Introduction to population pharmacokinetics "pharmacometrics"

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Outline

- Introduction to pharmacometrics
- Structural modelling
  - Disposition kinetics
  - Semi-mechanistic models
  - Absorption models
- Variability
  - Inter-individual variability
  - Residual variability
- Covariate modelling
- Model diagnostics
- Antimalarial examples
Introduction to pharmacometrics

Pharmacometrics:
“the science of developing and applying mathematical and statistical models to characterize, understand and predict a drug’s pharmacokinetics, pharmacodynamics and biomarker-outcome behavior”[1]

- Pharmacokinetics
  "what the body does to the drug"
- Pharmacodynamics
  "what the drug does to the body"
- Biomarker-outcome behavior
  disease progression, relationship between biomarkers and clinical endpoints etc. ~

“All models are wrong but some are useful…”

George Box, PhD

Introduction to pharmacometrics

- Model-based view
  - Set of mathematical relationships
  - Separate components to describe complex systems
- To improve the description of pharmacological data
- To give a mechanistic understanding of the drug/human interaction (learning vs confirming)
- To explore and optimize dose regimens
- To explore and optimize future clinical trials
Introduction to pharmacometrics

- Information → Integration → Knowledge
  - Interpretation
  - Study design

- Data → Execution → Study
  - Observation

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Martin Bergstrand
Dissertation, UU, 2011
Introduction to pharmacometrics

PM Model

Integration
+ Facilitate integration of different sources of information
+ Inter-/extrapolation

Knowledge

Study design
+ Identify what to study
+ Design optimization
+ Trial simulation

Information

Interpretation
+ Facilitate mechanistic interpretation
+ Higher power for statistical inference

Data

Execution
+ Individualized dosing
+ Adaptive design

Study

Observation
Introduction to pharmacometrics

Population pharmacokinetics (POP-PK)

Non-compartmental analysis

- $C_{\text{max}}$
- $t_{1/2}$
- AUC

Standard two stage

- $CL = \frac{\sum CL_i}{n}$

Mixed effects modelling

- POP prediction
- NONMEM

Complexity

Toxicity

Therapeutic failure

Percent maximal effect

Drug concentration

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Introduction to pharmacometrics

Nonlinear mixed-effects model

Covariate model
- Fixed effects
  - Individual parameter estimates (CL, Ka, V)
  - Sampling-schedules
  - Dosing
  - Covariates
  - Formulation

Structural model

Random effects model
- Random effects
  - Measurement errors
  - Inter-individual random effects
  - Intra-individual random effects
  - Model-misspecification
  - Unknown factors

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Introduction to pharmacometrics

- Pharmacometrics (population PK/PD)
  - The aim of the pharmacometric model is to describe pharmacological responses quantitatively and qualitatively.

\[ \text{Gut compartment} \xrightarrow{ka} \text{Central compartment} \xrightarrow{\lambda = \frac{CL}{V}} \text{Effect compartment} \]

\[ C_P = \frac{\text{Dose} \times ka}{V \times (ka - \frac{CL}{V})} \times \left[ e^{-\frac{CL}{V} \times t} - e^{-ka \times t} \right] \]

\[ E = \frac{E_{\text{max}} \times C_P}{E_{C_{50}} + C_P} \]
Introduction to pharmacometrics

Linear regression
\[ Y = a \times x + b \]

Minimisation of squared residuals (SS):
\[ \sum [Y_{i,\text{observed}} - Y_{i,\text{predicted}}]^2 \]

\[ C = C_0 \times e^{-k \times t} \]
\[ C_0 = \text{Dose}_{\text{IV}}/V \quad k = \text{CL}/V \]

Reparametrisation:
\[ C = [\text{Dose}_{\text{IV}}/V] \times e^{-(\text{CL}/V) \times t} \]

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New combinations of parameter values are tested iteratively until convergence is reached.

The best model parameters are those that correspond to the lowest SS (loglikelihood in nonlinear mixed-effects modelling).
Structural modelling

1-compartment disposition model (IV administration)

**IV bolus**

Central Compartment \((V_c)\)

\[
\frac{dA}{dT} = -\frac{CL}{V_c} \times A
\]

Central (1) Compartment \((V_1)\)

\[
\frac{dA}{dT} = -K_{10} \times A\]

\[A(0) = \text{Dose}\]

\[C_0 = \frac{\text{Dose}}{V_1}\]

\[K_{10} = \frac{CL}{V_1}\]

\[C = \frac{A}{V}\]

\[t_{1/2} = \frac{\ln 2}{K_{10}} = \frac{\ln 2 \times V_1}{CL}\]
Structural modelling

2-compartment disposition model (IV administration)

Central (1) Compartment ($V_1$)

Peripheral (2) Compartment ($V_2$)

$\frac{dA_1}{dT} = -K_{10} \times A_1 - K_{12} \times A_1 + K_{21} \times A_2$

$\frac{dA_2}{dT} = K_{12} \times A_1 - K_{21} \times A_2$

$A_1(0) = \text{Dose}$

$A_2(0) = 0$

$C_0 = \frac{\text{Dose}}{V_1}$

$C_1 = \frac{A_1}{V_1}$

$K_{10} = \frac{\text{CL}}{V_1}$

$K_{12} = \frac{Q}{V_1}$

$K_{21} = \frac{Q}{V_2}$

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Structural modelling

2-compartment disposition model (PO administration)

\[
\frac{dA_3}{dT} = K_{23} \times A_2 - K_{32} \times A_3
\]

A1(0) = Dose
A2(0) = 0
A3(0) = 0

Peripheral (3) Compartment \( \left( \frac{V_3}{F} \right) \)

\[
K_{32} \downarrow \uparrow K_{23}
\]

Central (2) Compartment \( \left( \frac{V_2}{F} \right) \)

\[
\frac{dA_1}{dT} = -K_{12} \times A_1
\]

\[K_{12} = K_a\]

\[
\frac{dA_2}{dT} = K_{12} \times A_1 - K_{23} \times A_2 + K_{32} \times A_3 - K_{20} \times A_2
\]

K20 = \( \frac{CL}{V_2} \)
K23 = \( \frac{Q}{V_2} \)
K32 = \( \frac{Q}{V_3} \)

Gut (1) Compartment \( (F \times \text{dose}) \)

Central (2) Compartment \( \left( \frac{V_2}{F} \right) \)

\[C_2 = \frac{A_2}{V_2}\]
Structural modelling

1-compartment disposition metabolite model (PO administration)

\[
\begin{align*}
\text{Gut (1) compartment (F\times\text{dose})} & : K_{12} \\
A1(0) &= \text{Dose} \\
\frac{dA1}{dT} &= -K_{12} \times A1 \\

\text{Central (2) Compartment (V)} & : K_{23} \\
A2(0) &= 0 \\
\frac{dA2}{dT} &= K_{12} \times A1 - K_{23} \times A2 \\

\text{Central (3) Compartment (V)} & : K_{30} \\
A3(0) &= 0 \\
\frac{dA3}{dT} &= K_{23} \times A2 - K_{30} \times A3 \\
\end{align*}
\]

\[
\begin{align*}
K_{12} &= K_a \\
K_{23} &= \frac{CL_P}{V_2} \\
K_{30} &= \frac{CL_M}{V_3} \\
\end{align*}
\]
Structural modelling

Semi-physiological model describing the metabolic auto-induction and saturable first-pass hepatic extraction of artemisinin[1]

Physiologically based pharmacokinetic modeling: methodology, applications, and limitations with a focus on its role in pediatric drug development. [2]


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Structural modelling

Optimal number of transit compartments

Gut Compartment ($F \times dose$)

Transit compartments (n)

Absorption Compartment

Central Compartment ($V_C/F$)

$CL/V_C$

1st order absorption

Transit absorption

Non-physiological Numerical difficulties


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Variability

Two main sources of variability
- Residual random variability - unexplained variability
- Inter-individual variability - between subject variability

Observation
Individual prediction
Population prediction

Residual error ($\varepsilon$): $C_{\text{observed}} - C_{\text{ipred}}$

Population estimate
Individual estimate

IIV($\eta$): $\theta_{\text{pop}} - \theta_{\text{ipred}}$

$\eta = \text{ETA}$
$\omega = \text{OMEGA}$
$\varepsilon = \text{EPSILON}$
$\sigma = \text{SIGMA}$

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Variability

\[ y_{ij} = f_i + \varepsilon_{ij} \]  
[Additive]

\[ y_{ij} = f_i \times (1 + \varepsilon_{ij}) \]  
[Proportional]

\[ y_{ij} = f_i \times (1 + \varepsilon_{1ij}) + \varepsilon_{2ij} \]  
[Combined]

Homoscedastic error -the residual variability is constant

Heteroscedastic error -the residual variability is proportional to the size of the variable (i.e. concentration)

Slope-intercept model -the residual variability is proportional at high predictions and constant at low
Covariate modelling

- Identify patient sub-groups at potential risk
- Increase the predictive performance of the model
- Increase the understanding of a studied system
- Increase the mechanistic interpretation of the model

Covariates

- Demographics (pregnancy, BMI)
- Lab values (bilirubin, AGP)
- Disease parameters (parasitemia)
- Therapy related (co-medication)
- Environmental (smoking)

Covariate modelling: Stepwise forward addition and backward elimination

(automated functionality in Pearl-speaks-NONMEM: SCM)

http://psn.sourceforge.net/pdfdocs/scm_userguide.pdf
Covariate modelling

Base model

Covariate model
Covariate modelling

Base model

Covariate model

Vc/F

ETA-Vc/F

Non-pregnant
Pregnant

Non-pregnant
Pregnant

Xpose
Covariate modelling

Covariate modelling: Stepwise forward addition and backward elimination

- Basic structural model
- Screen all covariates - Add the covariate with lowest OFV
  - Add the covariate with lowest OFV
  - Add the covariate with lowest OFV
  
  Reduced final covariate model

- Stepwise forward addition (p<0.05)

- Backward elimination (p<0.01)
  - Screen all covariates - Add the covariate with lowest OFV
  - Screen all covariates - Add the covariate with lowest OFV
  - Screen all covariates - Add the covariate with lowest OFV
  - Remove non-significant covariates
  - Full covariate model - No significant covariates left
Covariate modelling

Covariate relationships

Can be implemented automatically in PsN
## Covariate modelling

<table>
<thead>
<tr>
<th>Covariate modelling</th>
<th>Population estimate (% RSE) [IIV]</th>
<th>ΔOFV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model</strong></td>
<td>CL/F (L/h)</td>
<td>Vc/F (L)</td>
</tr>
<tr>
<td>Base model</td>
<td>70.1 (12.5) [31.5]</td>
<td>32.1 (19.5) [59.5]</td>
</tr>
<tr>
<td><strong>Forward addition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covariate 1-CL</td>
<td>60.3 (10.7) [21.5]</td>
<td>32.6 (19.5) [59.5]</td>
</tr>
<tr>
<td>Covariate 2-Vc</td>
<td>60.5 (10.5) [21.5]</td>
<td>22.1 (12.5) [39.5]</td>
</tr>
<tr>
<td>Covariate 3-CL</td>
<td>60.1 (10.3) [20.5]</td>
<td>22.2 (12.5) [39.5]</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Backward elimination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covariate 1</td>
<td>70.2 (13.5) [30.5]</td>
<td>22.2 (12.5) [39.5]</td>
</tr>
<tr>
<td>Covariate 2</td>
<td>60.2 (10.5) [20.5]</td>
<td>29.2 (14.5) [59.5]</td>
</tr>
<tr>
<td>Covariate 3</td>
<td>60.2 (10.5) [21.5]</td>
<td>22.2 (12.5) [39.5]</td>
</tr>
<tr>
<td>Final model</td>
<td>60.2 (10.5) [21.5]</td>
<td>22.2 (12.5) [39.5]</td>
</tr>
</tbody>
</table>
Covariate modelling

“Absence of evidence is not evidence of absence”  
*Carl Sagan (1934-1996)*

Full covariate model
(implement the group covariate on all relevant parameters and bootstrap)

- **Vp/F**: Not significant
- **Q/F**: Not significant
- **Ka**: Significant
- **Vc/F**: Significant
- **CL/F**: Significant

---

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Model diagnostics

Basic Goodness-of-fit diagnostics

Substantial and systemic deviations/trends indicate model-misspecification

Basic Goodness-of-fit diagnostics

Model diagnostics

Substantial and systemic deviations/trends indicate model-misspecification

Basic Goodness-of-fit diagnostics
## Model diagnostics

### Numerical diagnostics
- Parameter values
- Parameter certainty

### Parameter estimates of the final model

<table>
<thead>
<tr>
<th>Parameter estimates of the final model</th>
<th>Population estimate a (% RSE b)</th>
<th>95% CI. b</th>
<th>IIV [%CV] a (% RSE b)</th>
<th>95% CI. b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>60.2 (10.5)</td>
<td>49.6-74.2</td>
<td>21.5 (27.0)</td>
<td>14.5-26.2</td>
</tr>
<tr>
<td>Vc/F (L)</td>
<td>22.2 (12.5)</td>
<td>18.2-25.6</td>
<td>39.5 (35.7)</td>
<td>21.7-50.7</td>
</tr>
<tr>
<td>Q1/F (L/h)</td>
<td>10.9 (14.9)</td>
<td>6.31-13.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vp1/F (L)</td>
<td>110 (14.8)</td>
<td>80.3-131</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ka (h⁻¹)</td>
<td>0.761 (4.97)</td>
<td>0.592-0.891</td>
<td>45.8 (22.1)</td>
<td>35.4-56.1</td>
</tr>
<tr>
<td>σ</td>
<td>0.285 (5.47)</td>
<td>0.255-0.314</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Covariate effects
- Pregnancy effect on CL (%)
- Pregnancy effect on Vc (%)

- Sample data randomly and re-fit the model for bootstrap diagnostics
- Stratify on important covariates

---

Bootstrap runX.mod -samples=2000
Model diagnostics

Simulation-based diagnostics

- Develop model
- Simulate from model
- Compare simulations to observed data

95% CI. of simulated
95th percentile
50th percentile
5th percentile

Observed
95th percentile
50th percentile
5th percentile

Prediction-corrected Visual Predictive Check

Simulate n (n=2000) concentrations at each observed concentration-time point

Obs. above:
6.0% (CI:2.4-8.4%)

Obs. below:
4.5% (CI:2.1-8.4%)

Time after dose (hr)

Concentration (ng/mL)

vpc runX.mod -samples=2000

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Population pharmacokinetics of lumefantrine

EGA was incorporated as a linear covariate on Vc

- Safe and effective artemether-lumefantrine treatment in adults
- Specific problem of low cure rates (84%) in pregnant women
- What dose is the right dose → M&S

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Tarning et al. AAC. 2009
Antimalarial examples

1: recrudescence, 2: re-infection, 3: non-failures

In silico (n=1000) dose optimization in pregnant women with malaria

Cumulative risk of recrudescence

No failures > 550 ng/mL
Antimalarial examples

Population pharmacokinetics and pharmacodynamics of piperaquine in children with uncomplicated falciparum malaria

Joel Tarning¹,², Issaka Zongo³, Fabrice A. Somé³, Noel Rouamba³, Parikh Sunil⁴, Philip J. Rosenthal⁴, Warunee Hanpithakpong¹, Natthapong Jongrak¹, Nicholas P. J. Day¹,², Nicholas J. White¹,², Francois Nosten¹,²,⁵, Jean-Bosco Ouedraogo³, Niklas Lindegardh¹,²

- 236 children (2-10 years) from Burkina Faso received a weight-based dose of DHA-PQ
- Capillary blood sampling (6 weeks)
- Nonlinear mixed-effects modeling

To define the population pharmacokinetic of piperaquine in the treatment of *falciparum* infection in children

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Time-to-event analysis:
The risk of a new malaria infection increased with 5.9% per 1 ng/mL decrease in day 7 concentration (HR 0.94, 95% CI 0.92 to 0.96)
Antimalarial examples

Manufacturer recommendations:
To wide binning of doses resulting in many under-dosed children

In silico dose-optimization using the final model
Antimalarial examples

Population pharmacokinetics of dihydroartemisinin and piperaquine in pregnant and non-pregnant women with uncomplicated malaria

Joel Tarning¹,², Marcus J. Rijken³, Rose McGready¹,²,³, Aung Phae Phyo³, Warunee Hanphithakpong¹, Nicholas P. J. Day¹,², Nicholas J. White¹,², Francois Nosten¹,²,³, Niklas Lindegardh¹,²

- 48 (24+24) Karen patients
- Standard DHA-PQ (3×40-320 mg) for 3 days
- Dense venous blood sampling (9 weeks)
- PQ and DHA analysed with LC-MS/MS
- NCA (traditional statistics)
- Nonlinear mixed-effects modelling
  - Covariate models
Antimalarial examples

2-compartment disposition model
(p<0.0001)

1-compartment disposition model

Concentration (ng/mL)

Time (hours)

LLOQ

Dihydroartemisinin

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Tarning et al. Submitted AAC
Antimalarial examples

1-compartment disposition model

2-compartment disposition model

Inaccurate structural model if only using the OFV and not simulation-based diagnostics
Thank you

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