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
Non-compartmental estimation of PK parameters

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Aims for the next hour

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

- Pharmacokinetic studies what the body does to a drug
- Characterization of Absorption, distribution, metabolism and excretion (ADME)
- Frequently measures the concentration of the drug in the blood or plasma
Concentration versus time data
Concentration versus time data
A one compartmental model with first order absorption and first order elimination:

\[ X_{it} = \frac{FDk_a}{V(k_a - k_e)} (\exp(-k_et) - \exp(-k_at)) + \epsilon_{it} \]

- \(D\)…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

+ 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, ...)

Mathematics & Statistics
Lancaster University
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)

+ 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

Recommended for bioequivalence assessment (CPMP/EWP/QWP/1401/98 Rev. 1)
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Recommended for bioequivalence assessment
(CPMP/EWP/QWP/1401/98 Rev. 1)
Describing the data (NCA)

• Uses linear approximation between measured time points
Describing the data

NCA‘

- Uses linear approximation between measured time points
- Extrapolates to $\infty$
  - typically log-linear
Pharmacokinetic parameters

![Pharmacokinetic Parameters Diagram](image-url)
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
  • 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)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Arithmetic mean</th>
<th>Geometric mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>tmax</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>AUCs</td>
<td></td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

- Arithmetic mean: \( \bar{X} = \frac{1}{n} \sum_{i=1}^{n} X_i \)

- Geometric mean: \( \tilde{X} = \sqrt[n]{X_1 X_2 \ldots X_n} = \exp\left(\frac{1}{n} \sum_{i=1}^{n} \log X_i\right) \)
  - 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

\[ \hat{AUC}_i = \sum_{j=1}^{J} w_j X_{t_j} \]

The weights, \( w_j \), equal

\[
\begin{align*}
    w_1 &= \frac{1}{2} (t_2 - t_1) \\
    w_j &= \frac{1}{2} (t_{j+1} - t_{j-1}) \\
    w_J &= \frac{1}{2} (t_J - t_{J-1})
\end{align*}
\]
Estimating the AUC

\[ \hat{AUC}_i = \sum_{j=1}^{J} w_j x_{t_{ji}} \]

The weights, \( w_j \), equal

\[ w_1 = \frac{1}{2} (t_2 - t_1) \]
\[ w_j = \frac{1}{2} (t_{j+1} - t_{j-1}) \]
\[ w_J = \frac{1}{2} (t_J - t_{J-1}) \]
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

\[ \hat{AUC} = \sum_{j=1}^{J} w_j \bar{Y}_t \]

\[ = \sum_{s=1}^{S} \frac{1}{n_s} \sum_{i=1}^{n_s} \sum_{j \in J_s} \frac{n_s}{N_j} w_j Y_{ij} \]
Estimating the AUC

\[ \hat{AUC} = \sum_{j=1}^{J} w_j \bar{Y}_t \]

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Estimating the AUC

\[
\hat{AUC} = \sum_{j=1}^{J} w_j \bar{Y}_t_j
\]

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

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

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

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

⇒ Can be answered by looking at difference or ratios
Inference based on ratio

- 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
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 single parameters

• **eqv**
  - Estimation ratio of AUCs
  - Confidence intervals for the ratio
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
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

```r
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

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

<table>
<thead>
<tr>
<th>id</th>
<th>sex</th>
<th>dose</th>
<th>auc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>30</td>
<td>13504.0</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>30</td>
<td>17751.0</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>100</td>
<td>49569.0</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>100</td>
<td>70503.0</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>30</td>
<td>20084.6</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>30</td>
<td>33447.0</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>100</td>
<td>75650.0</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>100</td>
<td>105848.0</td>
</tr>
</tbody>
</table>

Concentration versus time plot (Complete Data Design)
Example: CIs

- CIs for average AUCs
  - Using geometric mean of individual AUCs
    
    ```r
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
    ```
• Using flexible batch design

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

Estimation for a batch design

<table>
<thead>
<tr>
<th>Estimate</th>
<th>SE</th>
<th>95% t-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC to tlast</td>
<td>48294.57</td>
<td>11737.53 (20539.72;76049.43)</td>
</tr>
</tbody>
</table>
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


