Pharmacokinetics
Introduction to Population PK

Helmut Schütz
BEBAC

PopPK: History

- 1972 The Birth of Population PK (FO)

COMPUTERS AND BIOMEDICAL RESEARCH 5, 441-459 (1972)

Modelling of Individual Pharmacokinetics for Computer-Aided Drug Dosage*

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PopPK: History

- 1977 NONMEM group established at UCSF (L. Sheiner, S. Beal)

- 1979 First NONMEM FO program

- 1986 First nonparametric method: NPML (A. Mallet)

- 1990 First FOCE method (M. Lindstrom, D. Bates)

- 1990 First Bayesian method: BUGS and PKBugs (A. Gelfand, A. Smith)

intra individual variability

inter individual variability

residual error
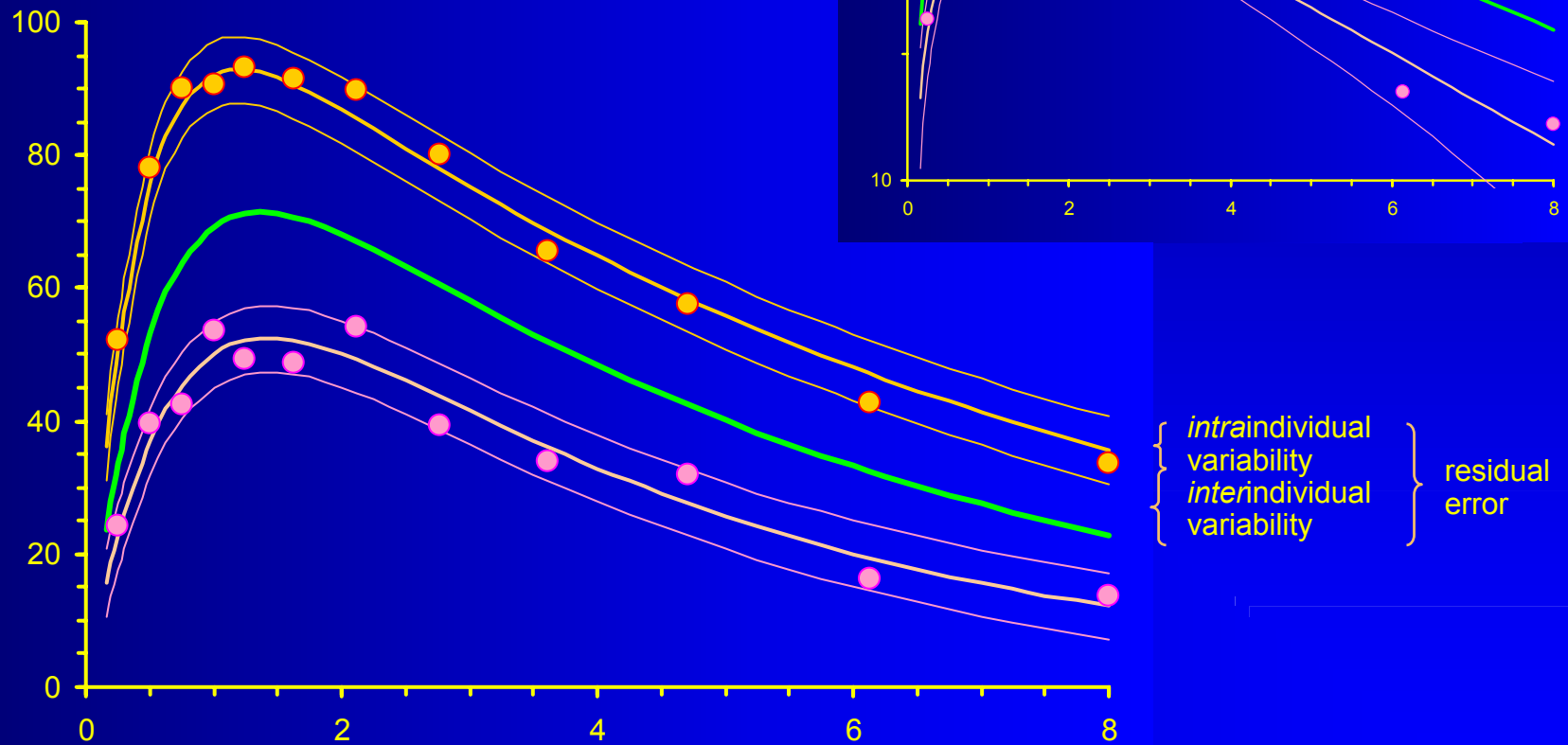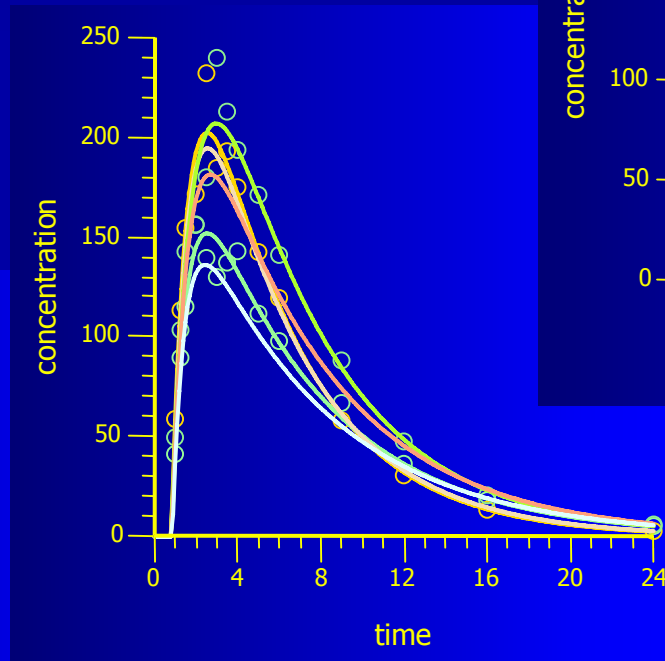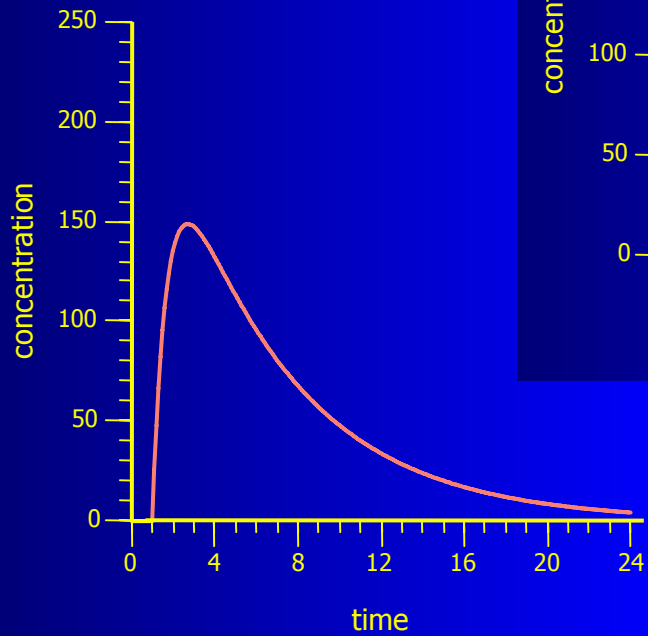
Classical PK modeling
(individual fits)
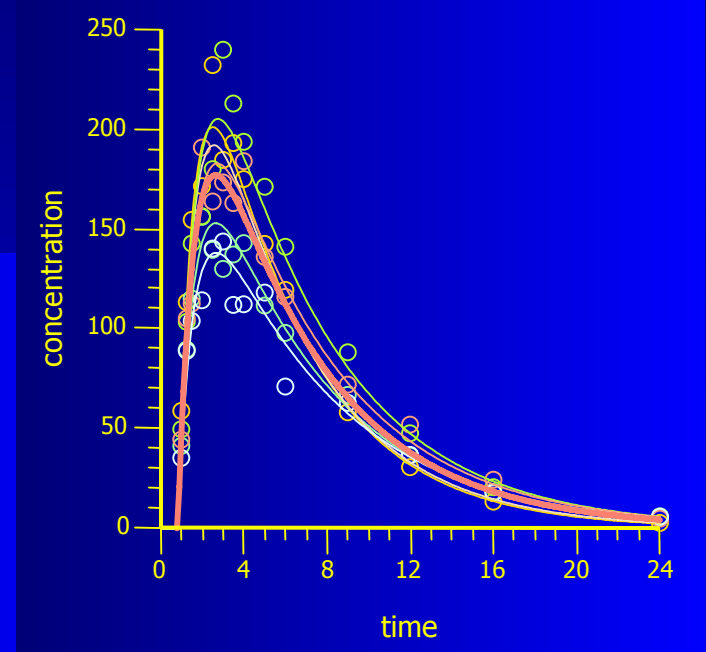
Population PK modeling
(individual fits + mean PK)

Classical PK *vs.* PopPK

- Classical PK
  - Two-Stage Approach
    1. Fitting individuals
    2. Averaging individuals' PK parameters; calculate variances
    - *Which* average?
      Geometric mean (V, CL), harmonic mean (k), median (t_{lag}), …
    - What if individuals best fitted by different models?
    - Covariates by regression analysis

Classical PK *vs.* PopPK

- Population PK
  - Simultaneous fit of all data
    - Separation of residual error into intra- and inter-individual components
    - Direct assessment of covariates

Classical PK *vs.* PopPK

- Example
  - One compartment, lag-time, n=6

		V (SD)	%RE	k_a (SD)	%RE	k_{el} (SD)	%RE	t_{lag}	%RE
theoretical		0.5000		1.3900		0.1738		1.0000	
classical	1	0.3416		1.2254		0.2153		0.8156	
	2	0.4982		1.4340		0.1640		0.8361	
	3	0.3596		1.2432		0.2070		0.8330	
	4	0.3231		0.9238		0.1856		0.8066	
	5	0.4077		1.2692		0.1636		0.8392	
	6	0.5786		1.6706		0.1519		0.8606	
	average	0.4087 0.0951	−18.3	1.2741 0.2628	−8.3	0.1797 0.0247	+3.4	0.8346	−16.5
naïve pooled		0.4951 0.1152	−1.0	1.9743 2.4785	+42.0	0.0963 0.0711	−44.6	0.7549 0.5184	−24.5
FOCE LB		0.4067	−18.7	1.2395	−10.8	0.1814	+4.4	0.8283	−17.2

Basics

- Nonlinear Mixed Effects Model
- Estimates Population PK parameters (V, CL, …): Fixed effects (thetas θ)
- Estimates variability
  - Random effects (etas η)
    - Intersubject variability
    - Interoccasion variability (day to day)
  - Residual error (epsilons ε)
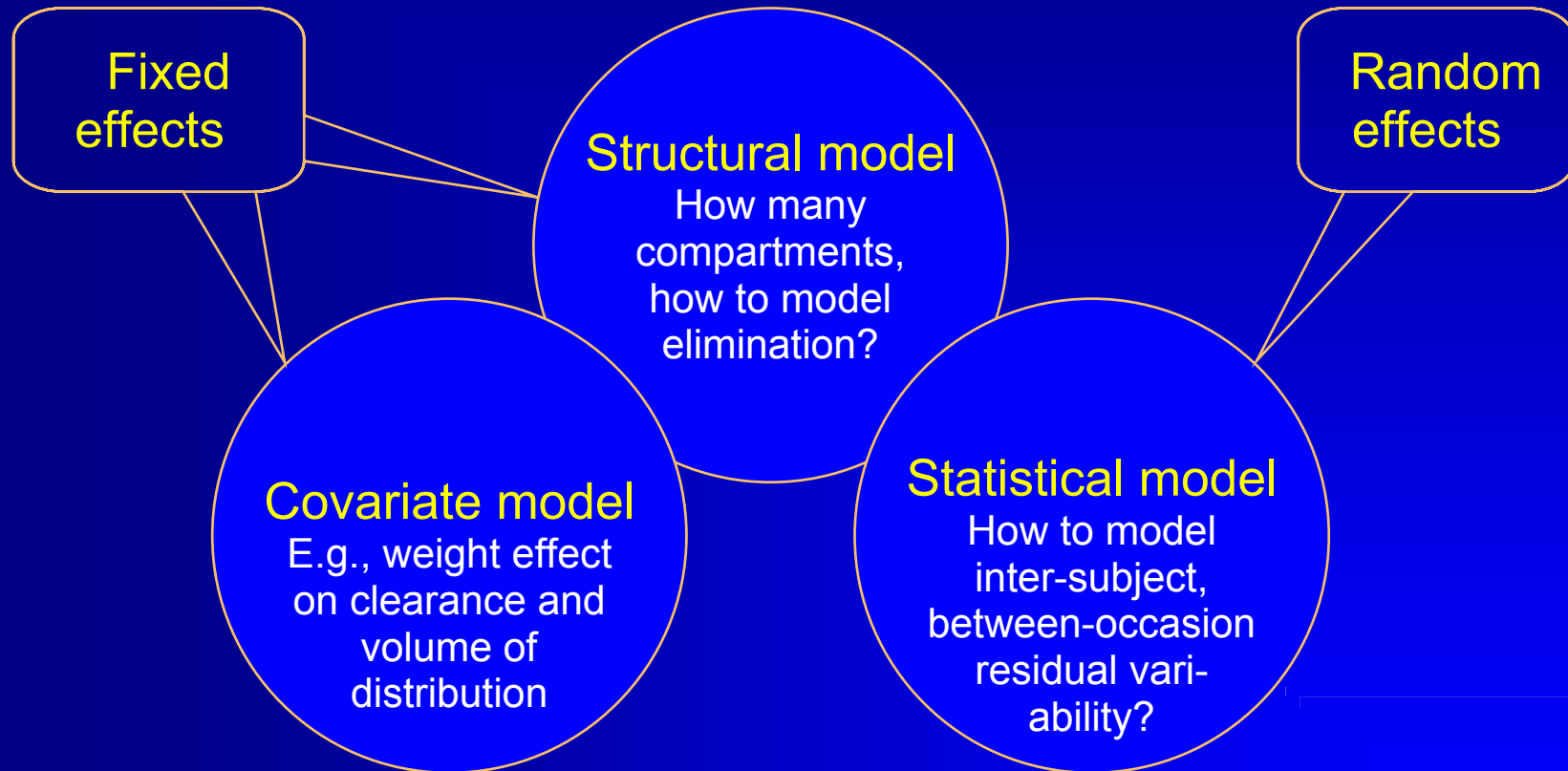   - Intrasubject: measurement error, model misspecification, …

Basics

- Identify factors determining intersubject variability: Covariates
  - Demographics: Age, body weight / surface area, sex, …
  - Genotypes: CYP450, …
  - Physiology: Renal (creatinine clearance) or hepatic impairment, disease state, …
  - Concomitant drugs
  - Others: Food, circadian variation, formulation, …

Model

$y_{ij} = f(\Theta_i) + \varepsilon_{ij}$, where

- y_{ij} is the jth observation of the ith subject
- f is a model that describes all observations
- Θ_i is a vector of subject i's parameter values (θ)
- ε_{ij} is the residual error of subject i's j[th] observation

- The elements of Θ_i are usually $\theta_i = \theta * e^{\eta}$, where
  - θ is the typical value for a parameter
  - ε^2 is the variance of η values

Pyry Välitalo, University of Kuopio, 1.10.2009

Components

Fixed effects

Structural model
How many compartments, how to model elimination?

Random effects

Covariate model
E.g., weight effect on clearance and volume of distribution

Statistical model
How to model inter-subject, between-occasion residual vari-ability?

Pyry Välitalo, University of Kuopio, 1.10.2009

Advantages

- Studies in the target population
- Sparse sampling (2–3 samples / subject)
  - Routine sampling in Phase II/III
  - Special populations (Pediatrics, cancer/AIDS, critical care patients, eldery, …)
- Missing data in 'rich data sets' not problematic
  - Imbalanced designs common
    - Different number of samples / subject
    - Different sampling times / subject

Advantages

- Covariates part of the model
  - Fewer restrictions on in-/exclusion criteria
  - 'What if' scenarios in planing further studies
  - Full model allows prediction of 'real world PK': more reliable dose regimen / posology

Disadvantages

- Complex methodology
  - Might require simulations (optimal sampling times); stepwise refinement of model during study
  - Statistical models not trivial
  - Expensive software with steep learning curve
  - Carl Metzler: *"PK Modeling – Art or Science?"*
- Time consuming
  - Easily ~10times longer than classical Two-Stage PK even by an experienced modeler

Disadvantages

- Validation might require multiple studies
  - Internal validation:
    Use only part of the data to set up a model and compare predictions with other part
  - External validation:
    Predictions *vs.* another study

- Cost/Benefit ratio
  - Unclear beforehand whether the model will give more than a trivial result (like: concentrations depend on body weight)

Example

- Intravenous dose, parameterized in CL and V, covariates: sex (categ.), weight, age (cont.) first 12 of 100 subjects (internal validation)

  - $A_{t=0}$ = Dose
    dA/dt = $-A \cdot CL/V$
    IPRED = A/V
    Y = IPRED + ε

  - Base model
    - Five parameters
      V = $\theta V * e^{\eta(V)}$
      CL = $\theta CL * e^{\eta(CL)}$
      Residual error (σ)
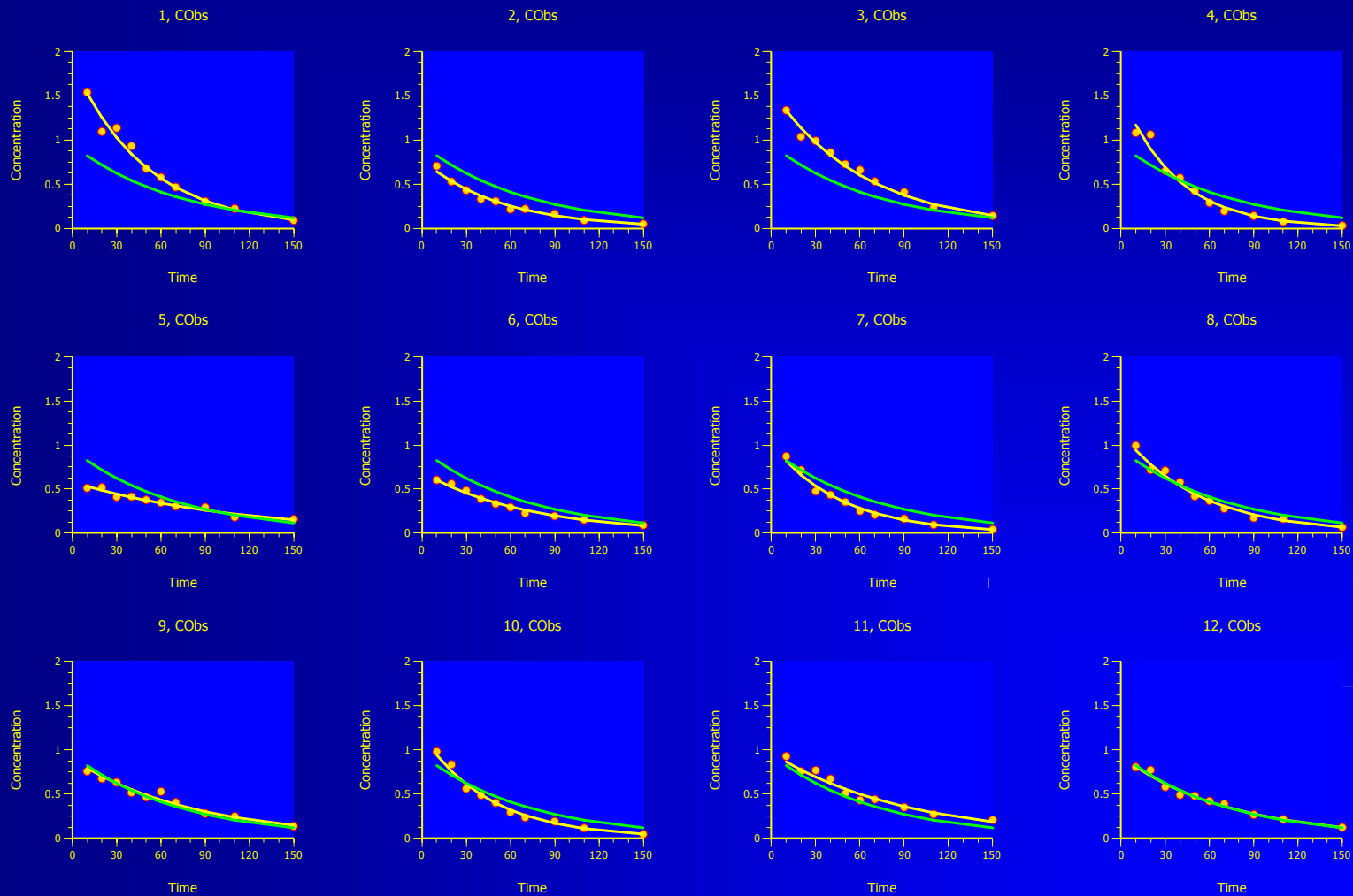
Example

Example

- Covariate model 1 (+ weight on V/CL, + age on CL)
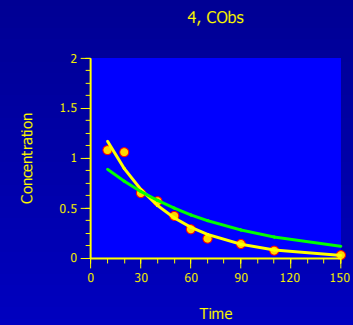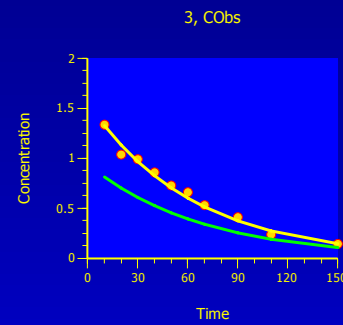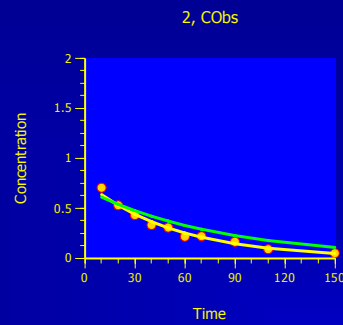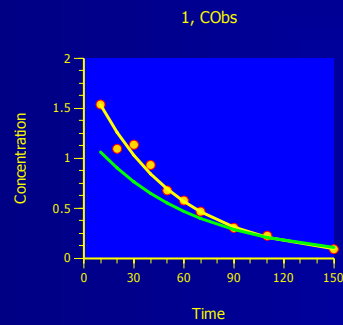 - Eight parameters
    $V = \theta V*(w/75)*e^{\eta(V)}$ scaling (cent. at 75 kg)
    $CL = \theta CL*(w/75)*(a/40)*e^{\eta(CL)}$ scaling (cent. at 75 kg / 40 a)
    Residual error (σ)
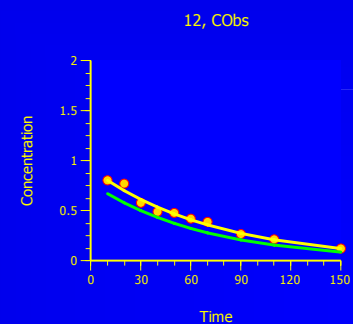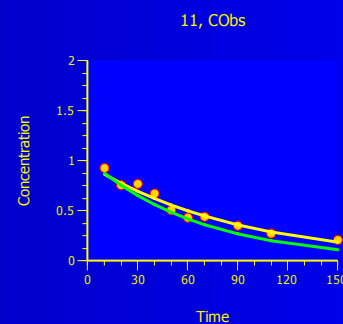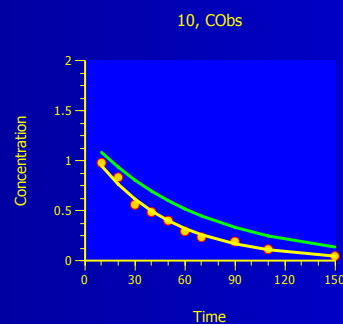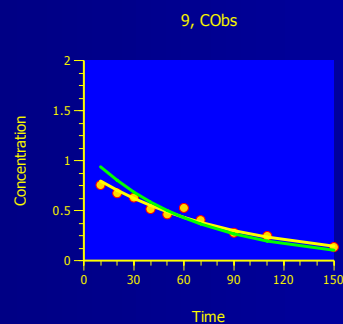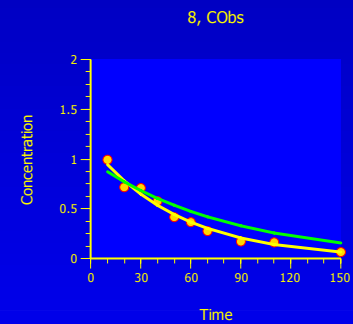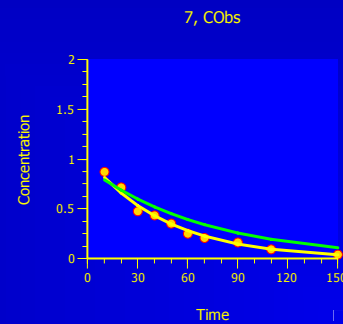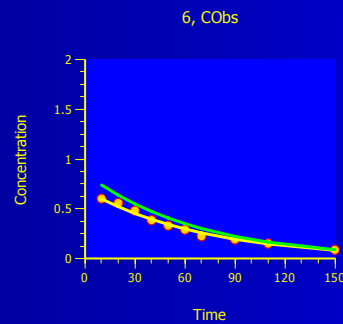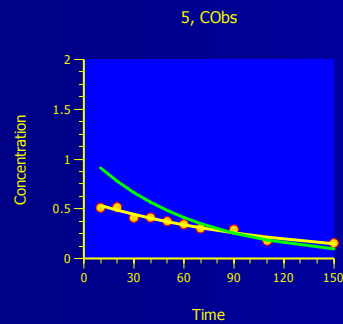
Example

Example

- Covariate model 2 (like 1 + sex on CL); categorial coding: male = 0, female = 1
  - Nine parameters
    $V = \theta V*(w/75)*((sex == 1)*\theta s1)*e^{\eta(V)}$ affects only females
 $CL = \theta CL*(w/75)*(a/40)*e^{\eta(CL)}$
    Residual error (σ)

Example

| model	θ	Estimate	CV%	AIC
base	V	10.582	11.600	−376.29
	CL	0.14682	7.7574	
	σ	0.086799	11.207	
covariate 1	V	9.2987	9.9556	−373.23
	CL	0.13512	8.5915	
	σ	0.086927	11.790	
	Vw	1.1300	56.603	
	VCL	0.92790	37.907	
	CLa	0.25116	77.422	
covariate 2	V	10.220	16.731	−366.07
	CL	0.11729	10.174	
	σ	0.084502	12.187	
	Vw	1.0697	66.305	
	VCL	1.4051	28.701	
	CLa	0.49579	40.647	
	Vsex	−0.048653	413.77	

Yes, but which model?

Example
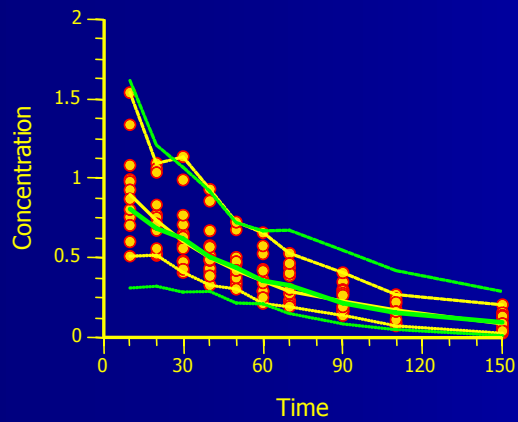
base model • cov. 1 model • cov. 2 model
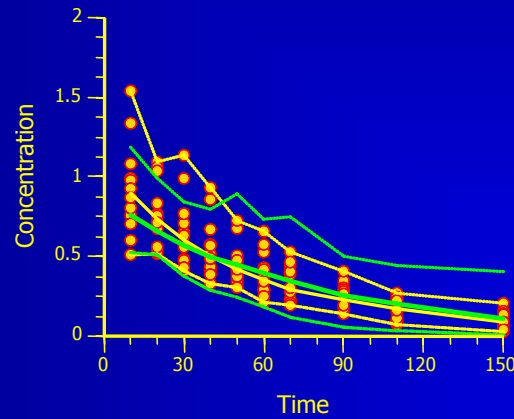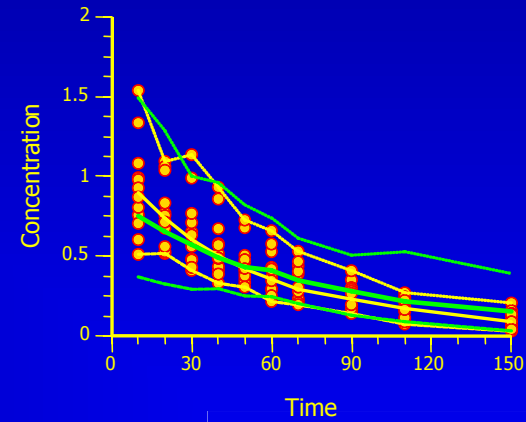
Example
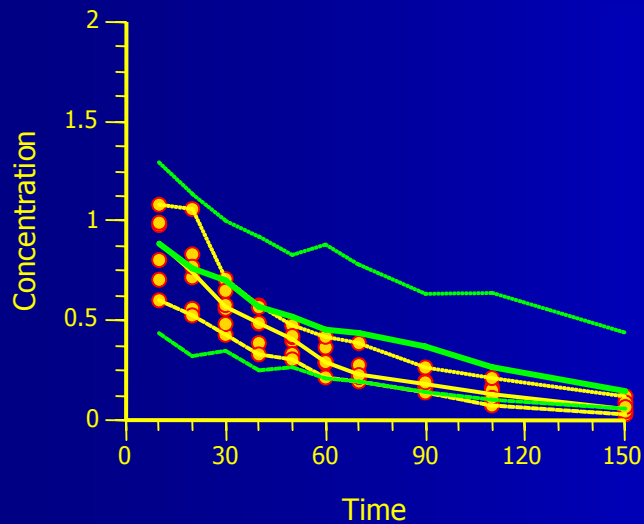
cov. 2 model (males)

cov. 2 model (females)

Example

cov. 2 model
(males)

cov. 2 model
(females)

Legend:
— 05%, 05%
— 05%, 50%
— 05%, 95%
— 50%, 05%
— 50%, 50%
— 50%, 95%
— 95%, 05%
— 95%, 50%
— 95%, 95%
• observed
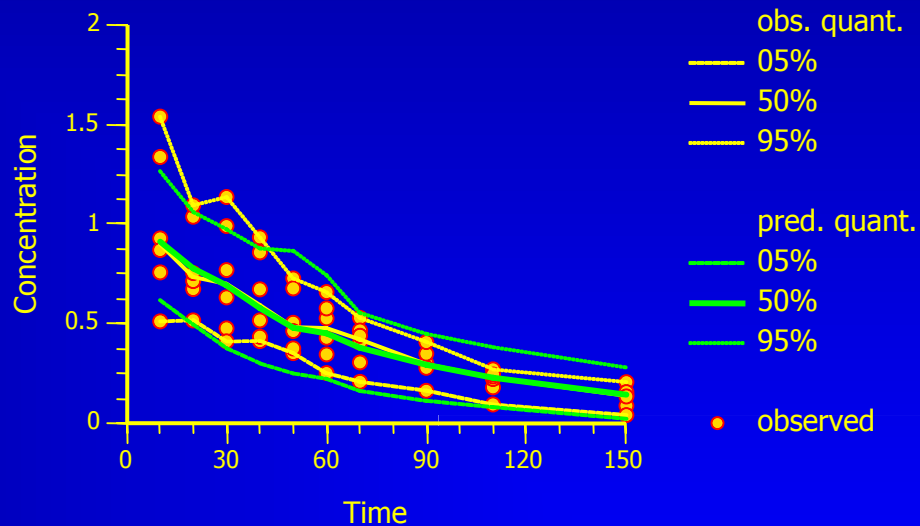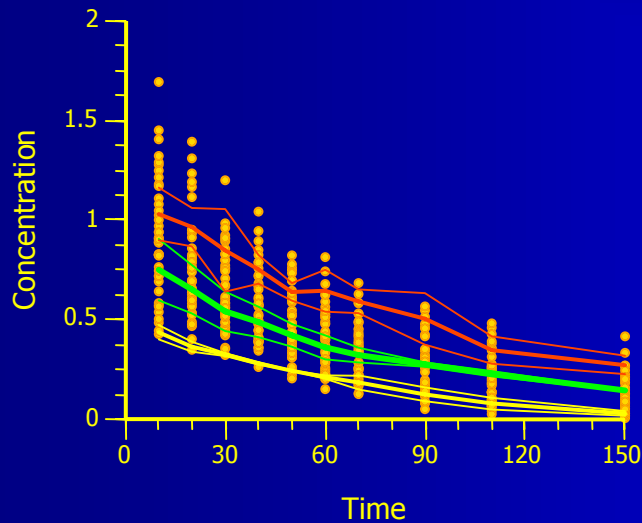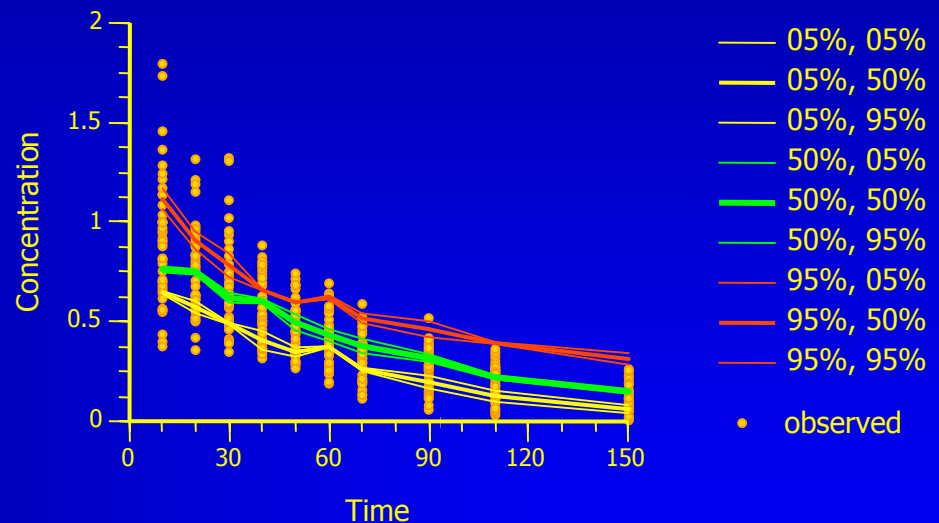
Predictive check / internal validation
Model based on first 12 subjects and observations of other 88 subjects
Estimated intersubject variabilities η too small; biased θ?
Better to estimate the model from 50% of subjects.

Example

cov. 2 model
(males)

cov. 2 model
(females)

Legend:
- 05%, 05%
- 05%, 50%
- 05%, 95%
- 50%, 05%
- 50%, 50%
- 50%, 95%
- 95%, 05%
- 95%, 50%
- 95%, 95%
- observed
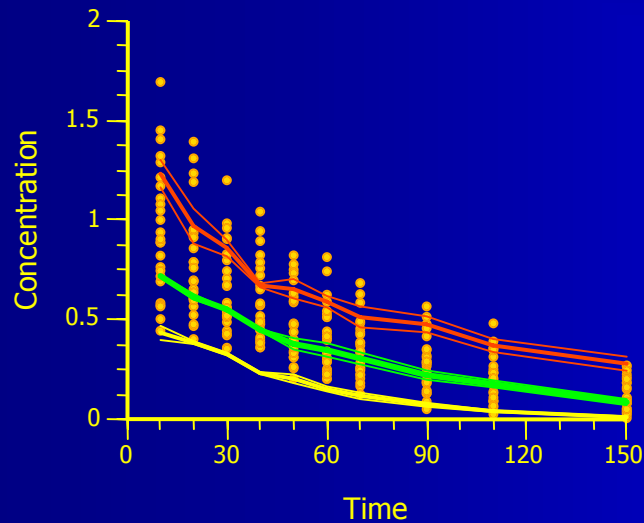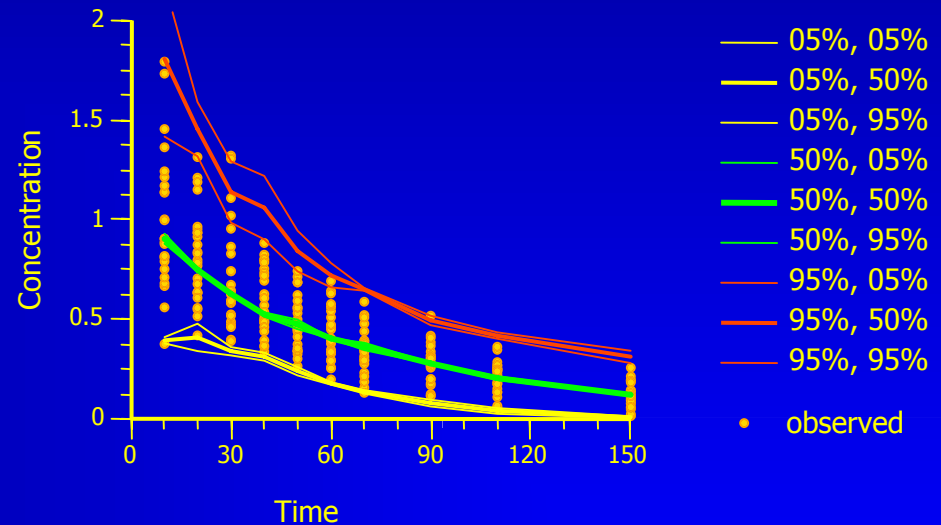
Predictive check / internal validation

Model based on first 50 subjects and observations of other 50 subjects

Model seems to be suitable for females only. Consider to go back to covariate 1 model (without stratification for sex).

Software

- NONMEM 7.3 (iconplc ~5500 U$/a)
- Phoenix/NLME 1.3 (Pharsight ~1900 U$/a)
- Monolix 4.2 (Lixosoft ?U$)
- SimBiology for MATLAB (Mathworks 3000 €)
- PopKinetics for SΛΛM II (TEG ?U$)
- Kinetica 5.0 (Thermo ~900 U$/a)
- Shareware
  - Pmetrics for R (USC/LAPK 895 U$ suggested)
    http://www.lapk.org/pmetrics.php

Software

- Freeware
  - ADAPT 5 (USC/BMSR)
    http://bmsr.usc.edu/software/adapt/
  - Boomer (David Bourne)
    http://www.boomer.org/
  - SAEMIX 0.96.1 for R
    http://cran.r-project.org/web/packages/saemix/index.html
  - PKTools/WinBUGS/PKBUGS (SD only)
    http://cran.r-project.org/web/packages/PKtools/index.html
    http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml
    http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/pkbugs.shtml

Still an Art?

- One compartment, 1st order absorption
  - 100 simulated datasets
  - 100 individuals / dataset
  - 4 samples / individual
  - Missing points at random (25%)
  - Initial estimates suggested for fixed effects
  - Blinded analysis by very experienced modelers
  - Software: SAS Prox nlmixed (FO and adaptive Gaussian), NONMEM V / VI FOCE, S-Plus nlme, ITPS, PEM, PEM, MCPEM, SAEM (Monolix)

Girard & Mentré, PAGE, Pamplona 2005

Still an Art?

V true= 27.2
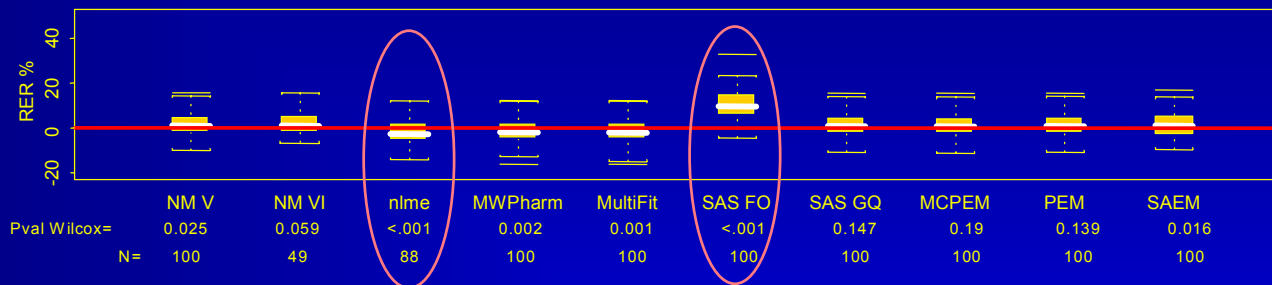
Ke true= 0.232

Ka-Ke true= 0.304

Thank You!
Introduction to Population PK
Open Questions?

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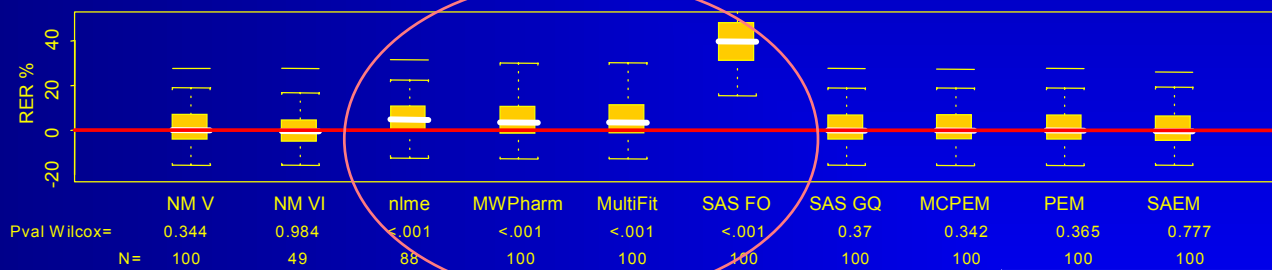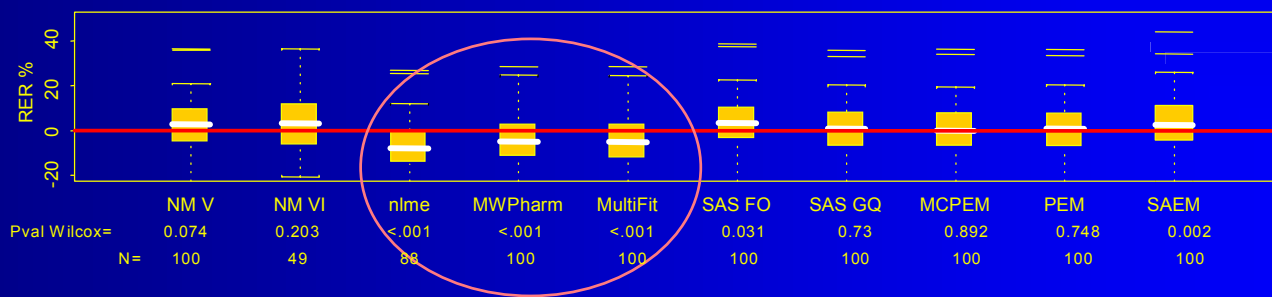 Comput Biomed Res 5/5, 441-59 (1972)
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