A practical introduction into PKPD modeling

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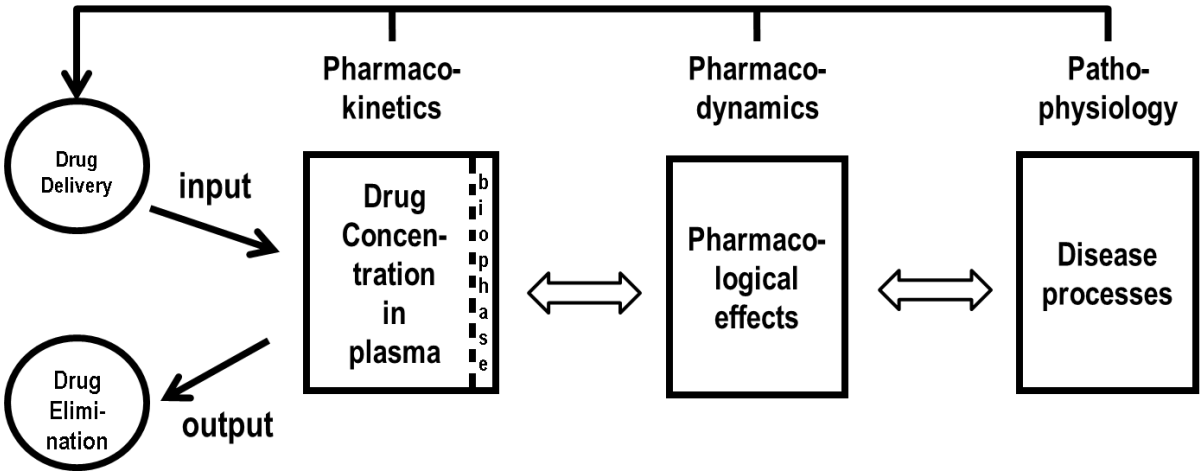
Cascade of pharmacological effects



1997 …the primairy objective of PK-PD modeling is to identify key properties of a drug *in vivo*, which allow the ***characterization of and prediction*** of the time course of drug effects under physiological and pathological conditions (intensity and duration) …

2012 Modeling and simulation have emerged as important tools for integrating data, knowledge, and mechanisms ***to aid*** in arriving at rational decisions regarding drug use and development.

Breimer and Danhof (1997) Clin Pharmacokinet. 32(4):259-267
Mould and Upton (2012) CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e6;

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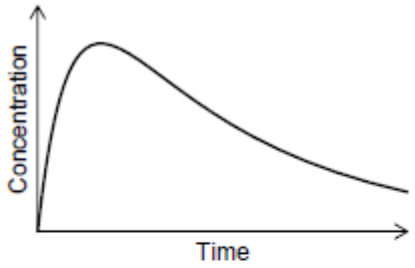
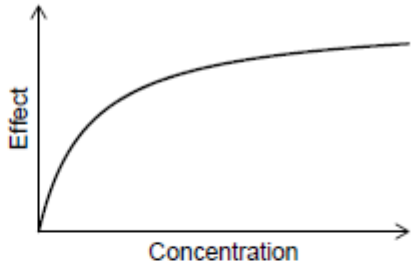
PK/PD modeling what is it?

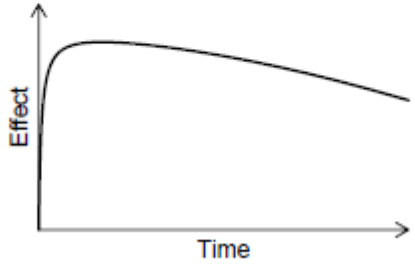
- Pharmacokinetic
- Pharmacodynamic
- Population



(a) PK model

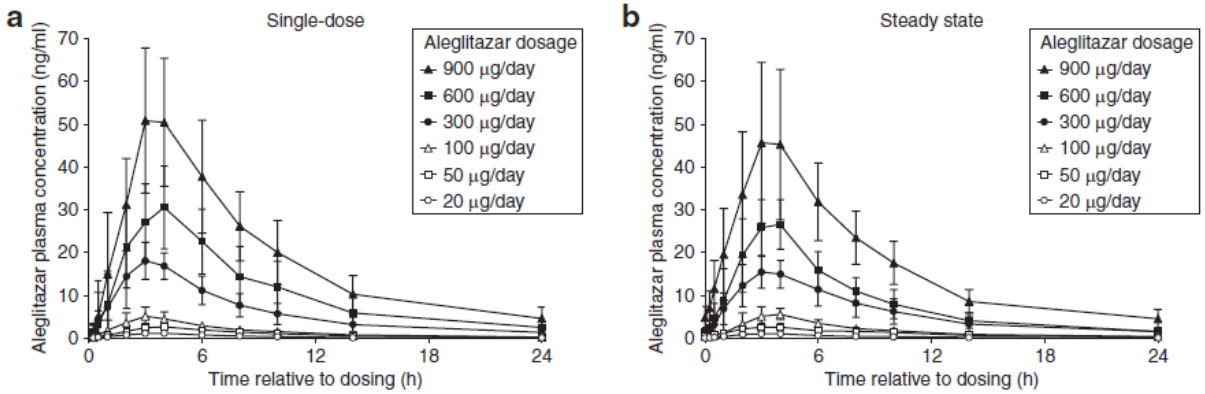


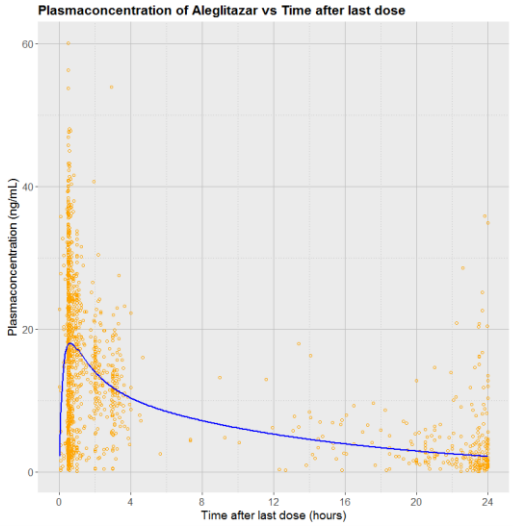
(b) PD model



(c) Combined PK/PD model

Variability (interindividual)





- HV versus patiënts
- Phase I/II versus Phase III/IV

What is a (mathematical) model?

- Model is a simplified approximation of a system
  - Trade-off between accuracy and simplicity:
    - Occam's razor: the simplest solution is usually the correct one.
    - Parsimony: preference for the least complex explanation for an observation
  - Mathematical model uses mathematical language to describe this system
  - Mathematical models can take many forms
    - Deterministic versus stochastic models (how much randomness?)
    - Non-linear versus linear models
    - Dynamic versus static models (change over time vs. equilibrium?)
    - Black versus white-box models (*a priori* information?)

What is a (mathematical) model?

- Important issues for PK (and PK/PD) are:
  - PK (and PD) variables show change over time
    - Need for dynamic models using differential equations
  - Variability: differences between individual subjects and within subject
    - Requires stochastic component
  - Prior knowledge, e.g. previous (pre-) clinical work
    - Requires white-box approach
  - Use of the model for extrapolations (simulation)
    - Can we use the model to simulate PK (and PK/PD) for extrapolation to other species, populations, and other dosage regimens

Population approach mixed effects modeling

- Structural Model
  - The underlying relationship between PK, time and PD response
  - For mechanistic models, understanding of ***Mechanism of Action*** is required
- Stochastic Model
  - Inter-subject variation
  - Intra-subject variation
  - Residual error

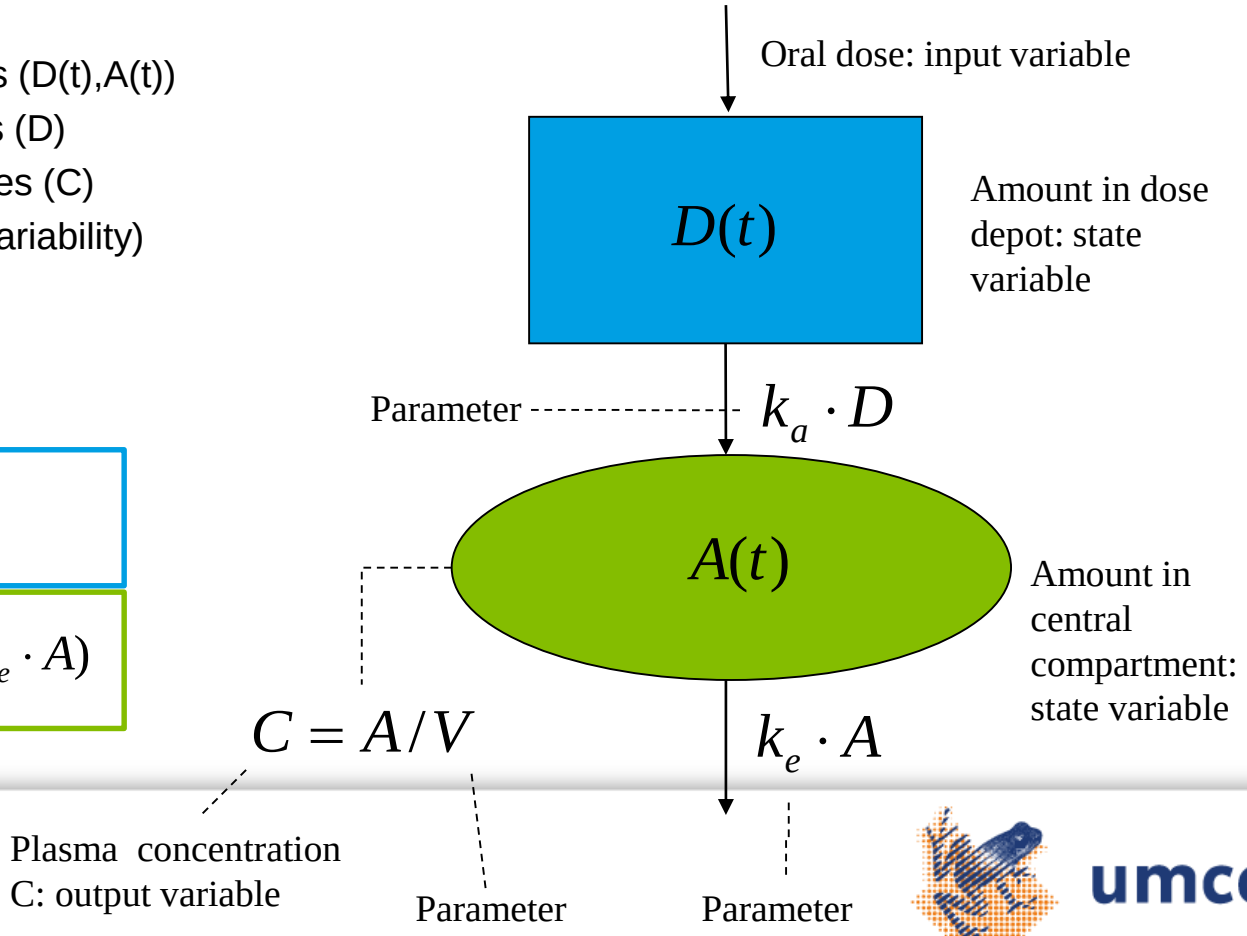
Building blocks of a dynamic PK model

Example: One-compartmental PK model with oral dose depot (plasma concentrations)

- Building blocks:
  - State variables (D(t),A(t))
  - Input variables (D)
  - Output variables (C)
  - Parameters (variability)
  - Equations

$$\frac{dD}{dt} = -(k_a \cdot D)$$

$$\frac{dA}{dt} = +(k_a \cdot D) - (k_e \cdot A)$$



Fitting a model to data

- How to assess the parameters (e.g. k_a, k_e and V)?
  - Using a priori information (white box approach):
    - Sources: physiology, physiochemical properties of drug
  - Using observations (data) and fitting model to data: Compartmental modeling
    - Minimizing the difference between observations and predictions by a fitting algorithm, which optimizes the parameter estimates in the model
    - Data-driven modeling
    - NONMEM

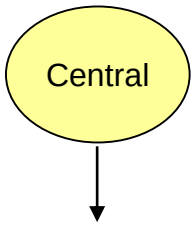
Population approach

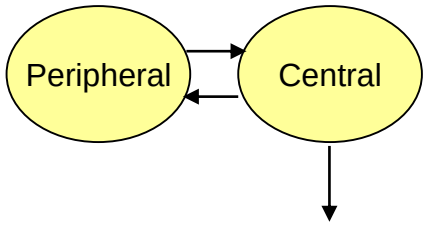
- Population approach uses mixed-effects modeling
  - Addresses the stochastic component as discussed earlier
- Three model elements
  - Structural model
  - Fixed effects
  - Random effects

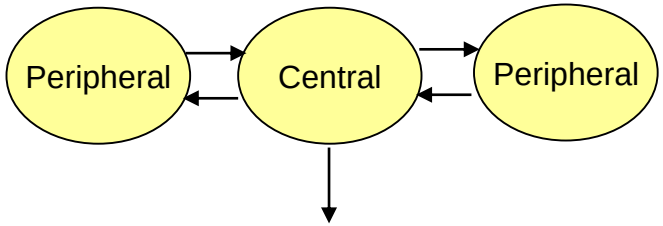
Mixed-effects models

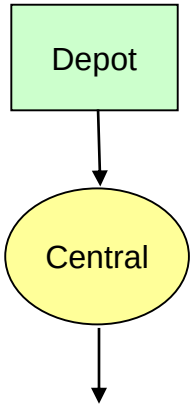
- The structural model describes how the dependent variable (output variable) relates to the independent variables (time and the input variables: slide 10)
- The fixed effects are the parameters associated with a population under repeatable levels of experimental factors
- The random effects are the parameters associated with individual “units” drawn from a population
  - Can be nested
- Mixed effects combines fixed and random effects

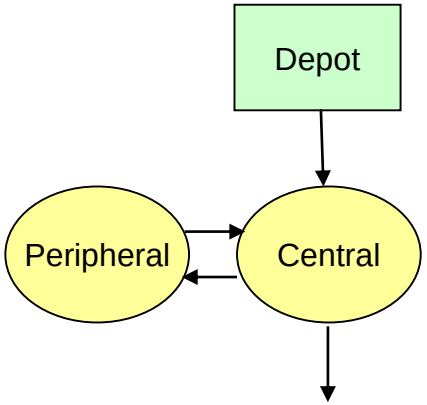
Which structural model?

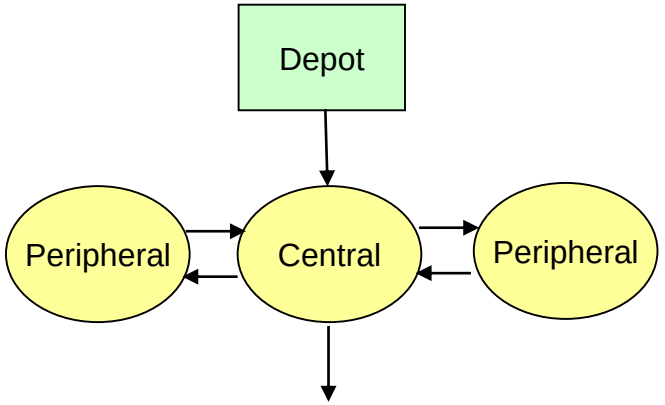












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Which model parameterisation (fixed effects)?

- Non-linear absorption
  - Saturated or carrier-mediated absorption
  - Poor aqueous solubility or slow release
  - Saturated portal plasma protein binding
  - Saturation of pre-systemic metabolism
  - Dose-related changes in gastric emptying, motility of blood flow
- Non-linear distribution
  - Concentration-dependant plasma protein binding
  - Saturable blood cell binding
  - Saturable tissue binding
- Non-linear elimination
  - Saturated elimination (e.g. Michaelis Menten kinetics)

Structural model with fixed effects

Observed concentration

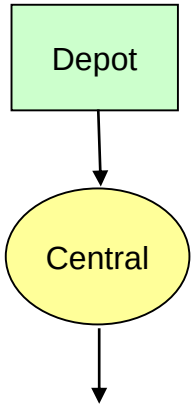
Structural model

Time

Individual parameters

Residual error

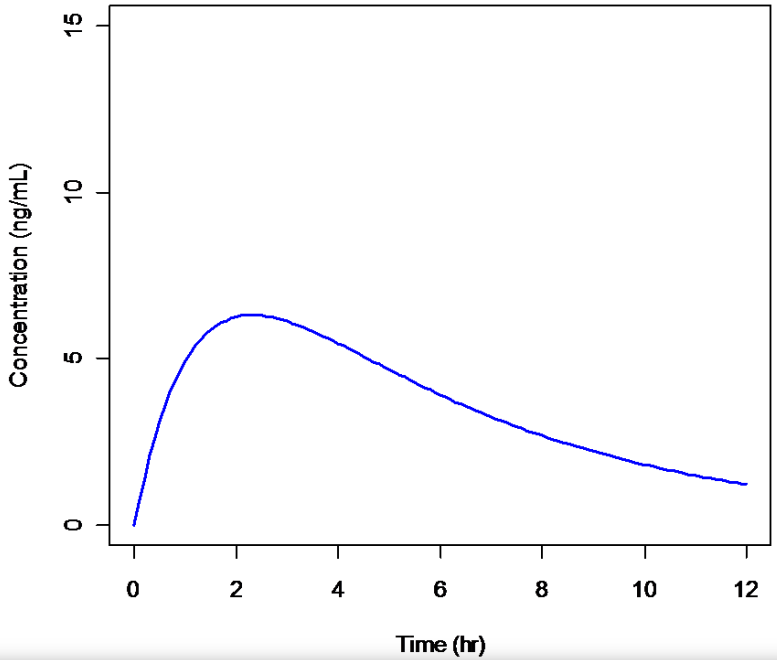
$$y_{ij} = f(t_{ij}, \mathbf{P_i}) + \varepsilon_{ij}$$



$$\frac{dD}{dt} = -k_a \cdot D$$

$$\frac{dA}{dt} = k_a \cdot D - k_e A$$

$$y_{ij} = A/V$$



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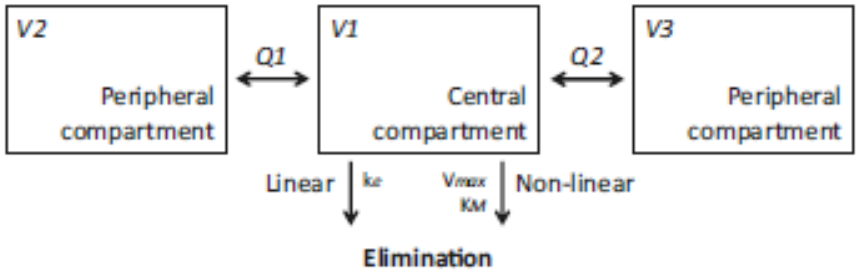
Example trastuzumab

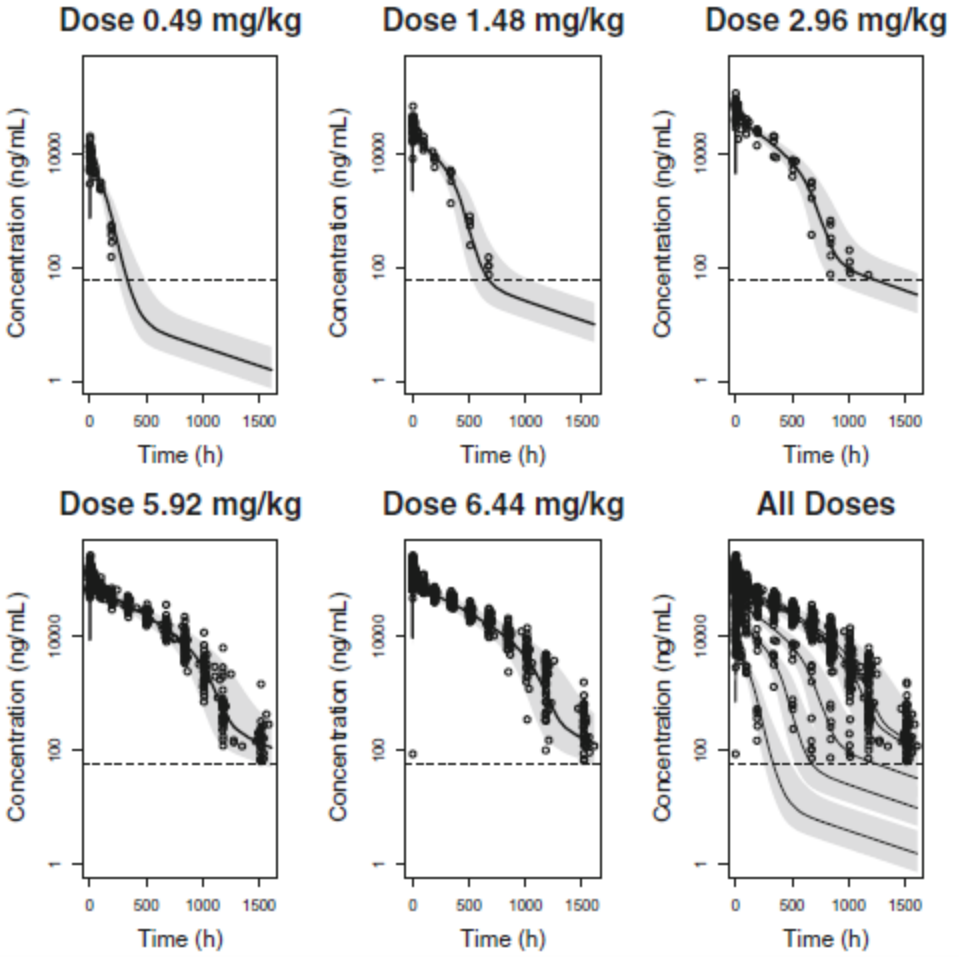


- Linear elimination (specific)

  k_e

- Nonlinear elimination (non-specific)

  $\frac{V_{max} \times C_p}{k_m + C_p}$



Inter-individual variability (IIV, random effect)

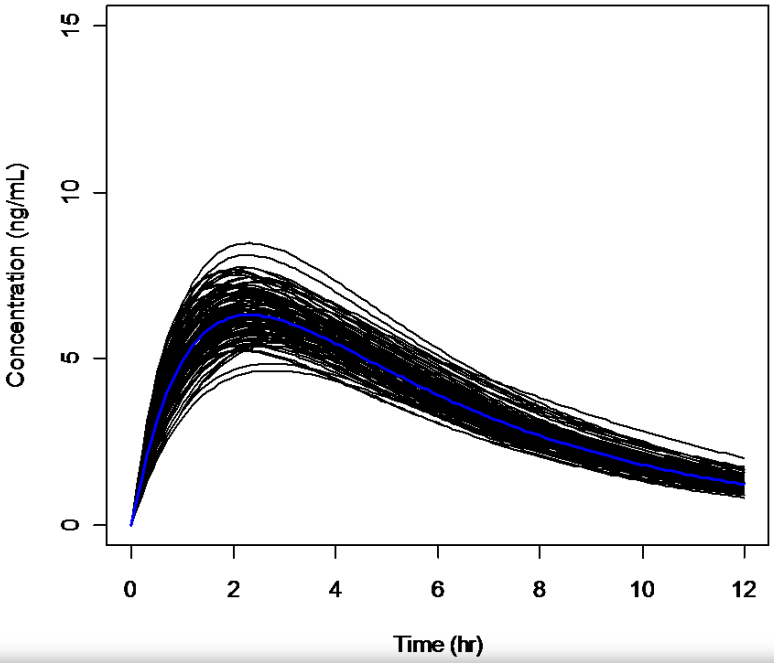
- Every subject is characterized by individual parameter set (P_i)
  - Part of this value can be explained by fixed effects (typical values) and the structural model (covariate relationship with age, weight, height etc). The remaining part is a random effect
  - IIV expresses biological variation

$$P_{ki} = \theta_k + \eta_{ki} \quad \text{Additive}$$

$$P_{ki} = \theta_k \cdot (1 + \eta_{ki}) \quad \text{Proportional}$$

$$P_{ki} = \theta_k \cdot \exp(\eta_{ki}) \quad \text{Log normal}$$

$$\boldsymbol{\eta} \sim N(0, \omega^2)$$



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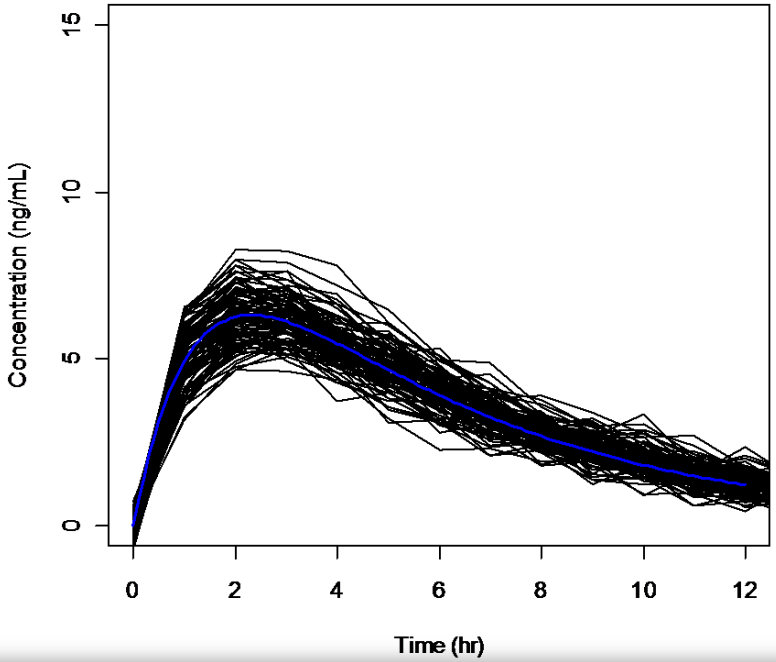
Intra-individual variability (random effect)

- Within each subject's response, as predicted by the structural model and the individual parameters some deviation from the observation remains:
  - Second level of random effects
  - unexplained effects, measurement errors, and other deviations

$$y_{ij} = f(t_{ij}, \mathbf{P_i}) + \varepsilon_{ij}$$
$$y_{ij} = f(t_{ij}, \mathbf{P_i}) \cdot (1 + \varepsilon_{ij})$$
$$y_{ij} = f(t_{ij}, \mathbf{P_i}) \cdot \exp(\varepsilon_{ij})$$
$$\log(y_{ij}) = \log\{ f(t_{ij}, \mathbf{P_i})\} + \varepsilon_{ij}$$
$$\varepsilon_{ij} \sim N(0, \sigma^2)$$



Data fitting and Minimum Value of Objective Function

- Based on maximal likelyhood (Fischer 1921);
  Estimation procedure that finds and estimate of θ such that the *likelyhood* of actually observing the data is *maximal*
- Problem 1; numerical overflow → log-likelyhood;

$$\sum_{i=1}^{n} Ln\left(\frac{1}{\sqrt{2\pi\sigma^2}} exp\left[\frac{-(Y_i-\mu)^2}{2\sigma^2}\right]\right)$$

- Problem 2; max is difficult → multiplied by -2
- MVOF= -2*log-likelyhood
- Chi-squared distributed! → p values can be used in model comparison

Pharmacometrician's workflow

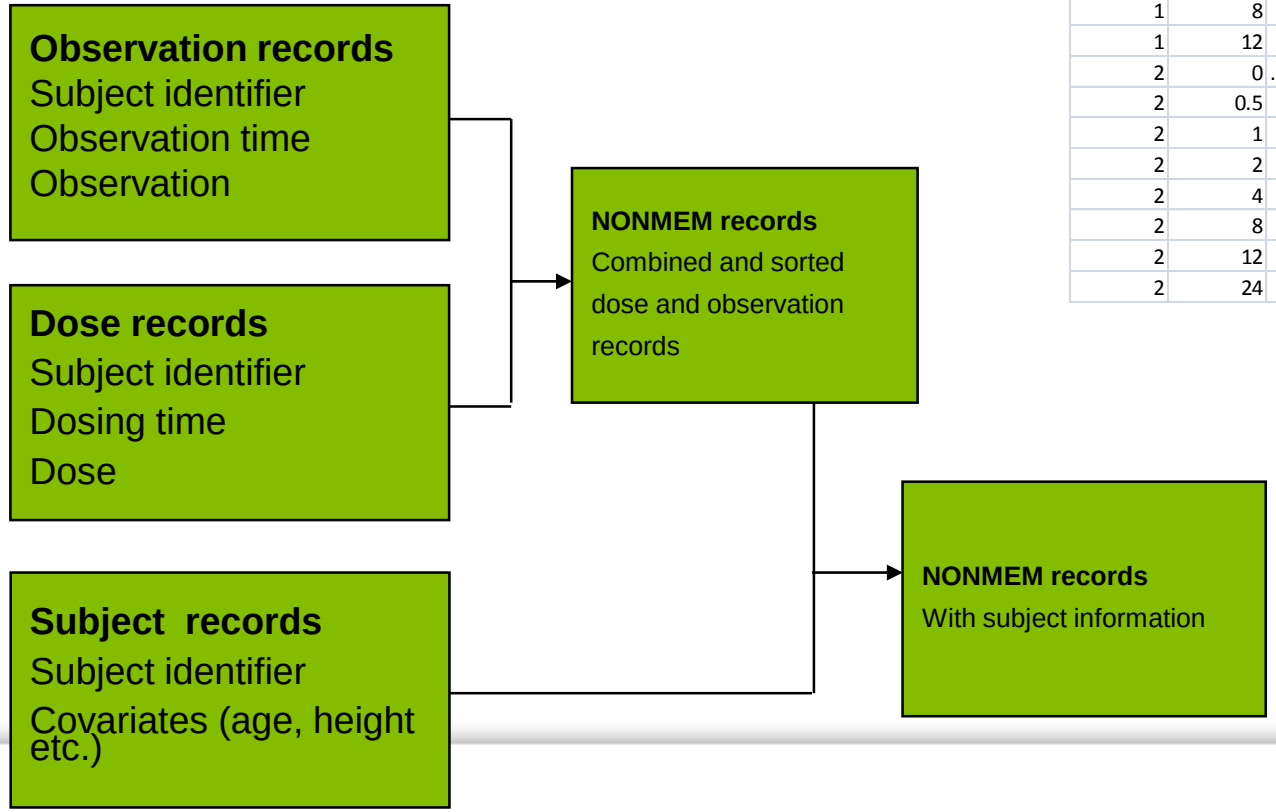
- Prepare the NONMEM data file
  - Using e.g. R and source data files in csv format (csv output format is supported by Excel and SAS)
- Graphical review of the data
  - Outliers, below LOQ values, errors
- Write the NONMEM control file
  - Requires programming skills (fortran-language)
  - Start with a simple model and then further develop your model to describe your data
- Run NONMEM
  - Failure to run often related to errors in data file or control file, but may also require modifications in the model
- Interpret the output
  - Parameter estimates, messages, and objective function value
  - Observed values versus predicted values, residuals

Dataset preparation PK model

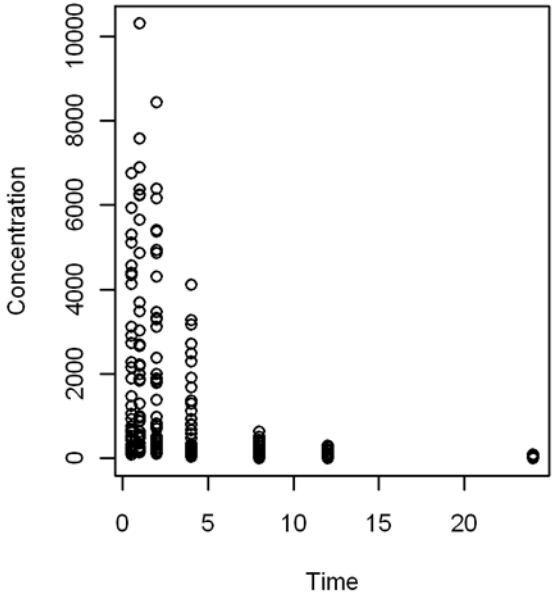
- Data file consists of records
  - Records are input to the control stream
  - One line per record
  - For our PK model, should contain at least
    - ID Subject identifier
    - TIME Time
    - DV Dependent variable (observed value)
    - AMT Bolus amount (zero if none)
    - MDV Missing DV (also for dose record)
  - Other data fields
    - CMT compartment number of observation or dose (larger models)
    - RATE infusion rate (duration not required as AMT is already specified
    - ADDL, II dose records for multiple dose
    - Covariates: e.g. weight, height, age, sex etc

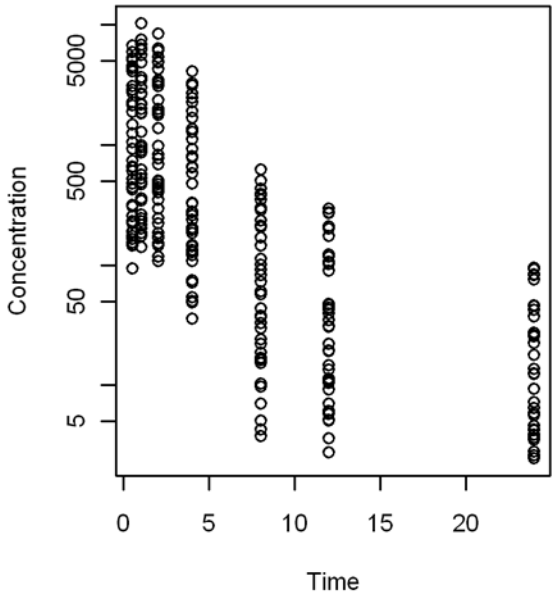
Dataset construction flow path

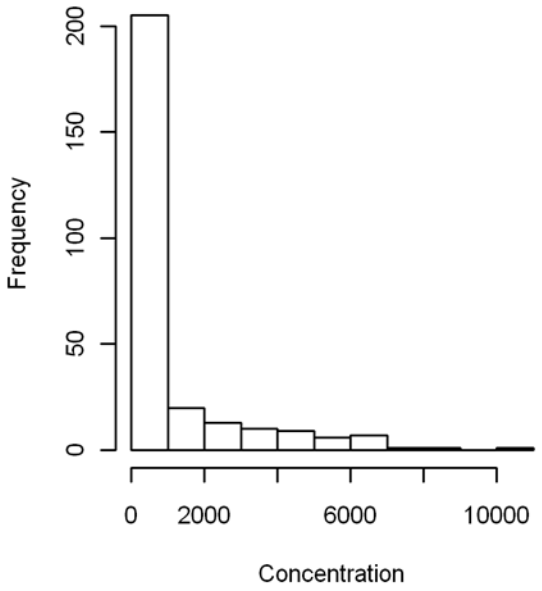
ID	TIME	DV	MDV	AMT	DOSE	WGT
1	0	.	1	300	0.3	77.1
1	0.5	166	0	0	0.3	77.1
1	1	248	0	0	0.3	77.1
1	2	138	0	0	0.3	77.1
1	4	53.3	0	0	0.3	77.1
1	8	11.8	0	0	0.3	77.1
1	12	2.36	0	0	0.3	77.1
2	0	.	1	1000	1	73.5
2	0.5	244	0	0	1	73.5
2	1	477	0	0	1	73.5
2	2	306	0	0	1	73.5
2	4	158	0	0	1	73.5
2	8	32.1	0	0	1	73.5
2	12	14.3	0	0	1	73.5
2	24	5.03	0	0	1	73.5



The data


Concentration
0
2000
4000
6000
8000
10000
0
5
10
15
20
Time


Concentration
5
50
500
5000
0
5
10
15
20
Time

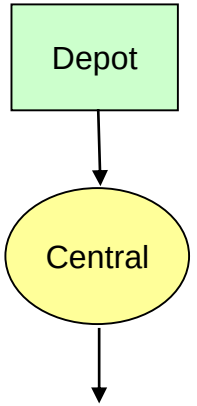

Frequency
0
50
100
150
200
0
2000
6000
10000
Concentration

NONMEM control stream

- Control stream is written as asci text
  - Tabs are not allowed
  - Maximum 80 characters per line
  - ; precedes comments
  - Some names are reserved; e.g. DV, PRED
  - Control stream consists of a series of $ records
  - Each $ record may have multiple statements

NONMEM control stream 1st model

```
$PROBLEM Example 02 1-compartmental with oral absorption
; One compartment model with linear elimination and linear absorption
$DATA PK.AJ062010-PC-001.2010-05-31.csv IGNORE=I
$INPUT ID TIME DV MDV AMT DOSE WGT
$SUB ADVAN2 TRANS2
$PK
   CL   = THETA(1)*EXP(ETA(1))      ; clearance
   V    = THETA(2)*EXP(ETA(2))      ; apparent distribution volume
   KA   = THETA(3)*EXP(ETA(3))      ; absorption rate parameter
   S2   = V                         ; Scaling factor central compartment
$ERROR
  Y= F*(1+ERR(1))
  IPRE=F
$THETA
  (0,0.1)      ; 1
  (0,0.6)      ; 2
  (0,1)        ; 3
$OMEGA
  0.16
  0 FIX
  0 FIX
$SIGMA
  0.02
$EST PRINT=5 MAX=9999 METHOD=1 INTERACTION POSTHOC NOABORT
$COV COMP
$TABLE ID TIME IPRE MDV CL DOSE WGT ETA1 ETA2 ETA3
NOPRINT ONEHEADER  FILE=result.txt
```



Warning: user takes care of units
- Avoid unit conversions in control stream

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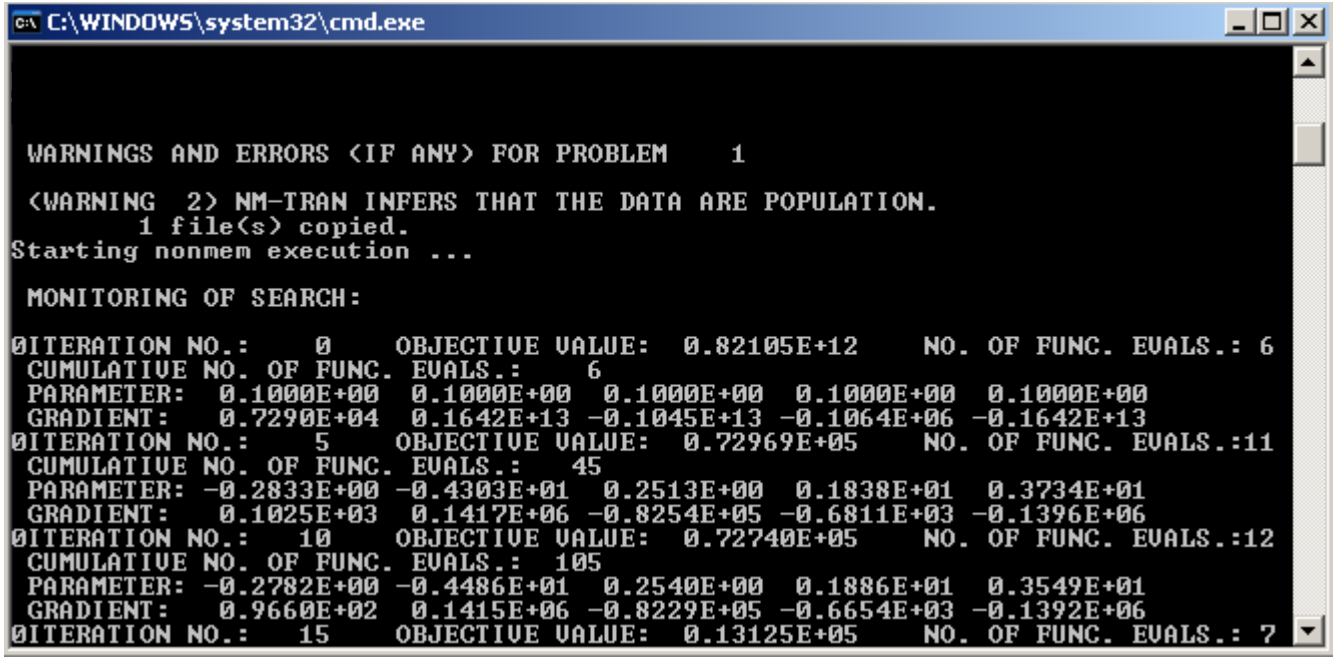
NONMEM run 1st model



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NONMEM output files

- Comprehensive output file with echo of control stream, computation details and parameter estimates (ascii file)
  - `output.txt`
- Table with output as specified in control stream
  - `result.txt`
- Processing of output:
  - Table with parameter estimates
  - Graphs for interpretation of results

Parameter estimates 1st model

THETA	Estimate	S.E.	RSE	LLCI	ULCI
TH 1 (CL)	0.371	0.021	5.66	0.33	0.412
TH 2 (V)	1.64	0.0811	4.95	1.48	1.8
TH 3 (KA)	3.86	0.466	12.1	2.95	4.77

OMEGA	Estimate	S.E.	RSE
VAR ETA 1	0.052	0.0206	39.6
COV ETA 1-2	0		
VAR ETA 2	0		
COV ETA 1-3	0		
COV ETA 2-3	0		
VAR ETA 3	0		

SIGMA	Estimate	S.E.	RSE
VAR EPS 1	0.299	0.0224	7.49

Correlation matrix of estimates

TH 1	1.000				
TH 2	0.639	1.000			
TH 3	0.050	0.468	1.000		
VAR ETA 1	0.392	-0.392	-0.454	1.000	
VAR EPS 1	0.118	0.572	0.277	-0.622	1.000

Covariance matrix of estimates

TH 1	4.39e-04				
TH 2	1.09e-03	6.58e-03			
TH 3	4.87e-04	1.77e-02	2.17e-01		
VAR ETA 1	1.69e-04	-6.54e-04	-4.35e-03	4.23e-04	
VAR EPS 1	5.54e-05	1.04e-03	2.89e-03	-2.87e-04	5.03e-04

MVOF 1st 3051.188

Look for:
- Realistic values for thetas ?
- Relative standard error (RSE) should be lower than 50%
-Variance of SIGMA compared with OMEGA
-Correlations in parameter estimates

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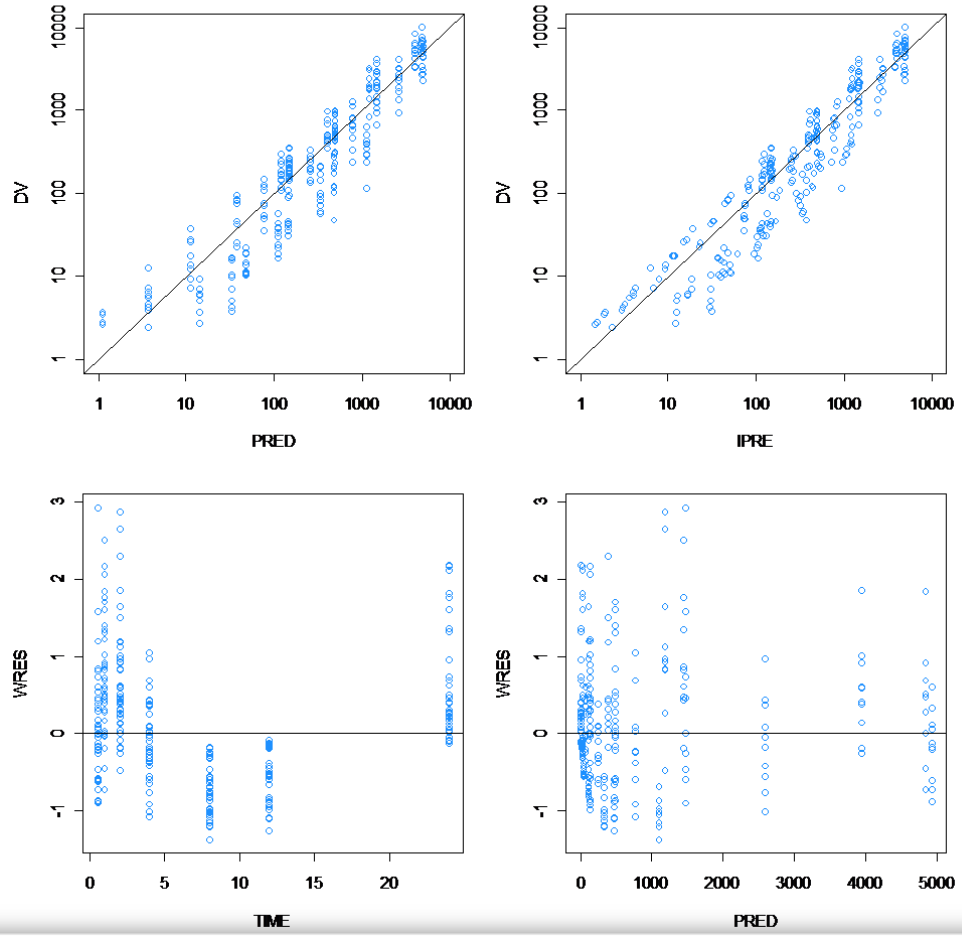
GOF plots 1st model



DV versus PRED should be centered around identity line

DV versus IPRE should be centered around identity line

WRES versus TIME should be centered around zero line
- Plot shows trend with time
- Not symmetrically distributed

WRES versus PRED should be centered around zero line
- Plot shows trend with PRED
- Not symmetrically distributed

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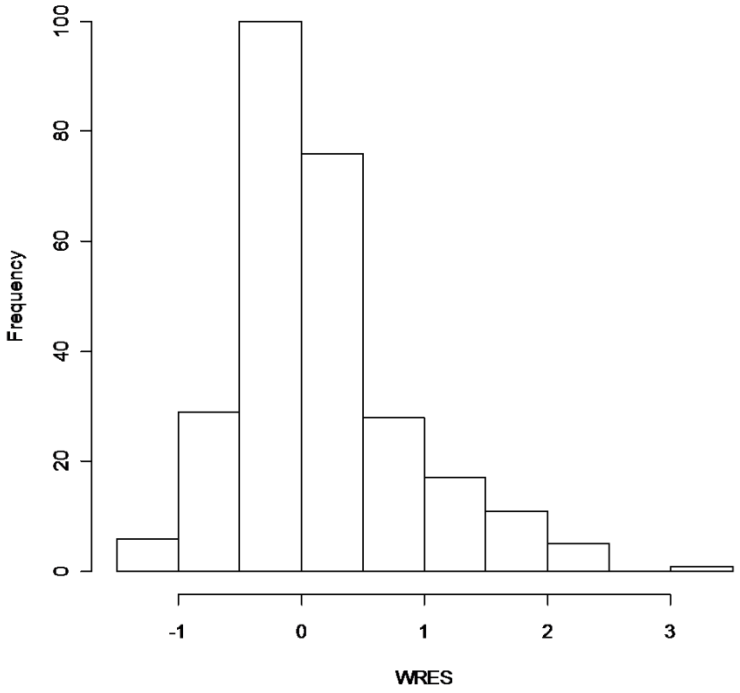
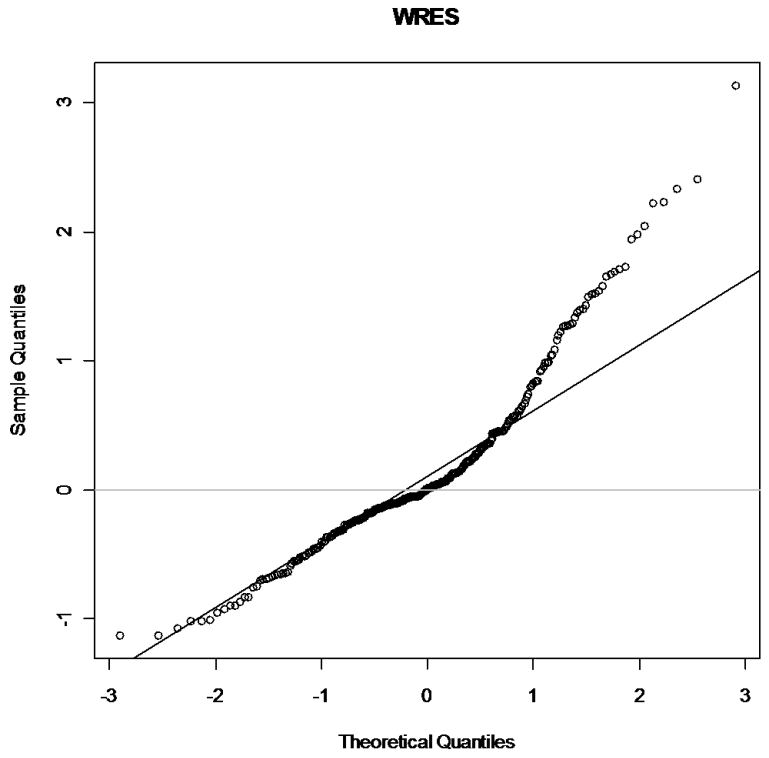
Weighted residuals 1st model

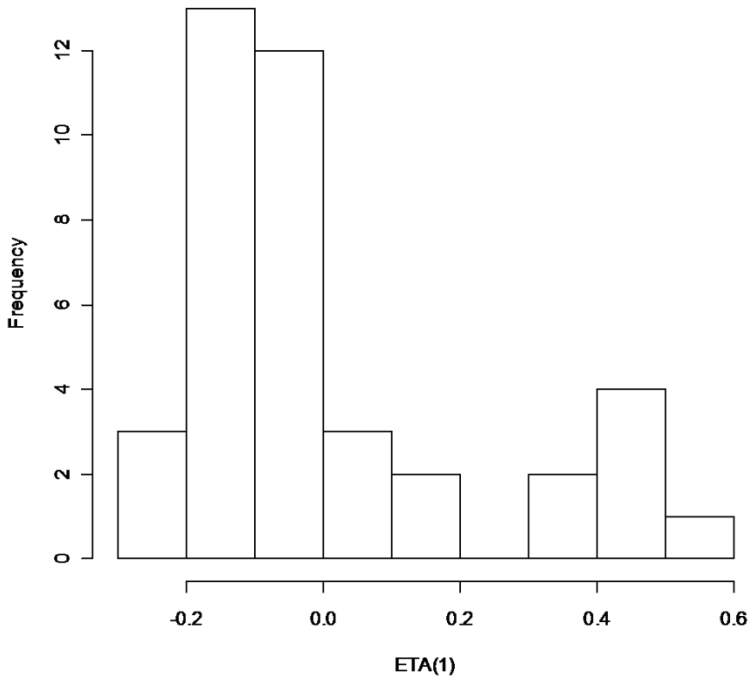




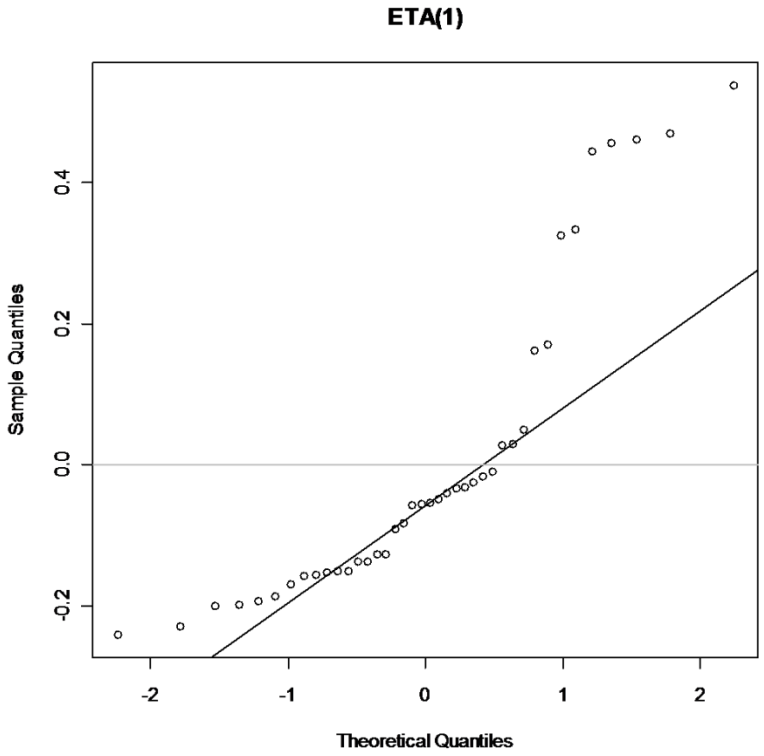
Histogram should not be skewed

QQ plot should show straight line

ETA distributions 1st model

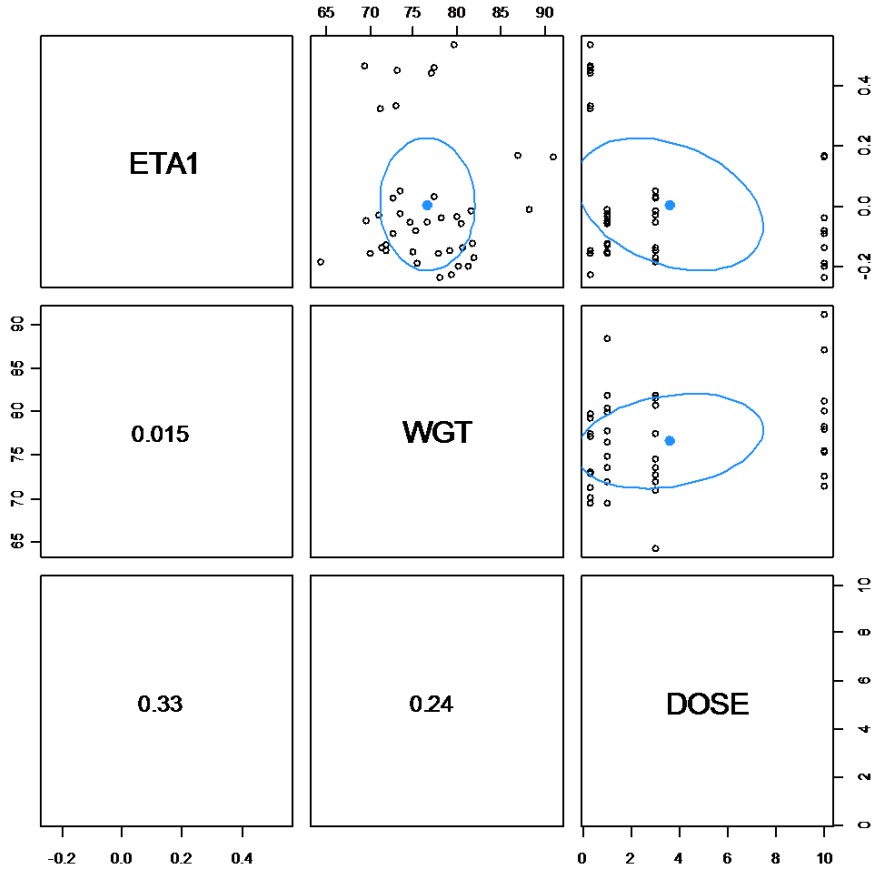


Histogram should not be skewed



QQ plot should show straight line

Matrix of ETA-covariate scatter plots 1st model



Plot may show presence of correlations between random effects and covariates

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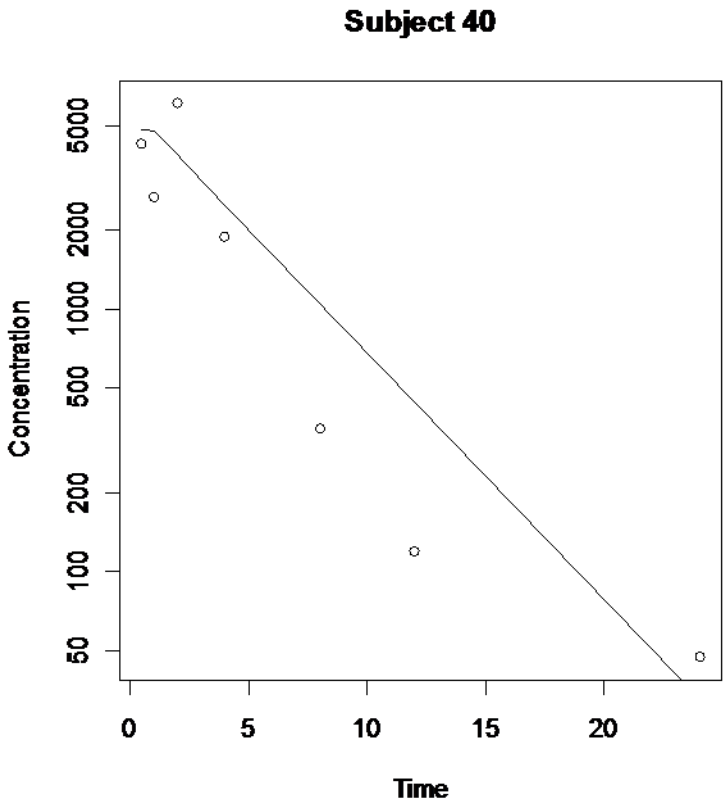
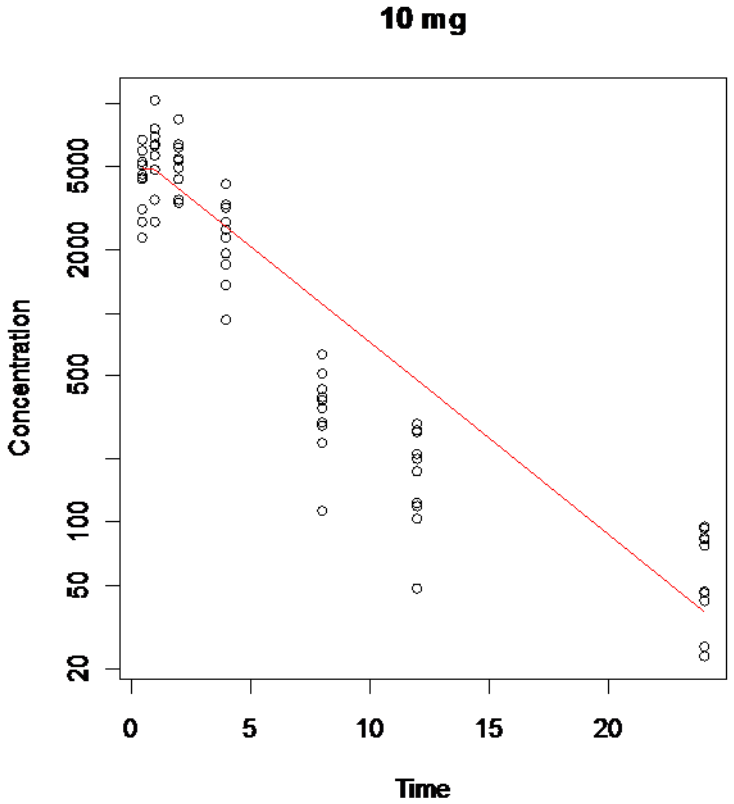
PK curves 1st model



Individual curve suggests one exponential phases and data two exponential phases



Population curve suggest one exponential phases and data two exponential phases

Second attempt

```
$PROBLEM Example 03 2-compartmental with oral absorption
; Two compartment model with linear elimination and linear absorption
$DATA PK.AJ062010-PC-001.2011-01-04.csv IGNORE=I
$INPUT ID TIME DV MDV AMT DOSE WGT
$SUB ADVAN4 TRANS4
$PK
   CL  = THETA(1)*EXP(ETA(1))      ; apparent clearance
   V2  = THETA(2)*EXP(ETA(2))      ; apparent central distribution volume
   KA  = THETA(3)*EXP(ETA(3))      ; absorption rate parameter
   V3  = THETA(4)                  ; apparent peripheral distribution volume
   Q   = THETA(5)                  ; apparent intercompartment clearance
   S2  = V2                        ; Scaling factor central compartment
$ERROR
  Y= F*(1+ERR(1))
  IPRE=F
$THETA
  (0,0.1)      ; 1
  (0,0.6)      ; 2
  (0,1)        ; 3
  (0,1.2)      ; 4
  (0,1.1)      ; 5
$OMEGA
  0.16
  0 FIX
  0 FIX
$SIGMA
  0.02
$EST PRINT=5 MAX=9999 METHOD=1 INTERACTION POSTHOC NOABORT
$COV COMP
$TABLE ID TIME IPRE MDV CL DOSE WGT ETA1 ETA2 ETA3
NOPRINT ONEHEADER  FILE=result.txt
```

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Parameter estimates 2nd

THETA	Estimate	S.E.	RSE	LLCI	ULCI
TH 1	0.383	0.0216	5.64	0.341	0.425
TH 2	0.397	0.0464	11.7	0.306	0.488
TH 3	0.662	0.0617	9.32	0.541	0.783
TH 4	0.676	0.0566	8.37	0.565	0.787
TH 5	0.0676	0.00451	6.67	0.0588	0.0764

OMEGA	Estimate	S.E.	RSE
VAR ETA 1	0.0805	0.0175	21.7
COV ETA 1-2	0		
VAR ETA 2	0		
COV ETA 1-3	0		
COV ETA 2-3	0		
VAR ETA 3	0		

SIGMA	Estimate	S.E.	RSE
VAR EPS 1	0.0641	0.00486	7.58

Correlation matrix of estimates

TH 1	1.000						
TH 2	0.005	1.000					
TH 3	-0.171	0.925	1.000				
TH 4	0.567	-0.429	-0.613	1.000			
TH 5	0.509	0.198	0.144	0.407	1.000		
VAR ETA 1	0.354	-0.283	-0.309	0.176	0.041	1.000	
VAR EPS 1	0.172	-0.157	-0.222	0.125	-0.263	0.075	1.000

Covariance matrix of estimates

TH 1	4.66e-04						
TH 2	4.71e-06	2.15e-03					
TH 3	-2.28e-04	2.65e-03	3.80e-03				
TH 4	6.92e-04	-1.13e-03	-2.14e-03	3.20e-03			
TH 5	4.96e-05	4.14e-05	4.01e-05	1.04e-04	2.03e-05		
VAR ETA 1	1.34e-04	-2.30e-04	-3.34e-04	1.75e-04	3.26e-06	3.06e-04	
VAR EPS 1	1.81e-05	-3.54e-05	-6.67e-05	3.43e-05	-5.78e-06	6.40e-06	2.37e-05

MVOF 1st 3051.188
MVOF 2nd 2580.531

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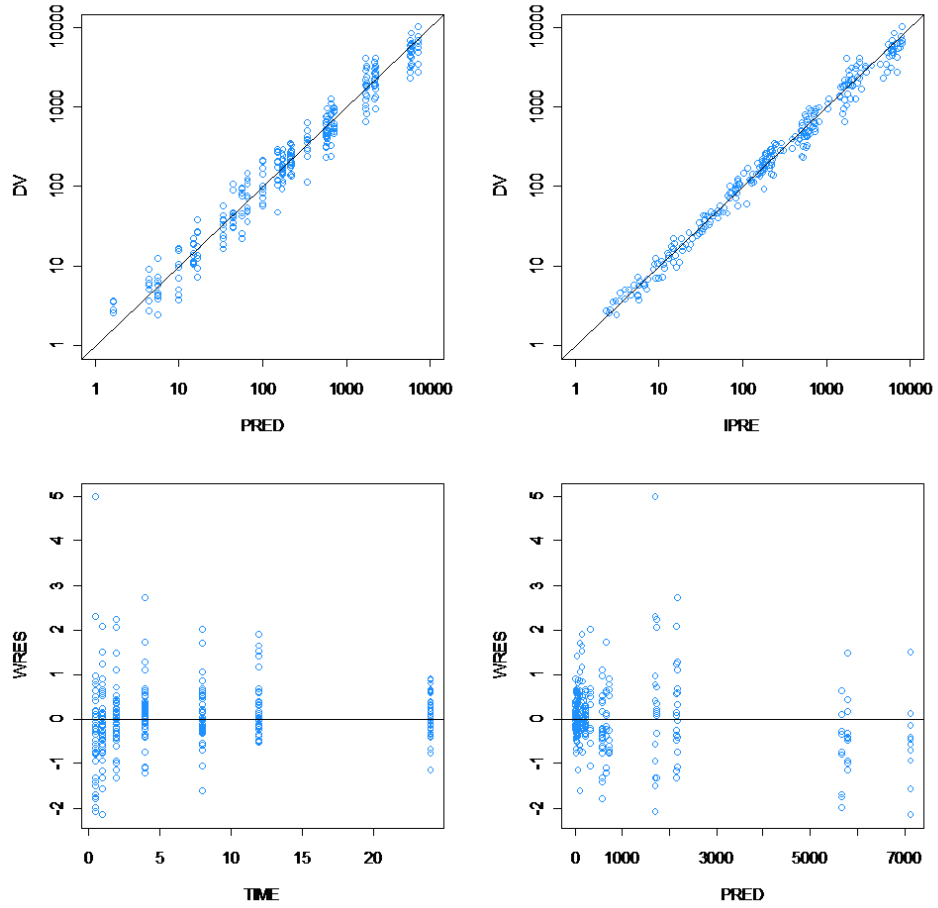
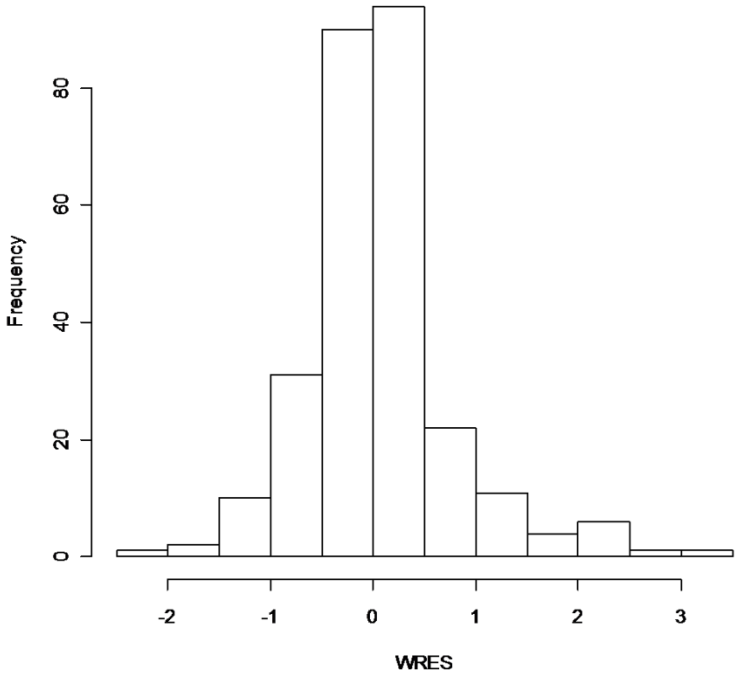
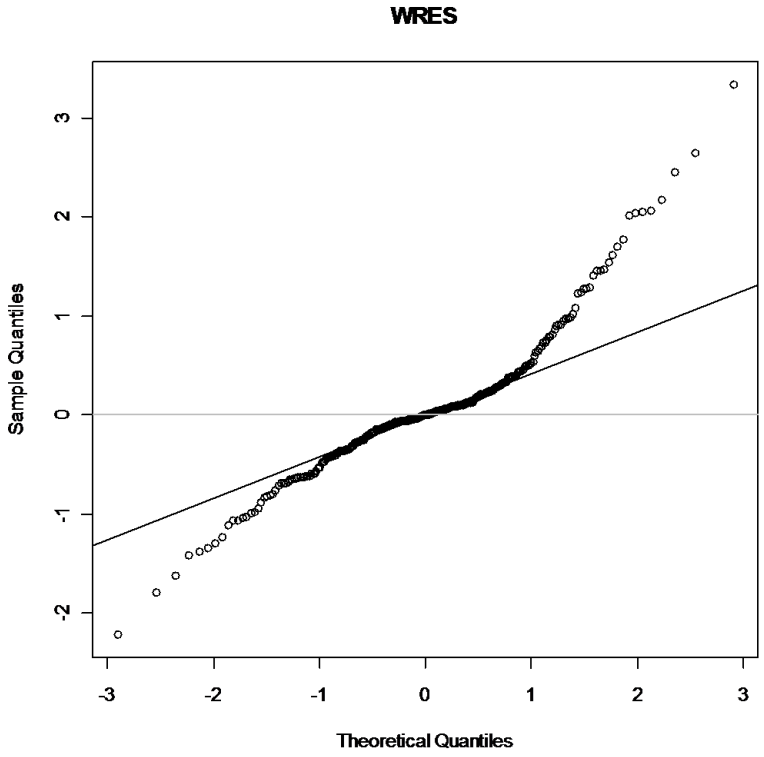
GOF plots 2nd

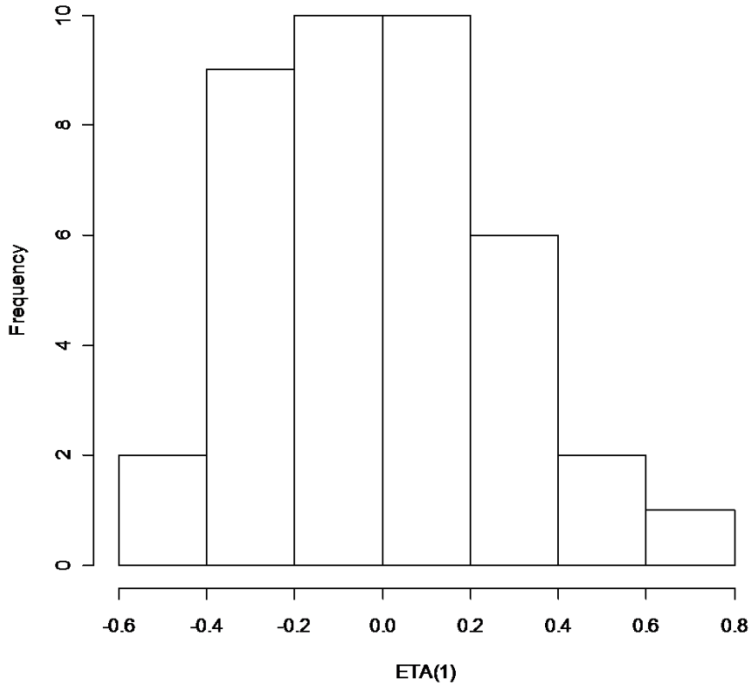


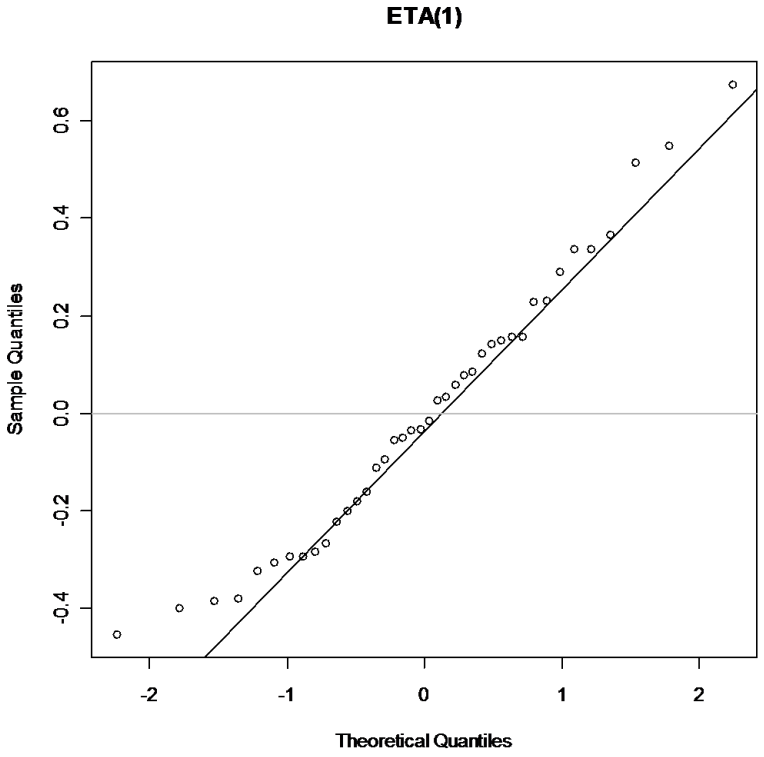
Weighted residuals 2nd



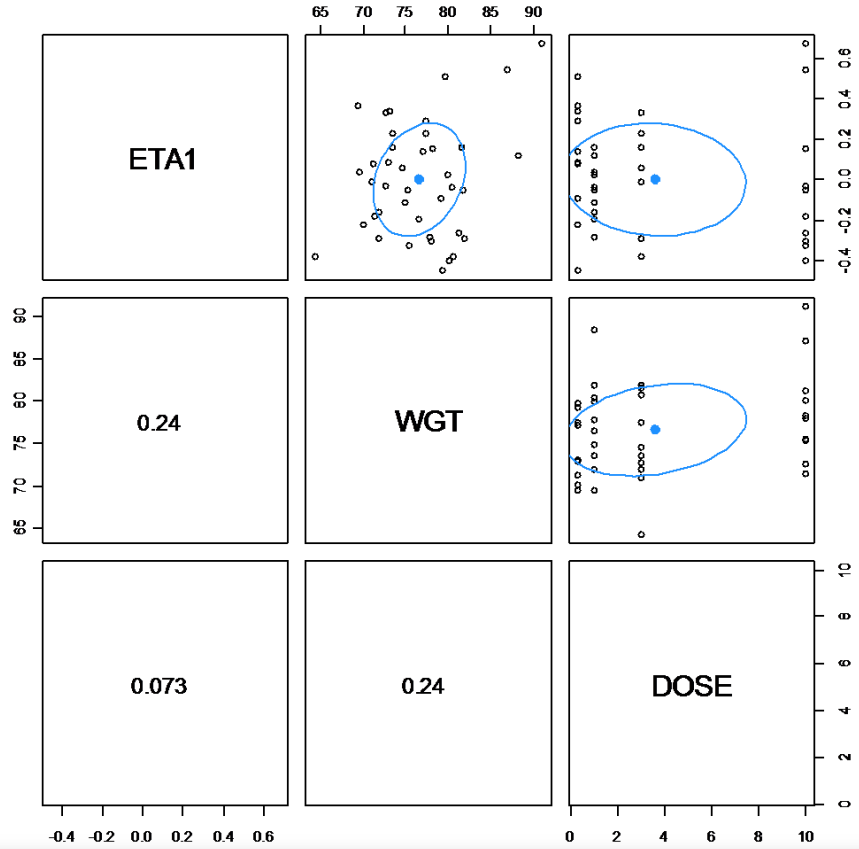


ETA distributions 2nd

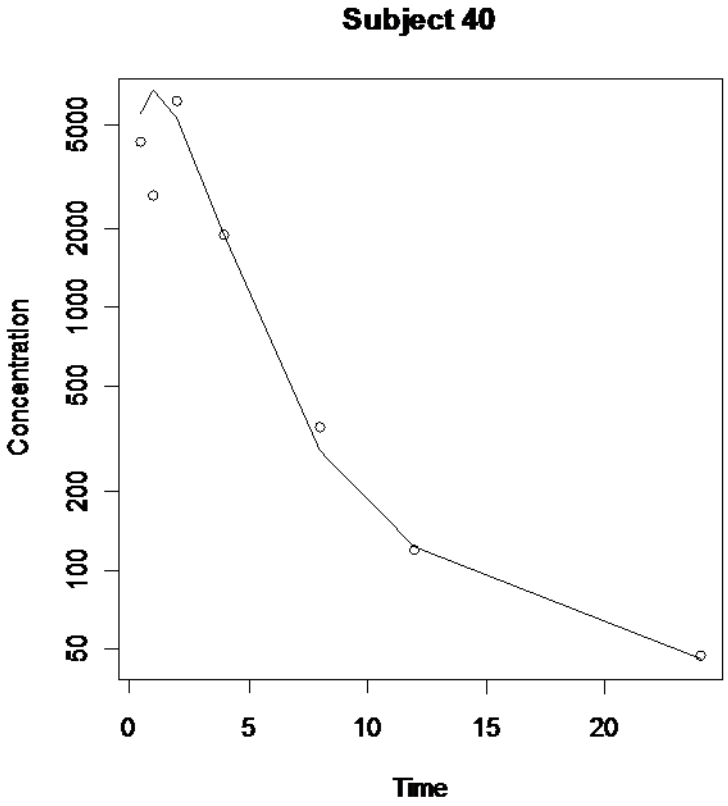


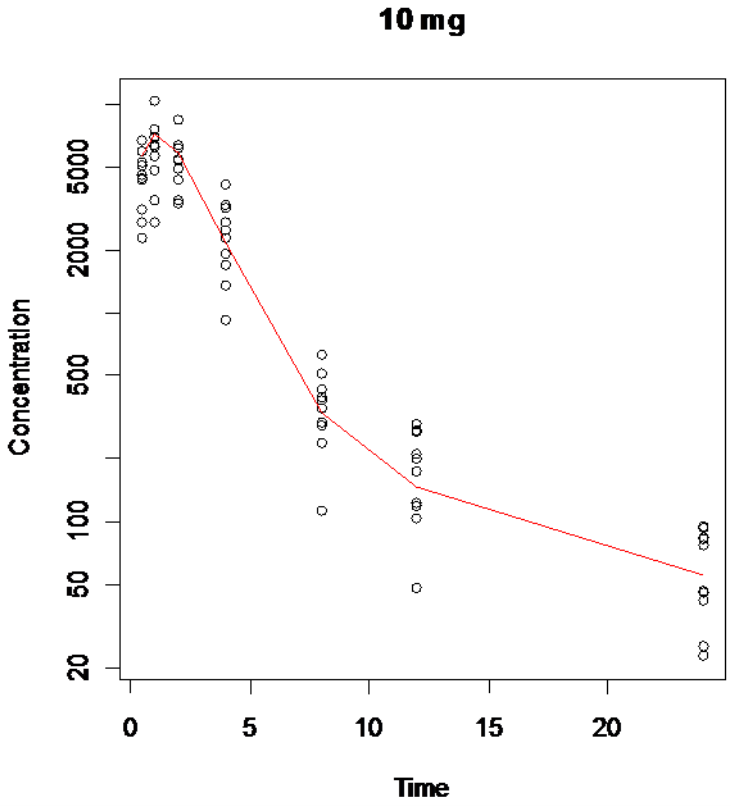


Matrix of ETA-covariate scatter plots 2nd



PK curves 2nd





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Model development

- After completing your initial model
  - Interpret GOF plots: model bias indicates that you may need a more complex model
  - Look at the parameter estimates:
    - Strong correlations between parameter estimates may indicate over-parameterization: reduce number of parameters by taking limiting cases
    - If the S.E. of the estimate is large compared with the estimate (%RSE >50%) this indicates large parameter uncertainty, and departure from the assumptions in NONMEM in the calculation of the covariance matrix of the estimate: bootstrap may be required to assess parameter uncertainty and model robustness
    - If the S.E. is low (%RSE <20%) , the S.E. is a fair approximation for the uncertainty expressed by the 95% CI

Model development

- Compare the distribution of the post hoc estimates with the (normal) distribution following from the variance estimated by NONMEM
  - Shrinkage may indicate too many terms in OMEGA
- Evaluate the Objective function value (OFV) compared with the OFV of alternative models
  - In some cases a Likelihood ratio test can be applied
- Perform a (visual) predictive check by
  - Simulating the parameter uncertainty and variability in the PK-curves and comparing this with the observations (large population sizes)
  - Simulating the median PK curve and its 95% CI for a small group and comparing this with the observed median

Final model

- Multiple criteria to decide whether you reached your best model
  - Not just look at the likelihood ratio test (is only valid in very specific cases)
  - Look at skewness and kurtosis of random effects
    - Deviation from normality may compromise your simulations
  - Look at covariance matrix of estimates
    - Parameter uncertainty
  - Consider robustness of model
    - Bootstrapping, Jackknifing, Leverage
    - Validation status (external and internal)
  - Clinical utility: Is the model fit for purpose ?

Recommended readings/video

- CPT: Pharmacometrics and Systems Pharmacology
  - Tutorials
- Metrum Institute
  - www.youtube.com/user/metruminst

www.umcg.nl

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