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Univariate and multivariate Bioequivalence of PK parameters

Thomas Jaki & Philip Pallmann

9:00 – 10:00	Non-compartmental estimation of PK parameters	Jaki
10:00 – 10:20	COFFEE BREAK	
10:20 – 10:40	Univariate Bioequivalence	Pallmann
10:40 – 10:50	Multiplicity and Bioequivalence	Jaki
11:50 – 11:20	Multivariate Bioequivalence	Pallmann
11:20 – 11:40	COFFEE BREAK	
11:40 – 12:30	Multivariate Bioequivalence	Pallmann

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Non-compartmental estimation of PK parameters

Thomas Jaki

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Medical and Pharmaceutical Statistics Research Unit

Aims for the next hour

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- Describe the role of PK in bioequivalence
- Determining sampling time points
- Discuss estimation of the AUC for different sampling designs
- Illustrate methods **using R**

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Pharmacokinetics (PK)

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- Pharmacokinetic studies what the body does to a drug
- Characterization of Absorbtion, distribution, metabolism and excretion (ADME)
- Frequently measures the concentration of the drug in the blood or plasma

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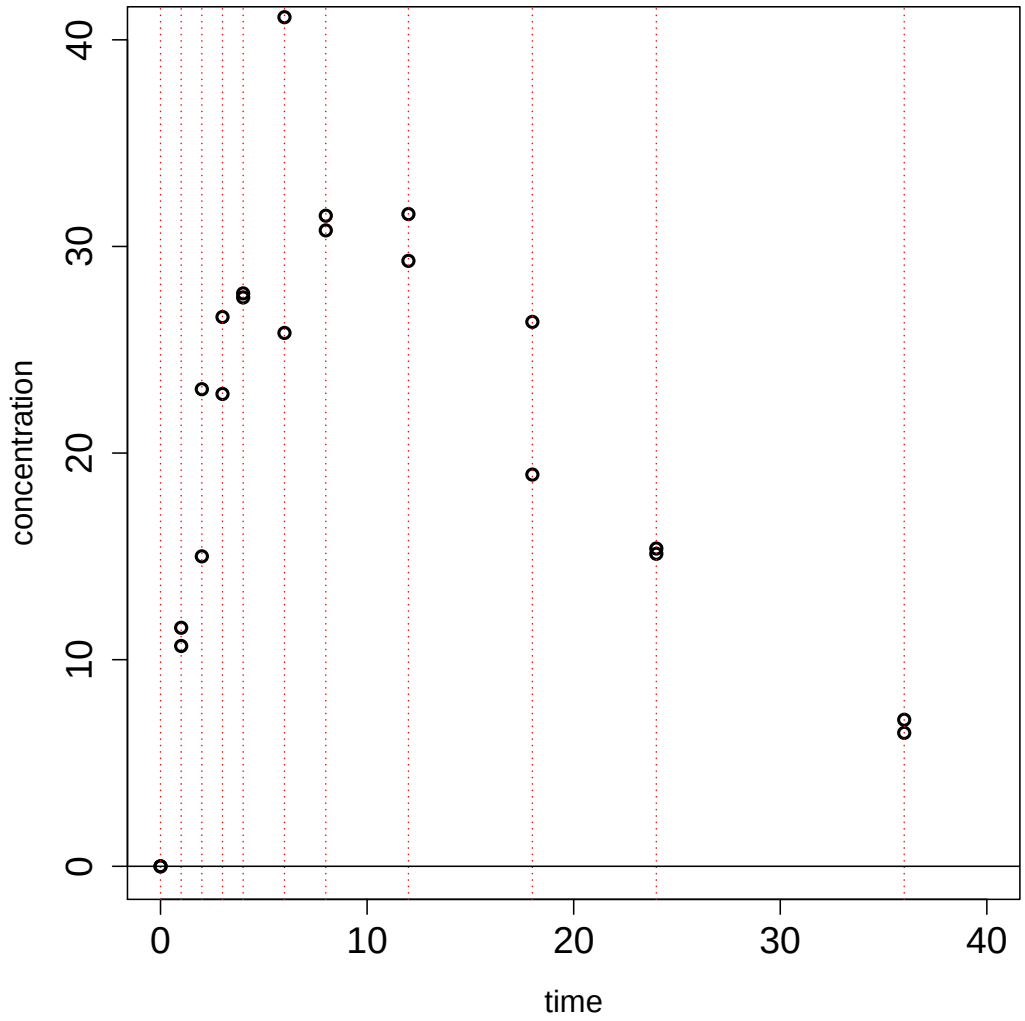
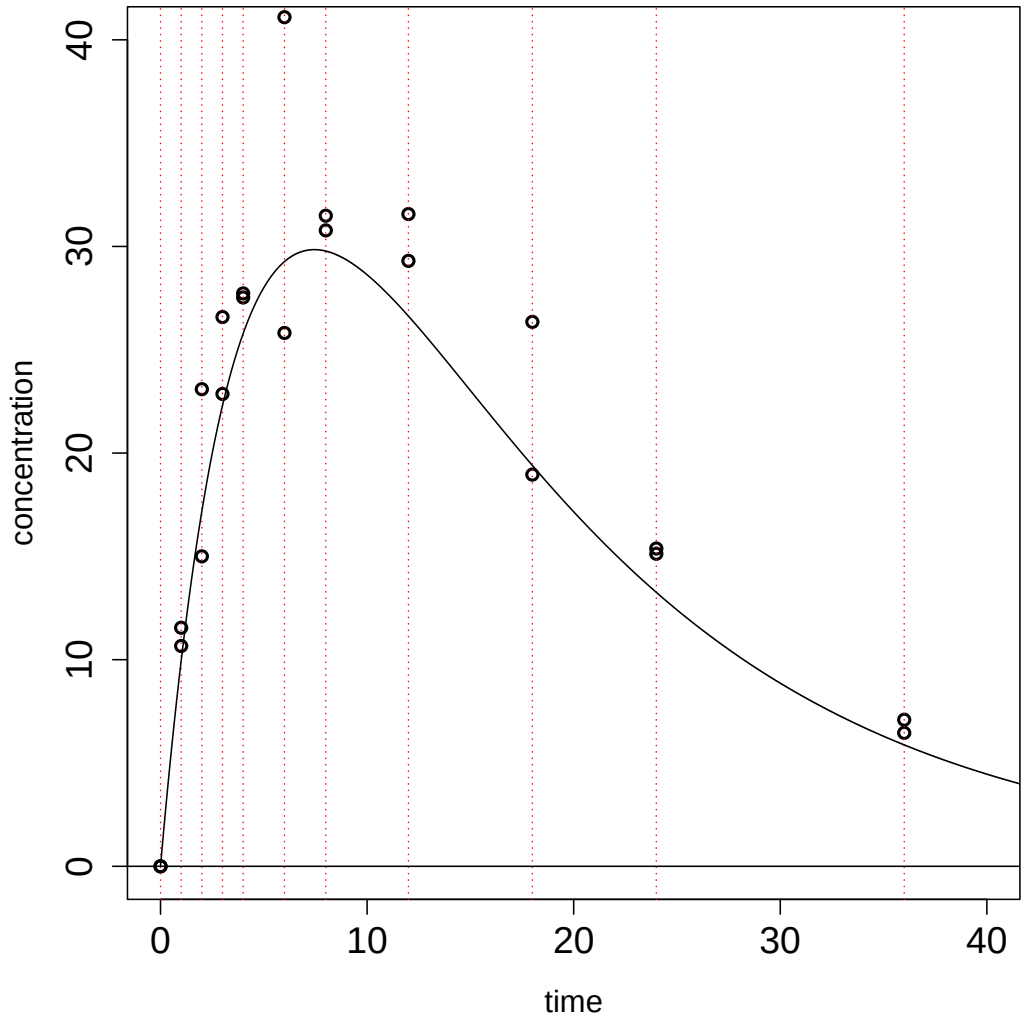
Concentration versus time data



Concentration versus time data



Compartmental models

A one compartmental model with first order absorption and first order elimination:

$$X_{it} = \frac{FDk_a}{V(k_a - k_e)} \left(\exp(-k_e t) - \exp(-k_a t)\right) + \epsilon_{it}$$

- D... dose administered
- F... bioavailability
- V... Apparent volume of distribution that reflects the extent of drug distribution within the compartment
- Some PK parameters are functions of the model parameters

Compartmental models

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+ Possible to simulate/predict new drug levels
+ Measurements do not have to be taken in a structured manner
+ Gives often more understanding of drug behavior

— Model development difficult, model validation even more
— Assumes a specific distribution for the concentrations
— Model fitting issues (convergence, local minima, ...)

Non-compartmental approach (NCA)

Under the additive heteroscedastic model the observed concentration for subject i at time t is

$$Y_{it} = \mu_t + \epsilon_{it},$$

where $\epsilon_{it} \sim G_t$.

Non-compartmental approach (NCA)

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+ Does not require knowledge of model
+ Few assumptions necessary
+ Yields PK parameters directly

— Data structure important
— Can not perform simulation/predictions of new drug levels
— Often less efficient than compartmental models

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Recommended for bioequivalence assessment
(CPMP/EWP/QWP/1401/98 Rev. 1)

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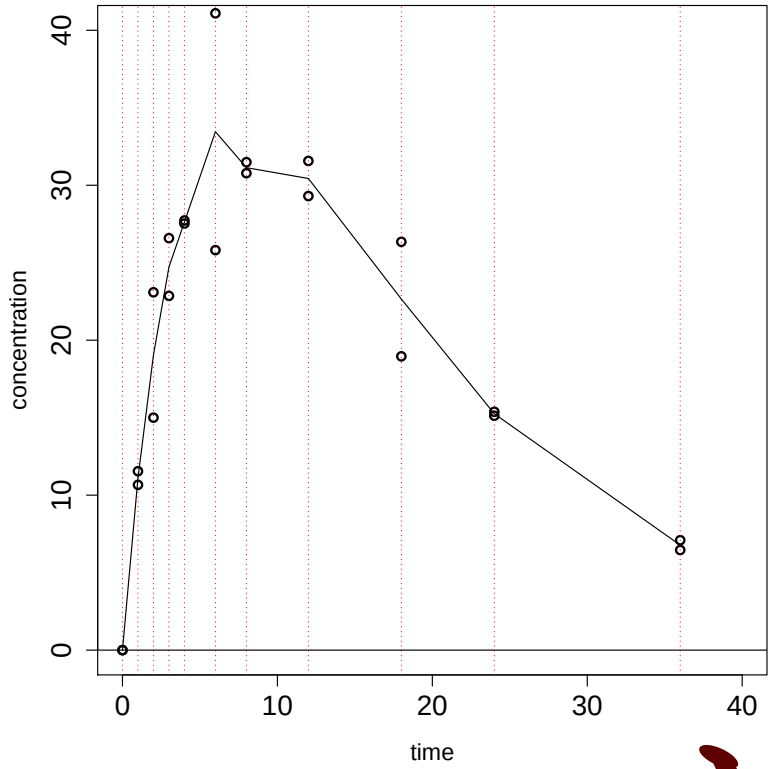
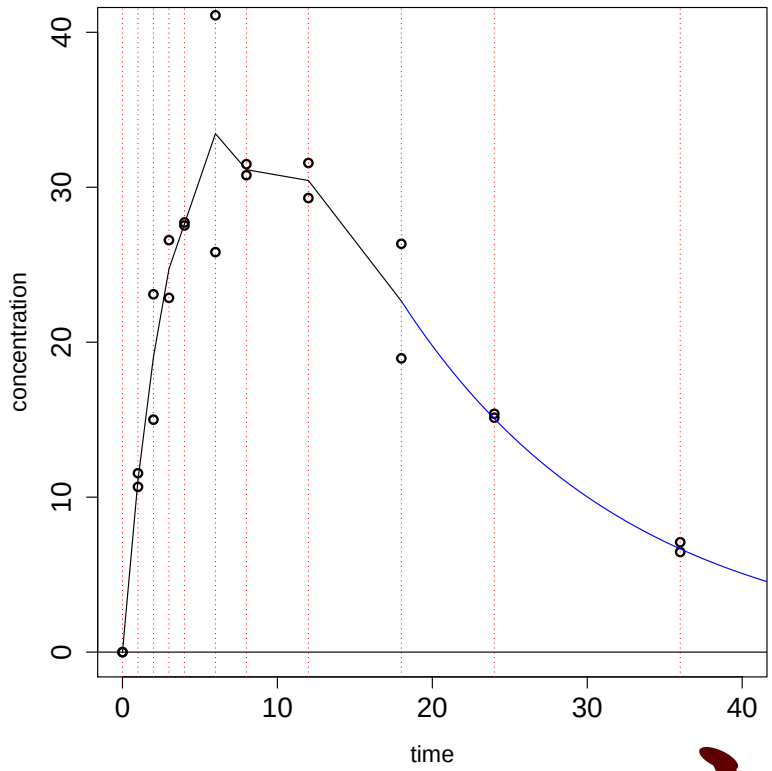
Describing the data (NCA)

- Uses linear approximation between measured time points

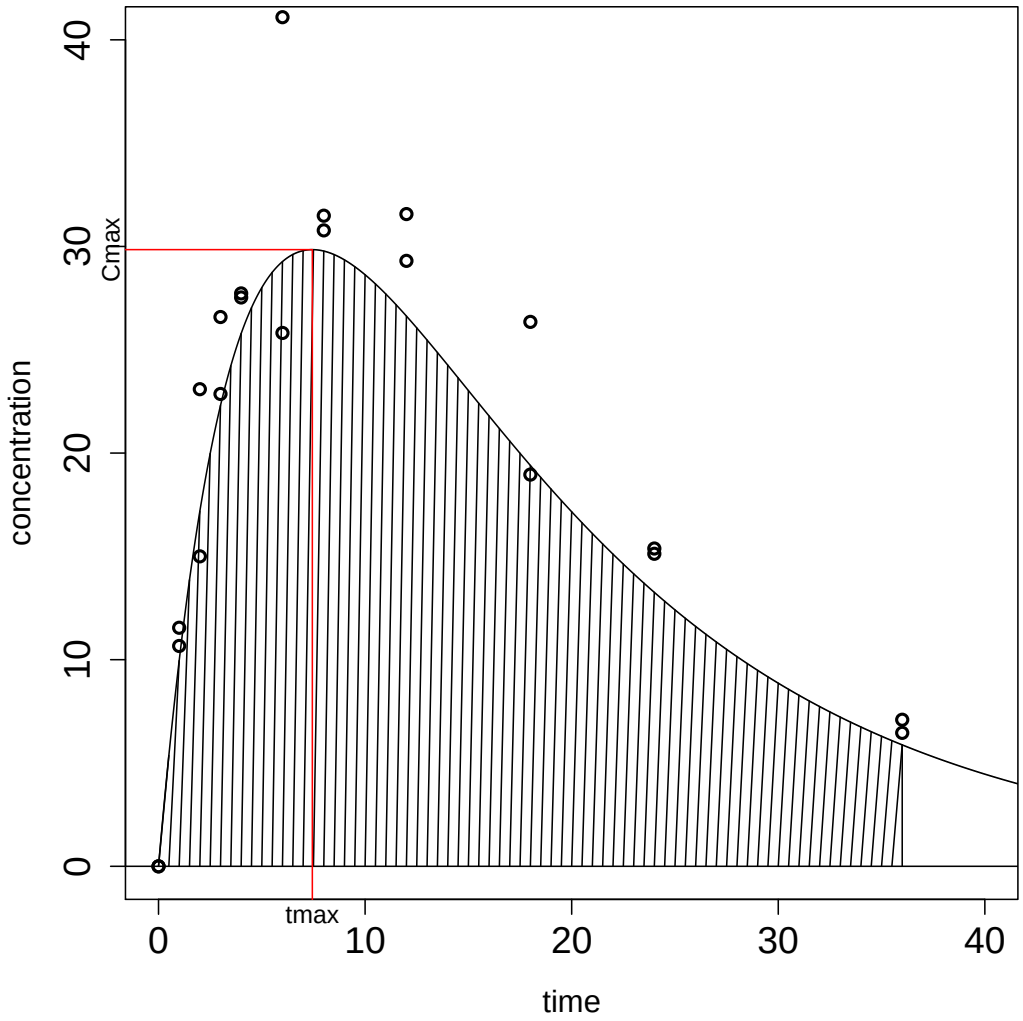


Describing the data NCA‘

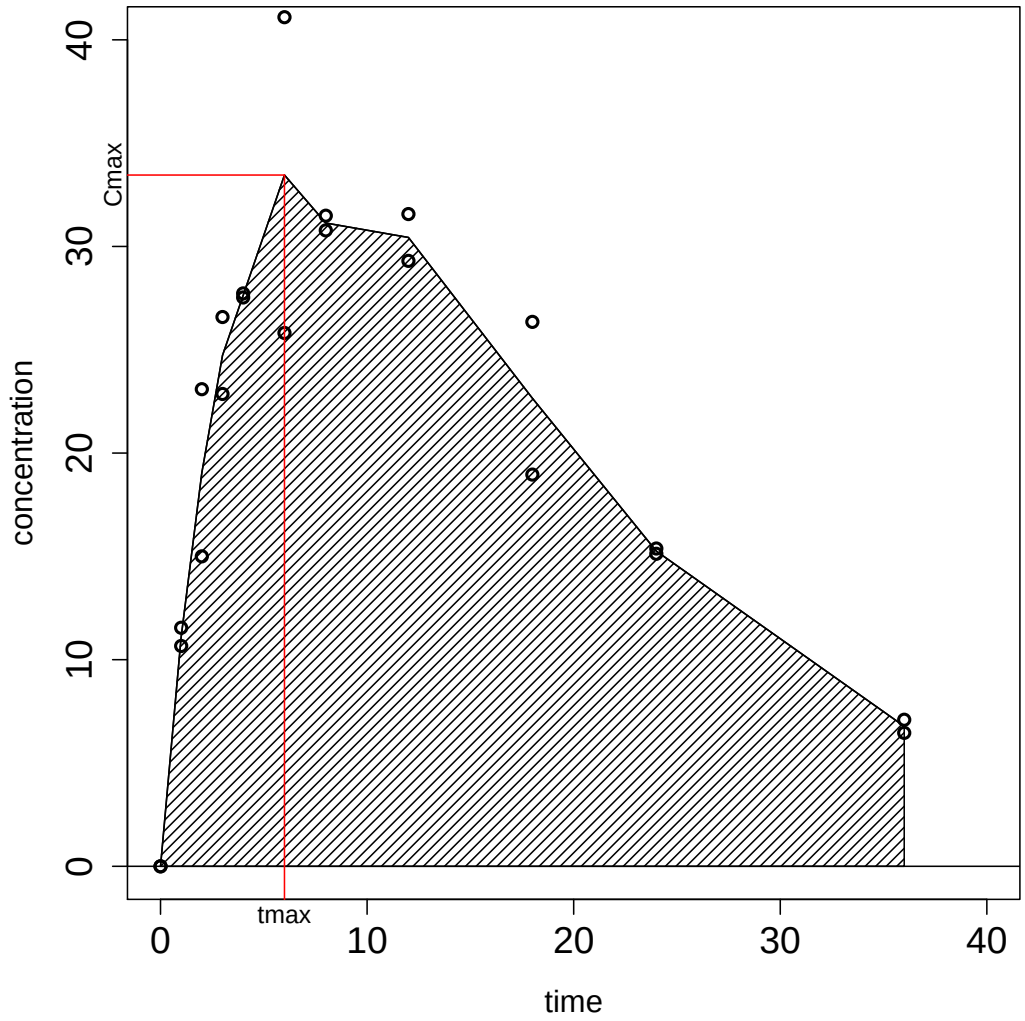
- Uses linear approximation between measured time points
- Extrapolates to ∞
  - typically log-linear



Pharmacokinetic parameters



Pharmacokinetic parameters



Sampling times

- Selection of time points is an important design consideration
  - Should be carefully planned to obtain maximum information for a minimum number of samples
- Suggestions for single dose studies (e.g. Cawello 2003, pp 133-134)
  - Take as many samples as possible
  - The observation period should be about three to five times of the supposed terminal half-life following tmax
  - Sample frequently at the beginning s
  - Take expert knowledge and ethical/financial constraints into account
  - Optimal designs Barnett et al (2018) and R package `microsamplingDesign`

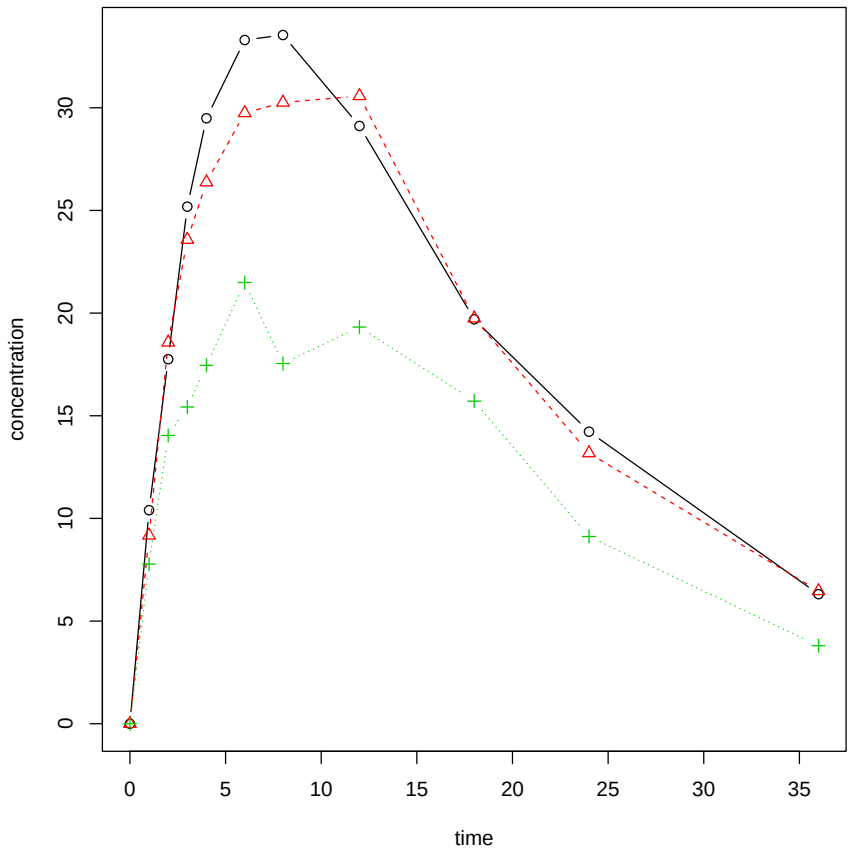
Sampling design

- Complete data designs
  - Samples are available for each subject at all time points investigated
- Sparse sampling designs
  - Used due to restrictions in blood volume
  - Each subject contributes measurements at some but not all time points
  - Batch design, serial sampling design

Analysis: Complete data design

Uses a two-stage approach:

- Stage 1: Calculation of PK parameters for each subject
- Stage 2: Individual estimates are used for inference



Summarizing individual PK parameters (Cawello, 2003)

Parameter	Arithmetic mean	Geometric mean	Median
Cmax		x	
tmax			x
AUCs		x	

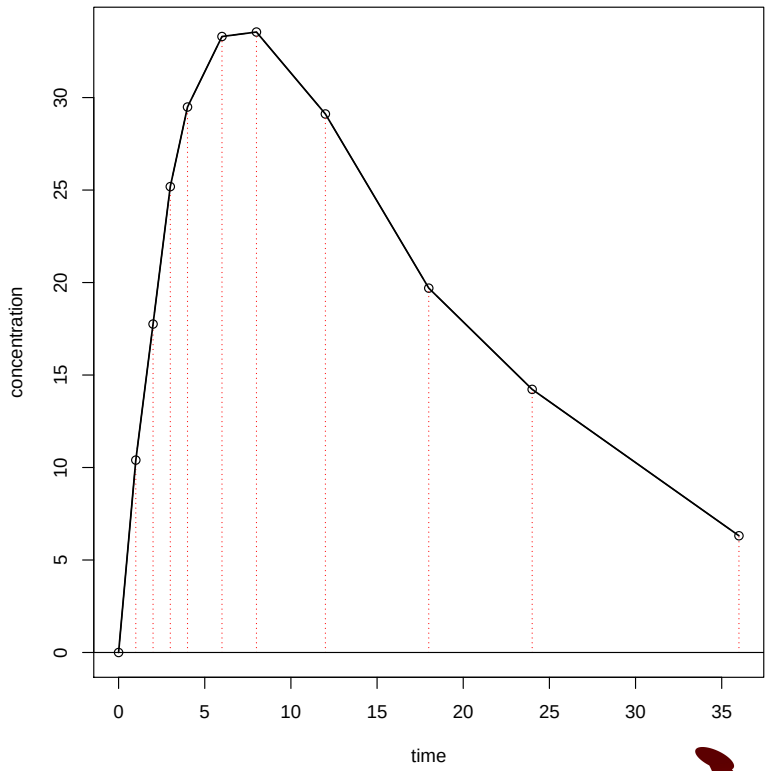
- Arithmetic mean: $\bar{X} = \frac{1}{n}\sum_{i=1}^{n} X_i$
- Geometric mean: $\tilde{X} = \sqrt[n]{X_1 X_2 \ldots X_n} = exp(\frac{1}{n}\sum_{i=1}^{n} \log X_i)$
  - Can be found by finding the mean of the log-transformed values and exponentiating
  - Comparisons can be based on t-test on transformed values

Estimating the AUC

$$\widehat{AUC}_i = \sum_{j=1}^{J} w_j X_{t_j i}$$

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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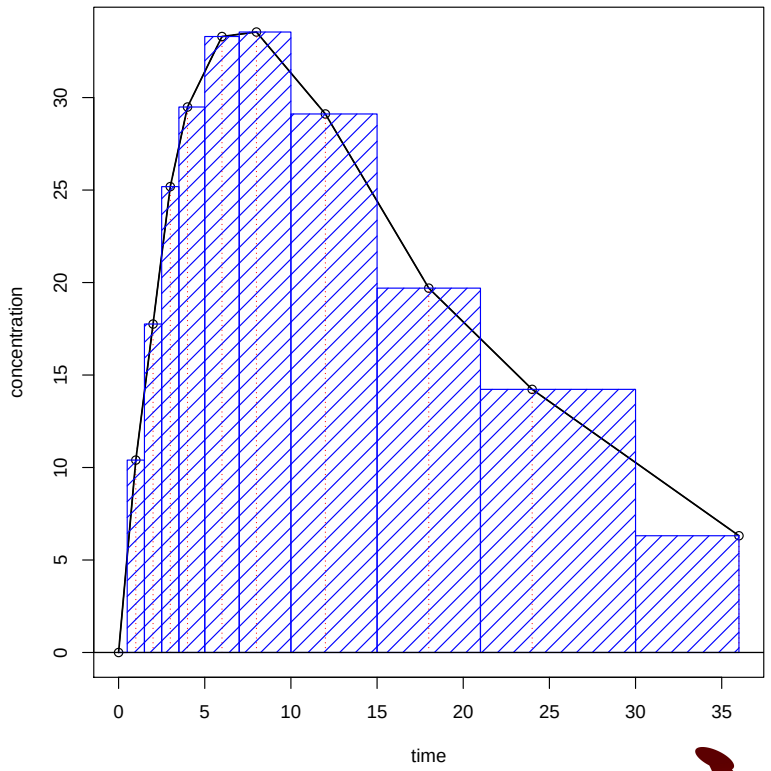
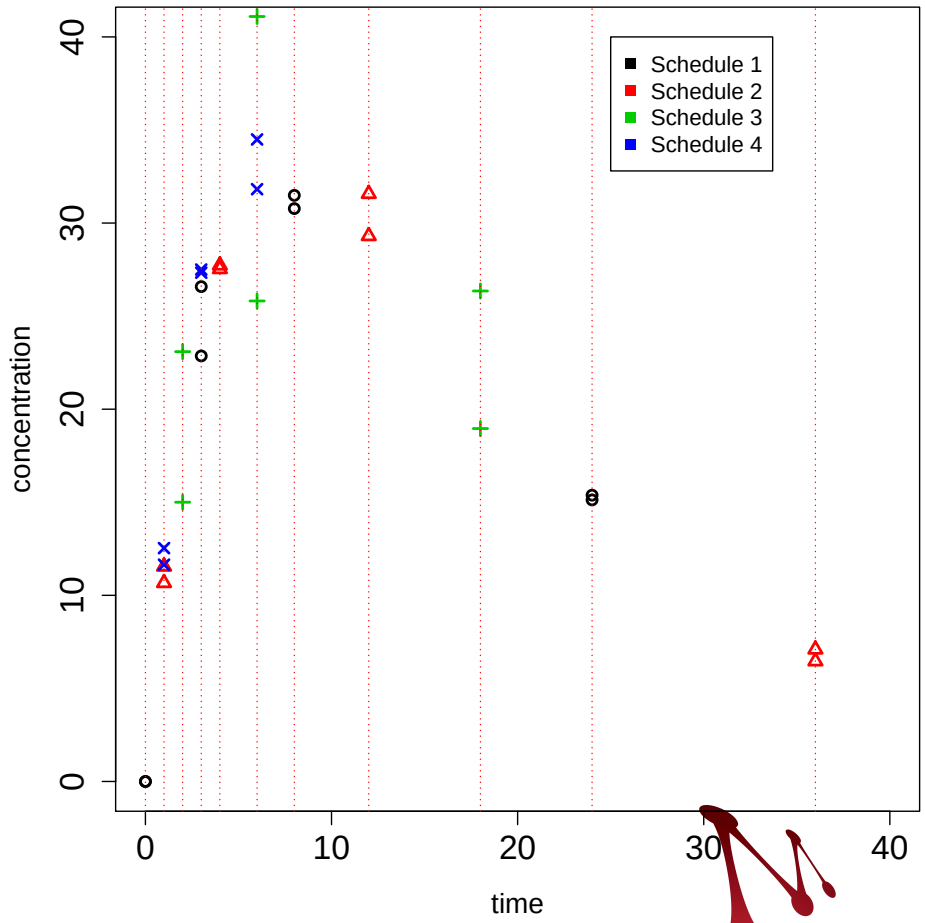


A sparse sampling design

(Jaki & Wolfsegger, 2012)

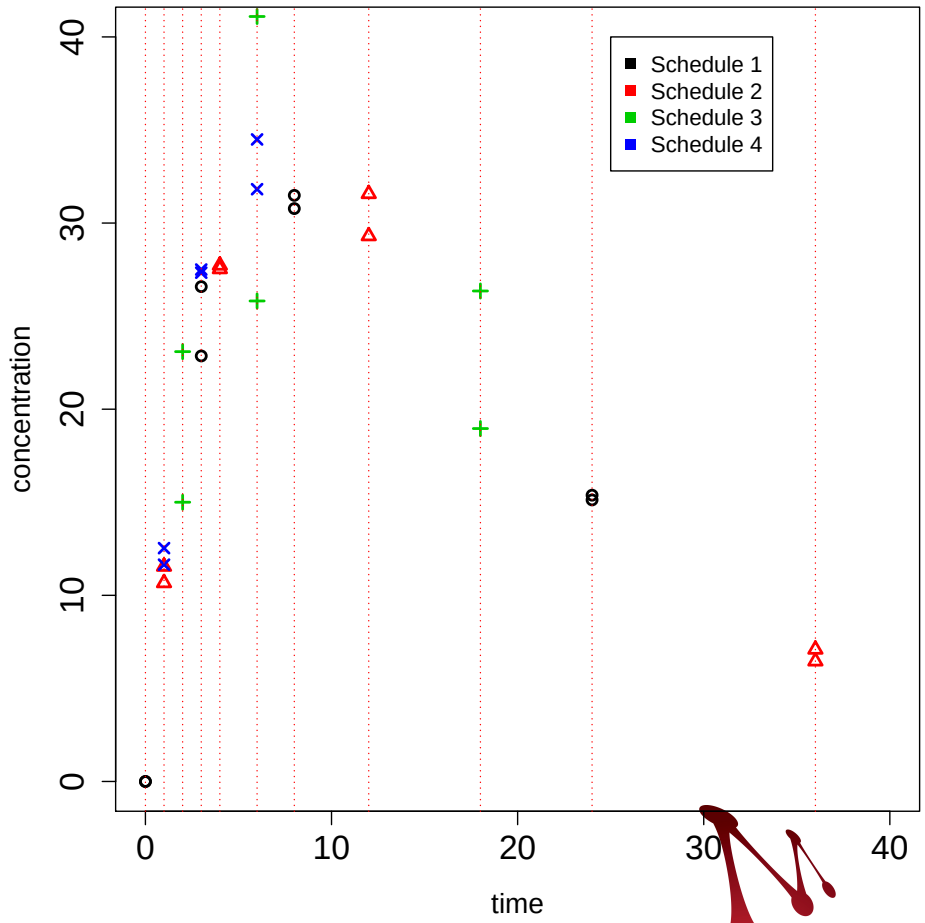
- Each subject is measured at at least 1 time point
- At least two subjects measured for each sampling schedule



A sparse sampling design

(Jaki & Wolfsegger, 2012)

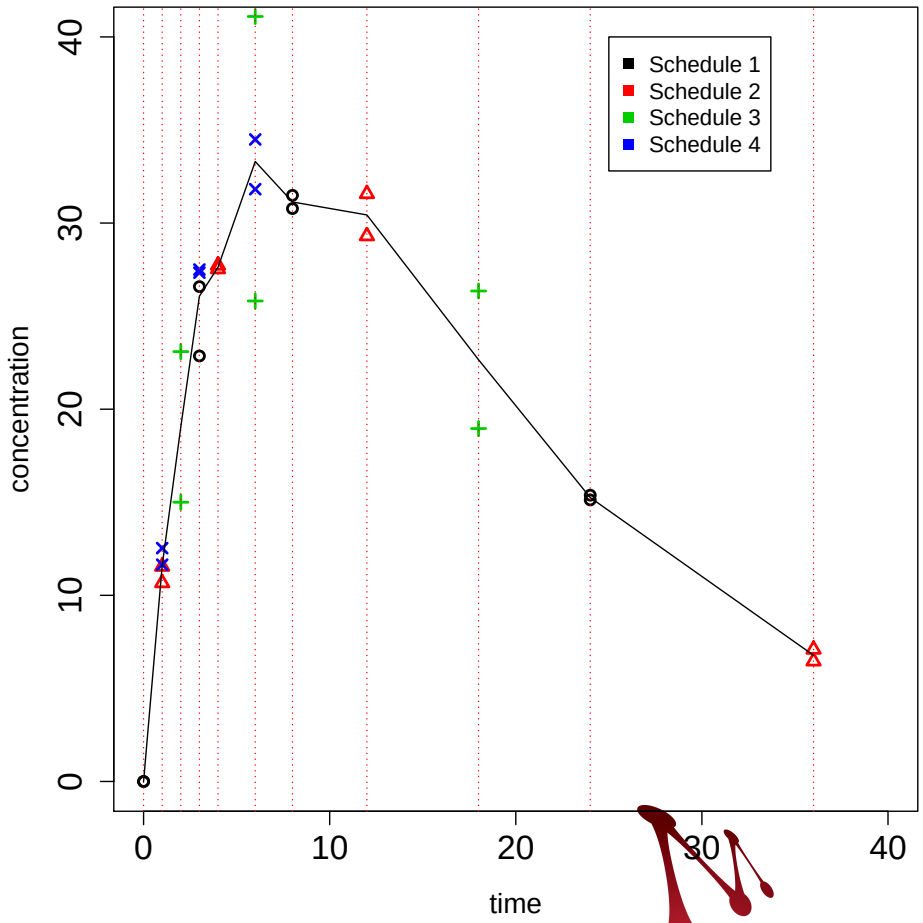
- Each subject is measured at at least 1 time point
- At least two subjects measured for each sampling schedule
- Other common designs are special cases
- Useful for complete data design with missing data



Estimating the AUC

$$\widehat{AUC} = \sum_{j=1}^{J} w_j \bar{Y}_{t_j}$$

$$= \sum_{s=1}^{S} \frac{1}{n_s} \sum_{i=1}^{n_s} \sum_{j \in J_s} \frac{n_s}{N_j} w_j Y_{ij}^s$$



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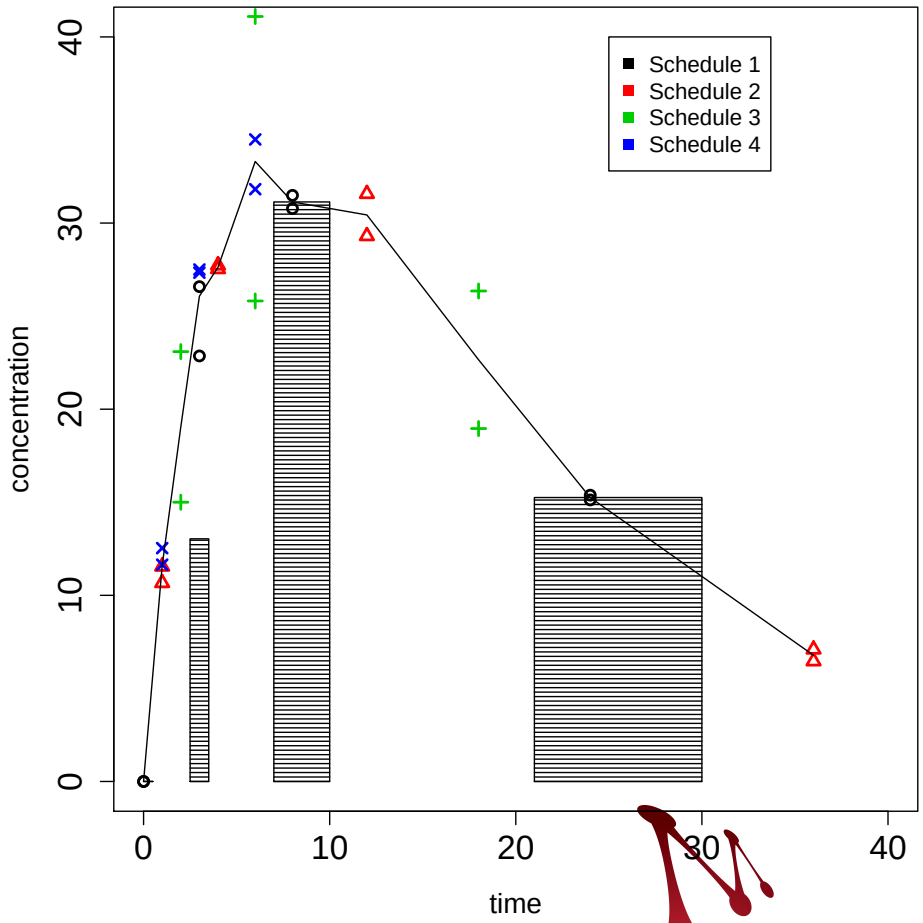

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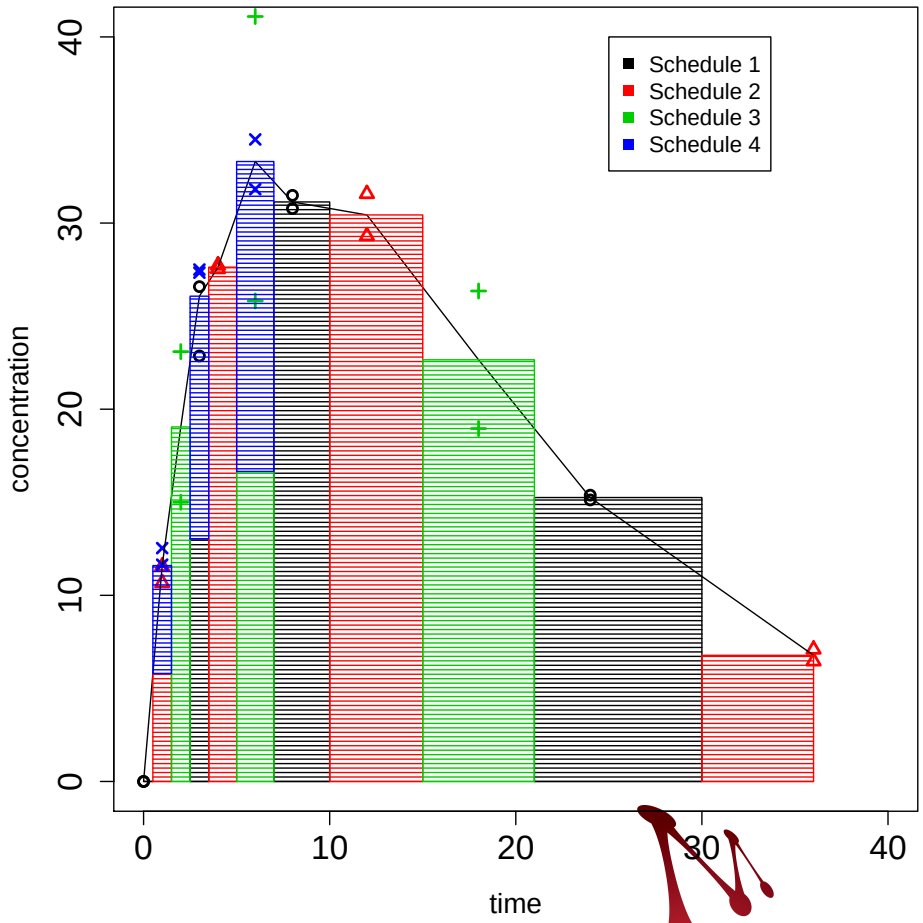

Variance

$$V\left[\widehat{AUC}\right] = \sum_{s=1}^{S} \frac{1}{n_s} \sum_{j \in J_s} \sum_{k \in J_s} \frac{n_s}{N_j} \frac{n_s}{N_k} w_j w_k \sigma_{jk}$$

$$\hat{V}\left[\widehat{AUC}\right] = \sum_{s=1}^{S} \frac{s_s^2}{n_s}$$

where s_s^2 is the sample variance of the individual contributions within schedule s.

Typical questions

- Are PK parameters different?
- Is exposure proportional to dose?
- Dose exposure change after repeated administration

$\Longrightarrow$ Can be answered by looking at difference or ratios

Inference based on ratio

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- Based around Fieller intervals (Fieller, 1954)
- Intervals around 1 indicate equal exposure
- Confidence intervals completely contained in [0.8,1.25] lead to rejection of hypothesis of inequivalence
- Available for dependent and independent parameters

R package `PK`

(Jaki & Wolfsegger, 2011)

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Core functions

- `auc`
  - Estimation AUC
  - Estimation of difference of AUCs
  - Confidence intervals of AUC and difference of AUCs
- `nca` - estimation of a number of PK parameters
  - Estimation of other PK parameters
  - Confidence intervals for singe parameters
- `eqv`
  - Estimation ratio of AUCs
  - Confidence intervals for the ratio

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Main arguments

- `data` - Data frame with concentrations, time and possibly group
  - Alternative: `conc`, `time` and `group`
- `method`: type of interval used
- `design`
  - All designs based on batch design
  - Individual AUCs in complete data design possible

Other functions

- `plot` visualises data
- `test` performs hypothesis test
- `estimator` - extracts point estimate
- `ci` - extracts confidence interval

Example

(from Nedelman *et al.*, 1995)

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Background: CPI975 was administered once to 4 treatment groups (2 sexes and 2 dose levels) and concentrations measured at 5 time points post dose.

Task I: Estimate the individual AUCs and visualize the results

Task II: Estimate the average AUC and evaluate if differences between sexes exist

Task III: Does dose-proportionality hold?

Example: Code

- Estimating individual AUCs

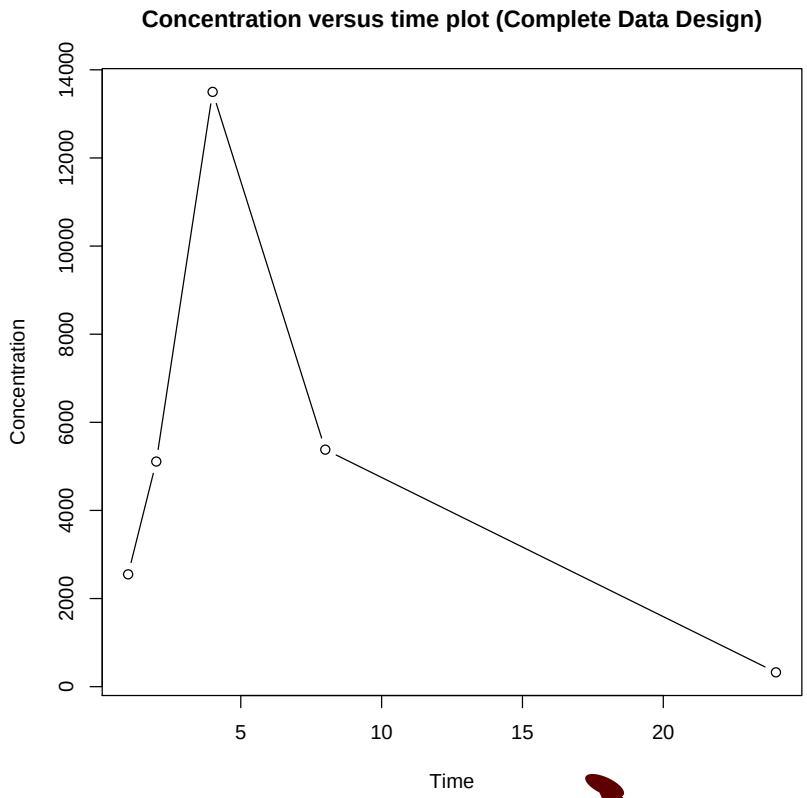
```
library(PK)
res <- data.frame(id=1:8, sex=rep(c("F","M"), each=4),
       dose=rep(rep(c(30,100) ,each=2), 2), auc=NA)

for(i in 1:8){
  ind_auc <- auc(data=subset(CPI,CPI$id==i),
          design="complete")
  res$auc[i] <- estimator(ind_auc)
}
```

Example: Results


```
res; plot(ind_auc)
```

	id	sex	dose	auc
1	1	F	30	13504.0
2	2	F	30	17751.0
3	3	F	100	49569.0
4	4	F	100	70503.0
5	5	M	30	20084.6
6	6	M	30	33447.0
7	7	M	100	75650.0
8	8	M	100	105848.0



Example: CIs

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- CIs for average AUCs
  - Using geometric mean of individual AUCs

```
t.test(x=log(res$auc), conf.level=0.95)

One Sample t-test

data:  log(res$auc)
t = 39.236, df = 7, p-value = 1.819e-09
alternative hypothesis: true mean is not equal to 0
95 percent confidence interval:
  9.914016 11.185616
sample estimates:
mean of x
 10.54982
```

Example: CIs

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- Using flexible batch design

```
avg_auc <- auc(data=CPI,design="batch",method="t")

Estimation for a batch design

                Estimate       SE              95% t-CI
AUC to tlast 48294.57 11737.53 (20539.72;76049.43)
```

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Summary

- Non-compartmental methods preferred in bioequivalence testing
- Non-compartmental methods for sparse sampling designs available
  - Methods can be used for complete data design with missing values
  - Confidence intervals for individual parameters, difference and ratio available
- Inference based on ratio preferred for ease of interpretation
- Relevant methods implemented in R package `PK`

References

Barnett H, Geys H, Jacobs T, Jaki T. (2018) Optimal Designs for Non-Compartmental Analysis of Pharmacokinetic Studies. Statistics in Biopharmaceutical Research. Published online ahead of print.

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Jaki T, Wolfsegger MJ (2011). Estimation of pharmacokinetic parameters with the R package PK. *Pharmaceutical Statistics.* 10(3), 284-288.

Nedelman JR, Gibiansky E, Lau DTW (1995). Applying Bailer's method for AUC confidence intervals to sparse sampling. *Pharmaceutical Research.* 12(1), 124-128.

Wolfsegger MJ, Jaki T (2009). Assessing systemic drug exposure in repeated dose toxicity studies in the case of complete and incomplete sampling. *Biometrical Journal.* 51(6), 1017-1029.