# Assessing systemic drug exposure in repeated dose toxicity studies in the case of complete and incomplete sampling

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# Outline

# Introduction

Repeated dose toxicity studies

- contribute to the development of safe medicinal products for human use
- are performed prior application of a compound in clinical trials
- are essential for the design of subsequent studies and for safety assessment in humans

# Toxicokinetics

Objective: Does systemic exposure change?

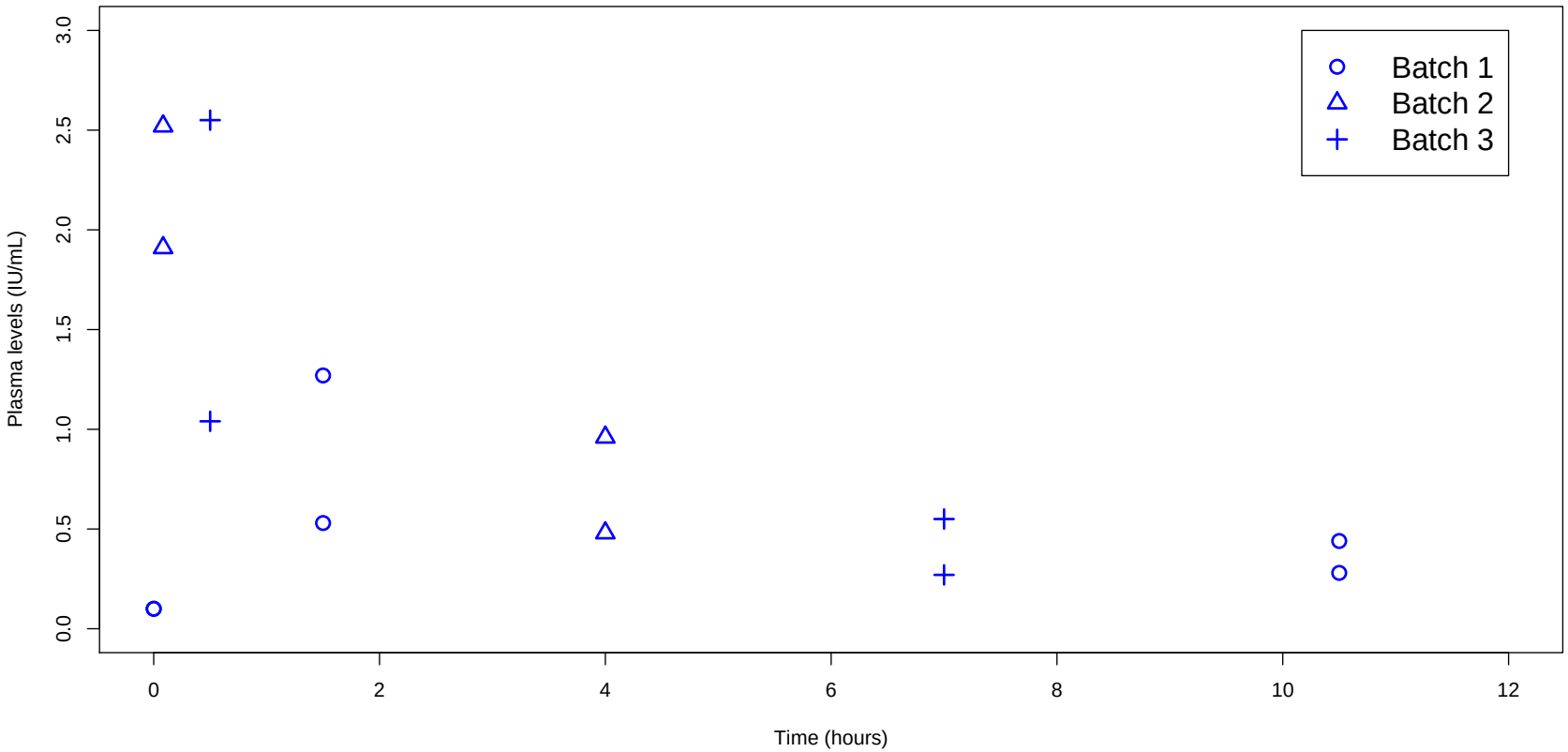
- Increase: damage to the eliminating organs, accumulation, non-linear kinetics, ...
- Decrease: auto-induction of metabolizing enzymes, neutralizing antibody formation to a biological, ...

Commonly used parameter for assessing drug exposure is the area under the concentration versus time curve (AUC).

# Sampling designs

- Complete data design: blood samples are available for each animal at all time points
- Batch design: each animal contributes samples at some, but not all time points
- Serial sampling design: each animal contributes exactly one sample

Figure 1: Example of a batch design after first administration



# The model

Concentration for animal $i$ at time $t$ after administration $k$:

$$Y_{itk} = \mu_{tk} + \epsilon_{itk},$$

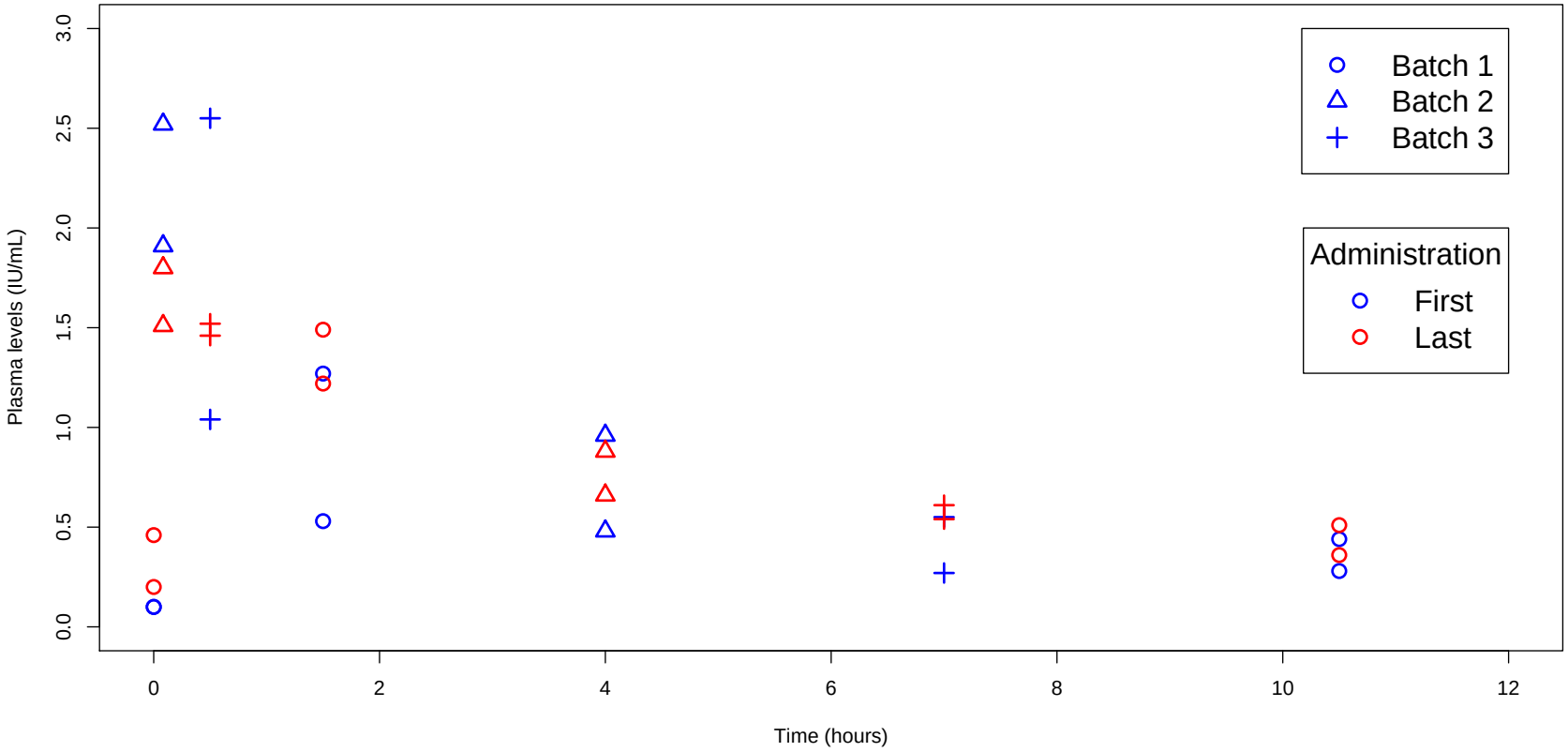
where $\epsilon_{itk} \sim G_{tk}$ with $1 \leq j \leq J$.

# Limitations

We consider the case where:

- A specific time point is used in exactly one batch
- Every animal belongs to exactly one batch and has measurements at all time points of this batch
- Animals, time points studied and batches are identical at first and repeated administration

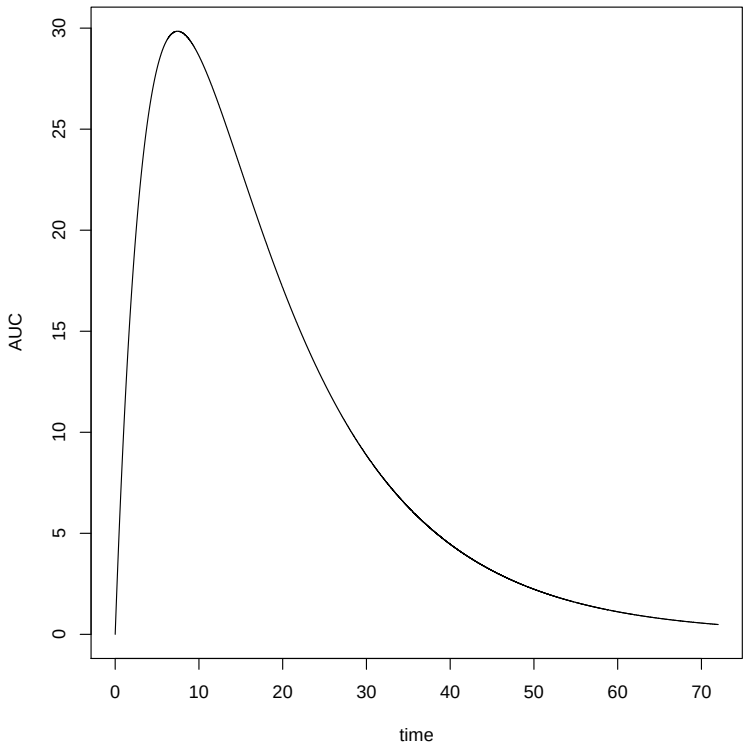
Figure 2: Example of a batch design after first and last administration



# Theoretical AUC

The theoretical AUC from 0 to the last observed time point for treatment $k$ is

$$AUC_k = \int_0^{t_{last}} \mu_{tk} dt.$$

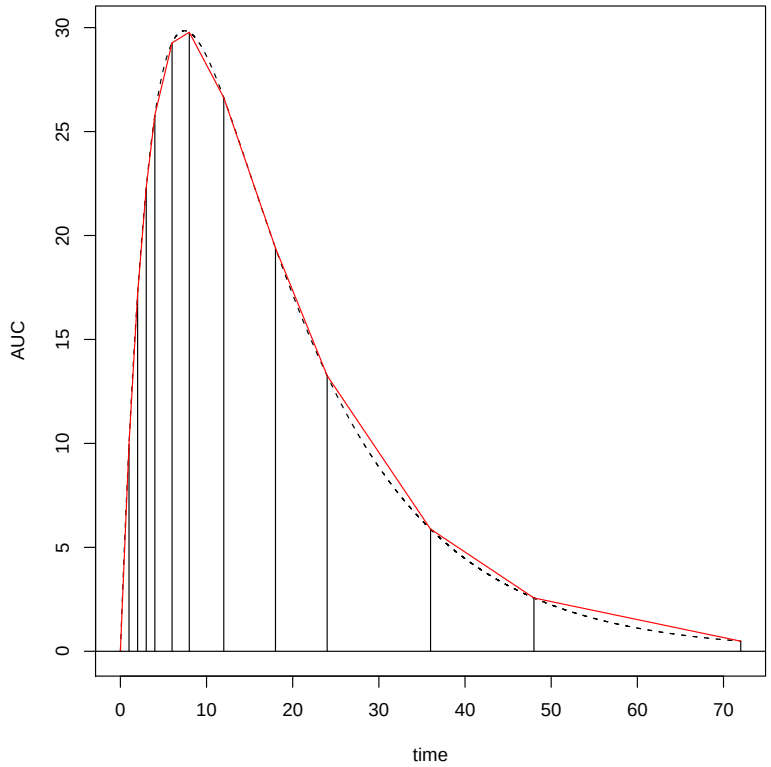


# Using the linear trapezoidal rule

$$AUC_k = \sum_{j=1}^{J} w_j \mu_{t_j k}$$

The weights, $w_j$, equal

$$\begin{aligned} w_1 &= \frac{1}{2}(t_2 - t_1) \\ w_j &= \frac{1}{2}(t_{j+1} - t_{j-1}) \\ w_J &= \frac{1}{2}(t_J - t_{J-1}) \end{aligned}$$



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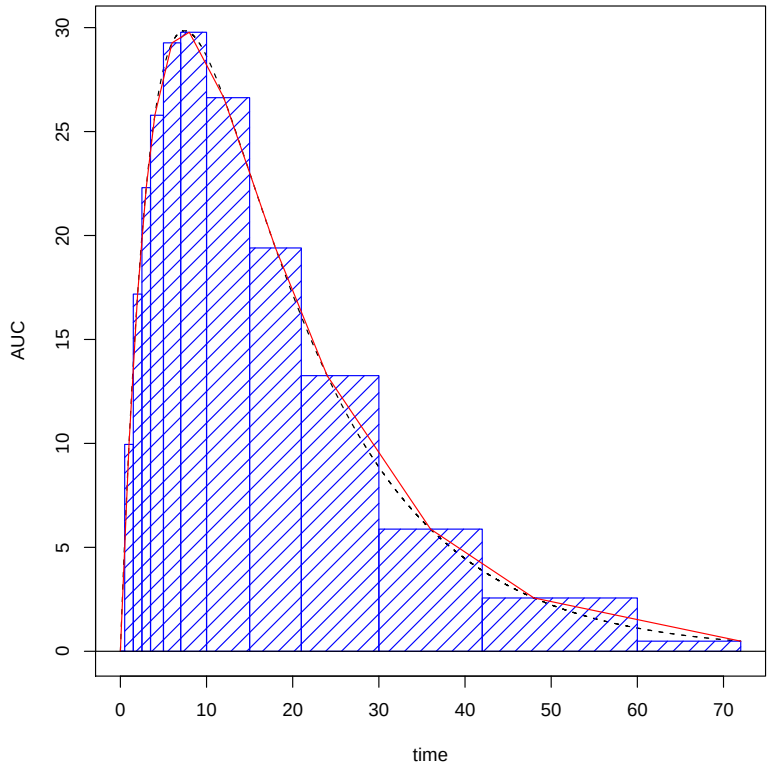
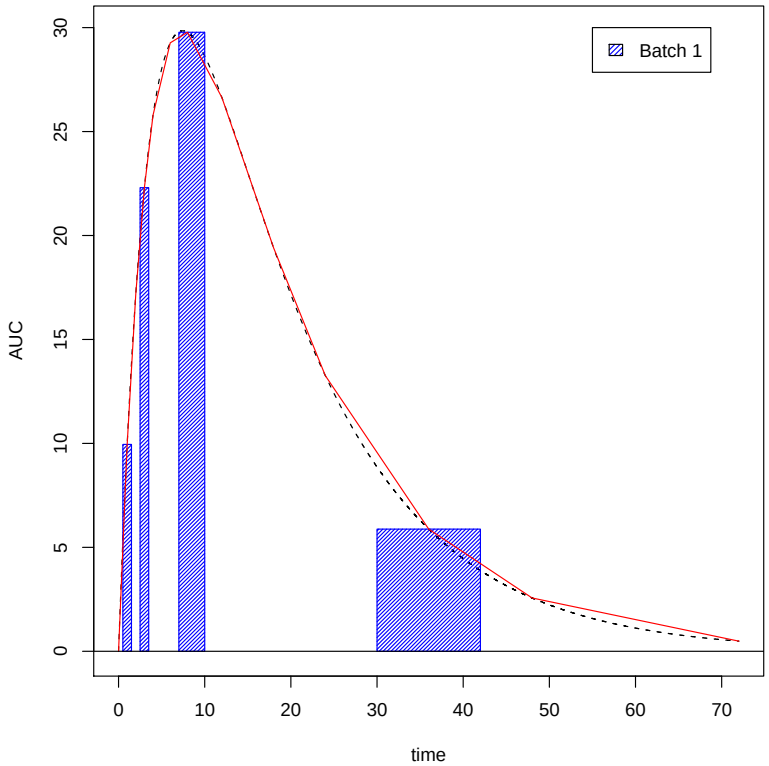


# Estimating the AUC

- $B$ batches with $n_b$ animals
- $J_b$ are indices of time points investigated in batch $b$

Partial AUC of animal $i$ of batch $b$:

$$\hat{A}_{b_i k} = \sum_{j \in J_b} w_j Y_{i t_j k}$$



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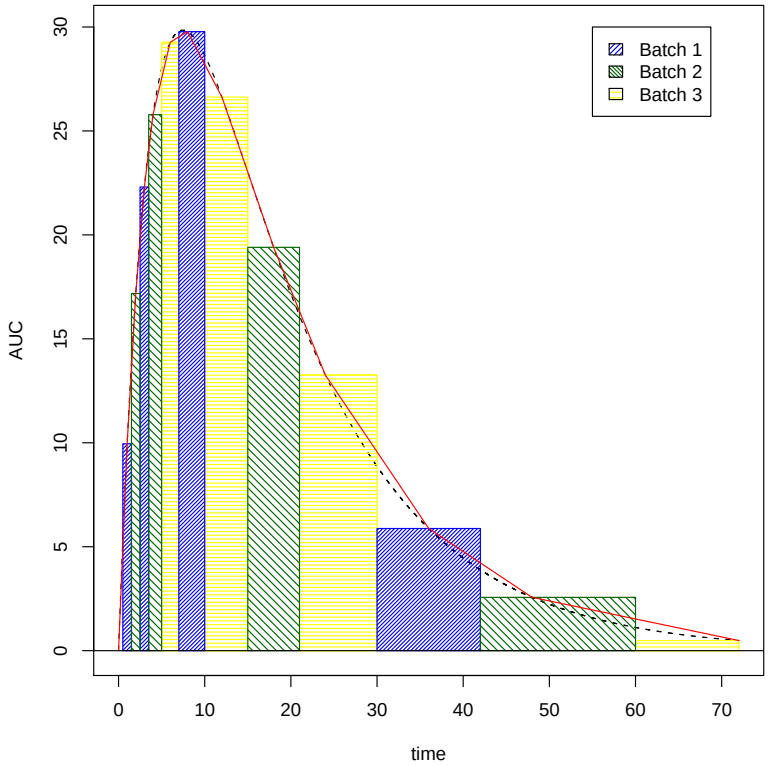
The total AUC can be estimated:

$$\widehat{AUC}_k = \sum_{b=1}^{B} \frac{1}{n_b} \sum_{i=1}^{n_b} \hat{A}_{b_i k}$$



# Estimating the AUC

Jaki and Wolfsegger (2009) showed that for equal sample size in each batch, $n_b = n$, $\widehat{AUC}_k \xrightarrow{d} N\left(AUC_k, \xi_k^2\right)$ with

$$\xi_k^2 = \frac{1}{n} \sum_{b=1}^{B} \sum_{j \in J_b} \sum_{l \in J_b} w_j w_l \sigma_{t_j t_l k}$$

which can be estimated by (Yeh 1990; Holder *et al.* 1999)

$$\hat{\xi}_k^2 = \sum_{b=1}^{B} \frac{1}{n_b(n_b-1)} \sum_{i=1}^{n_b} \left( \hat{A}_{b_i k} - \frac{1}{n_b} \sum_{l=1}^{n_b} \hat{A}_{b_i k} \right)^2$$

# Confidence interval for the difference between AUCs

Using the paired structure of the experiment:

$$\begin{aligned}\hat{\delta} &= \sum_{b=1}^{B} \frac{1}{n_b} \sum_{i=1}^{n_b} \hat{A}_{b_i k} - \sum_{b=1}^{B} \frac{1}{n_b} \sum_{i=1}^{n_b} \hat{A}_{b_i 1} \\ &= \sum_{b=1}^{B} \frac{1}{n_b} \sum_{i=1}^{n_b} \hat{\delta}_{b_i}\end{aligned}$$

where $\hat{\delta}_{b_i} = \hat{A}_{b_i k} - \hat{A}_{b_i 1}$.

# Confidence interval for the difference between AUCs

$$
\begin{aligned}
E(\hat{\delta}) &= AUC_k - AUC_1 \\
V(\hat{\delta}) &= \vartheta^2 = \xi_k^2 + \xi_1^2 - 2\xi_{1k} \\
\widehat{V}(\hat{\delta}) &= \hat{\vartheta}^2 = \sum_{b=1}^{B} \frac{1}{n_b(n_b-1)} \sum_{i=1}^{n_b} \left( \hat{\delta}_{b_i} - \frac{1}{n_b} \sum_{l=1}^{n_b} \hat{\delta}_{b_l} \right)^2 \\
\hat{\xi}_{1k} &= \frac{1}{2}(\hat{\xi}_k^2 + \hat{\xi}_1^2 - \hat{\vartheta}^2) \\
\hat{\delta} &\xrightarrow{d} N\left(AUC_k - AUC_1, \vartheta^2\right)
\end{aligned}
$$

# Confidence interval for the ratio of AUCs

A $1-\alpha$ Fieller-type confidence interval (CI) for the ratio is:

$$\left[\hat{\Delta}+\left(\frac{c}{1-c}\right)\left(\hat{\Delta}-\frac{\xi_{k1}}{\xi_1^2}\right)\pm \frac{t_{1-\frac{\alpha}{2},\nu}}{\widehat{AUC}_1(1-c)}\sqrt{\xi_k^2-2\hat{\Delta}\xi_{k1}+\hat{\Delta}^2\xi_1^2-c\left(\xi_k^2-\frac{\xi_{k1}^2}{\xi_1^2}\right)}\right]$$

where $c=\xi_1^2\widehat{AUC}_1^{-2}t_{1-\frac{\alpha}{2},\nu}^2$

# Methods compared

- Fieller approach using covariance between AUCs (Fieller-dep-t) based on t-distribution
- Fieller approach assuming independent AUCs based on a t-distribution (Fieller-ind-t)
- Asymptotic Fieller interval based on normal distribution (Fieller-dep-z)
- Asymptotic Wald-type interval based on the asymptotic normal distribution of the ratio (Asymptotic)

# Data generation

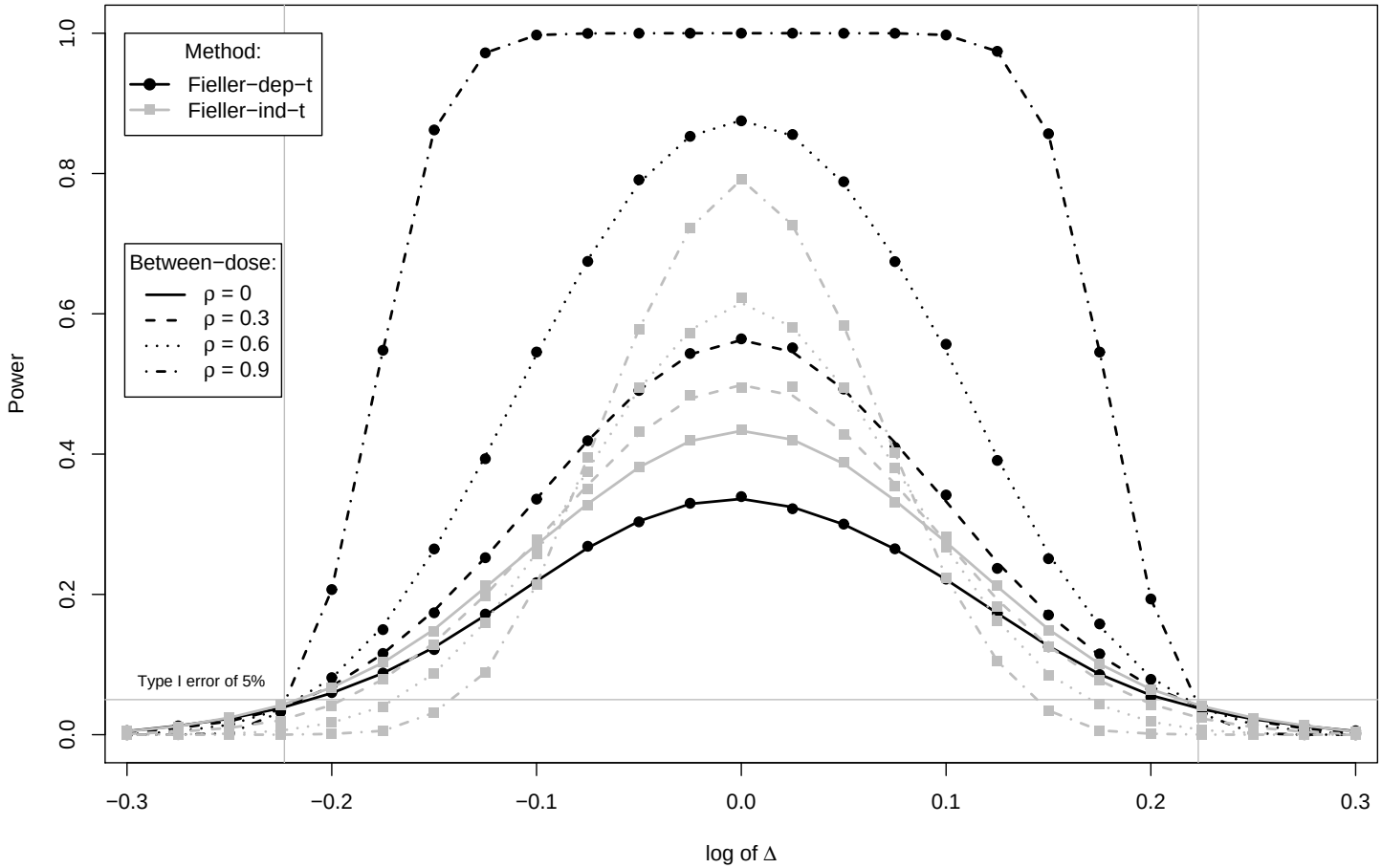
- One-compartmental model after IV bolus administration
- 3 batches with 3 time points with $n = 3$ and $6$
- Within-batch correlations: dependence of measurements between time points per animal
- Between-dosing correlations: dependence of measurements between first and last dosing per animal
- CV of $Y_{it_jk}$ was set to 20% for all time points greater zero and follow a log-normal distribution

Table 1: Empirical coverage for log-normally distributed drug levels with identical coefficient of variation of 20% for $\Delta = 1$ and using a nominal coverage of 90%

| Intra-animal correlation | | | Method | | | |
|---|---|---|---|---|---|---|
| within-batch | between-dosing | N | Fieller-dep-t | Fieller-ind-t | Fieller-dep-z | Asymptotic |
| 0 | 0 | 3 | 0.9227 | 0.9159 | 0.8497 | 0.8479 |
| | | 6 | 0.9051 | 0.9065 | 0.8794 | 0.8786 |
| 0.3 | 0 | 3 | 0.9233 | 0.9152 | 0.8489 | 0.8468 |
| | | 6 | 0.9045 | 0.9057 | 0.8786 | 0.8775 |
| | 0.3 | 3 | 0.9215 | 0.9698 | 0.8473 | 0.8446 |
| | | 6 | 0.9064 | 0.9716 | 0.8801 | 0.8783 |
| 0.6 | 0.3 | 3 | 0.9239 | 0.9617 | 0.8480 | 0.8445 |
| | | 6 | 0.9048 | 0.9596 | 0.8791 | 0.8769 |
| | 0.6 | 3 | 0.9243 | 0.9936 | 0.8495 | 0.8457 |
| | | 6 | 0.9050 | 0.9969 | 0.8790 | 0.8766 |
| 0.9 | 0.3 | 3 | 0.9226 | 0.9544 | 0.8483 | 0.8455 |
| | | 6 | 0.9041 | 0.9530 | 0.8778 | 0.8756 |
| | 0.6 | 3 | 0.9212 | 0.9868 | 0.8458 | 0.8421 |
| | | 6 | 0.9045 | 0.9903 | 0.8773 | 0.8751 |
| | 0.9 | 3 | 0.9241 | 0.9999 | 0.8501 | 0.8448 |
| | | 6 | 0.9047 | 1.0000 | 0.8788 | 0.8761 |

N per batch

Figure 3: Empirical power curves for a within-batch $\rho = 0.9$ and N=3 per batch



# Summary

- Maintains nominal coverage and was slightly conservative for small sample sizes per batch
- Uniformly superior in power to the corresponding interval not incorporating the dependence between the AUCs as long as a correlation exists
- Measure for variability while additionally allowing to formally test for difference as well as for equivalence
- Framework that can be applied to a wide range of investigations where changes between pre- and post values are of interest

# References

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