R.E.)
Emax model, well designed sequence	Informative	✓	✓	✓
	Uninformative	✓	✓	✓
Emax model, sub-optimal sequence	Informative	✓	✓	✓
	Uninformative	✓	✗	✗

When trials are well designed in terms of dose sequences and sampling points, an accurate estimation can be expected.

When dose sequence is poorly designed, only informative priors and an absence of IIV ensure accurate estimates. When uninformative priors are chosen, the estimate for IIV of ED_{50} results biased.

Discussion

Discussion

- The Bayesian sequential integration is an appealing approach, as it allows to analyze each study immediately instead of waiting for the end of data collection

- 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 parameter identifiability issues
  - The specification of informative prior distributions
  - The allocation of random effects on parameters that are not highly correlated with other parameters

- **Major limitation**: Parameter correlation matrix is not incorporated during the sequential integration. This is object of further research.

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Thank you for your attention!

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