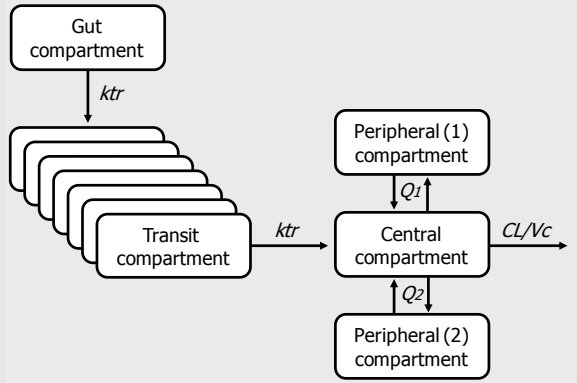
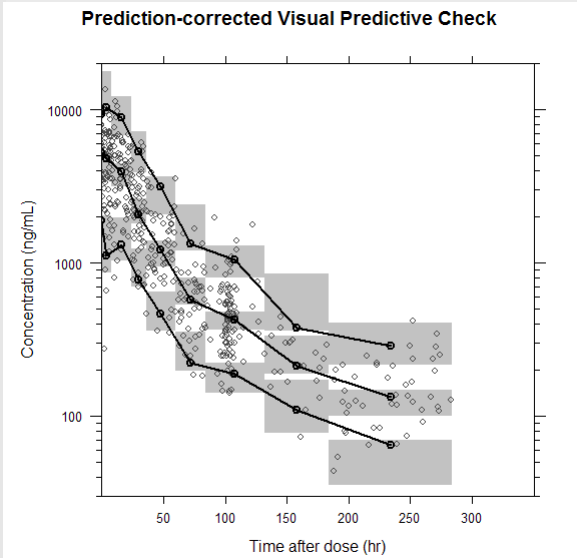
Introduction to population pharmacokinetics "*pharmacometrics*"

Dr. Joel Tarning

Mahidol-Oxford Tropical Medicine Research Unit (MORU)

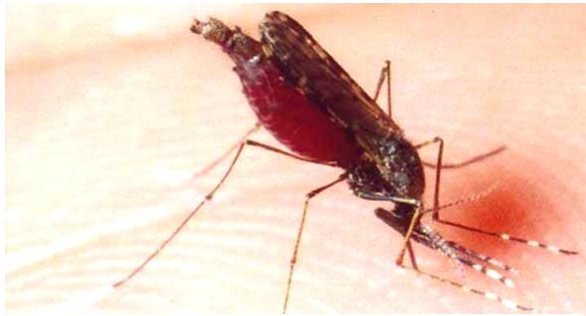
Joel@tropmedres.ac

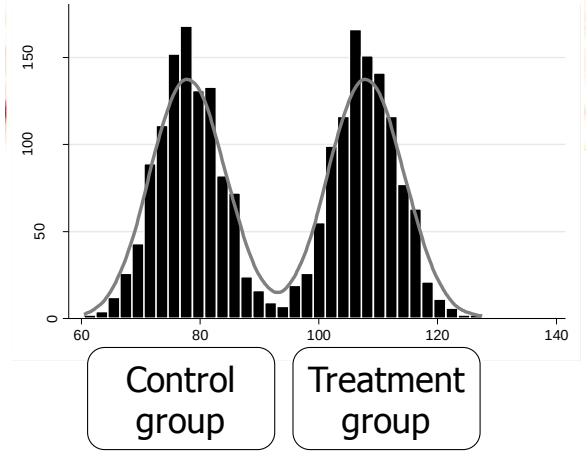




Outline

- 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

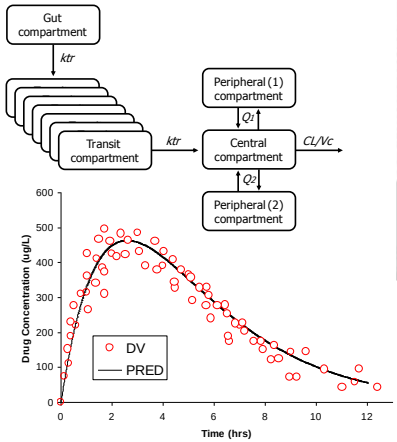
Pharmacometrics:

"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…"

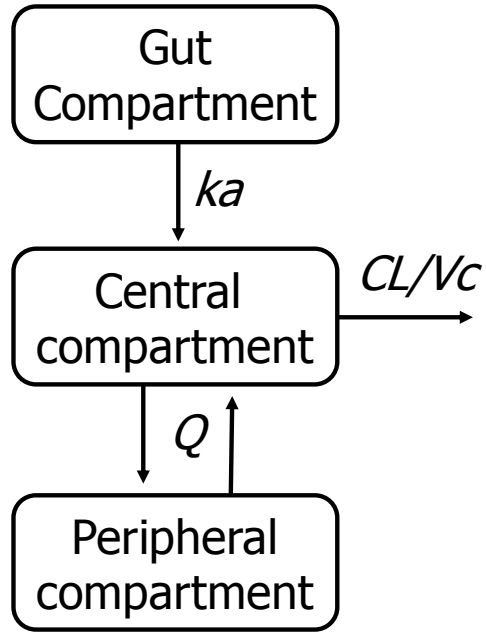
George Box, PhD

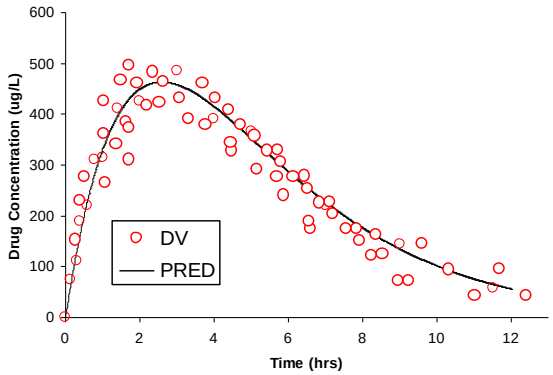


[1] Ette, E.I. and P.J. Williams, Pharmacometrics: The Science of Quantitative Pharmacology. 2007: John Wiley & Sons.

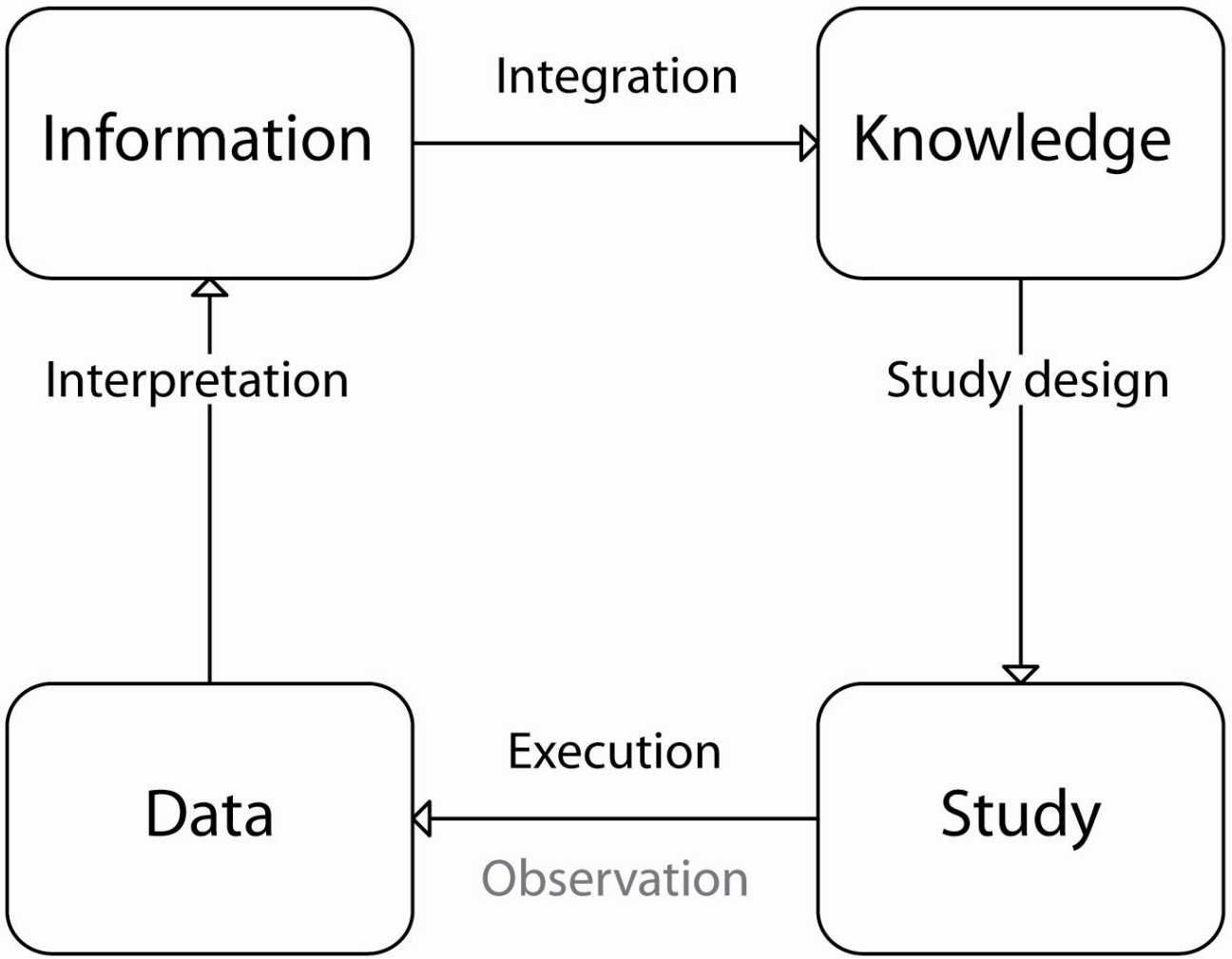
Introduction to pharmacometrics

- 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

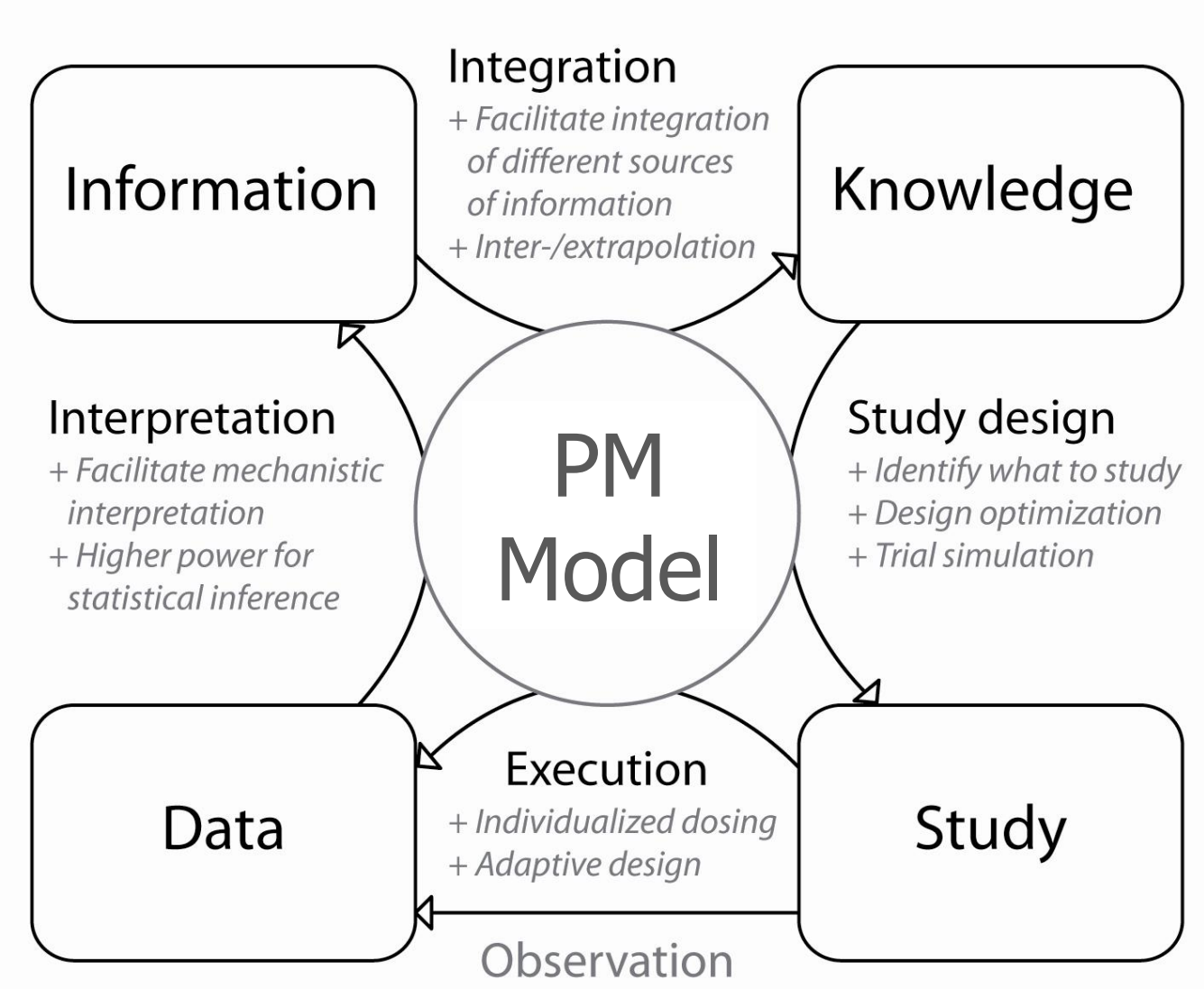




Introduction to pharmacometrics



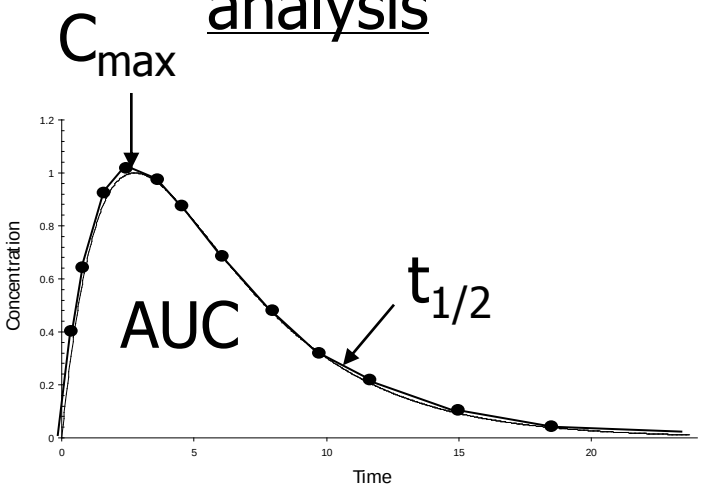
Introduction to pharmacometrics



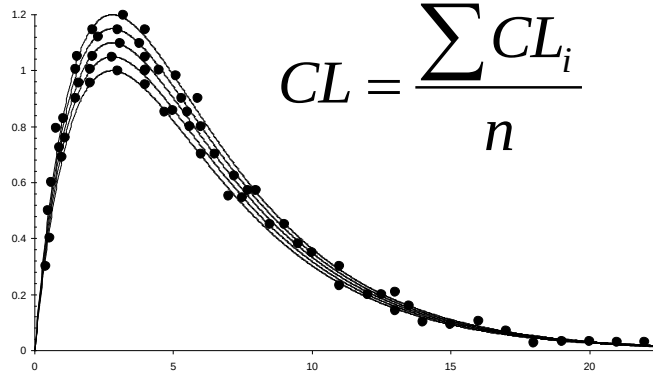
Introduction to pharmacometrics

Population pharmacokinetics (POP-PK)

Non-compartmental analysis

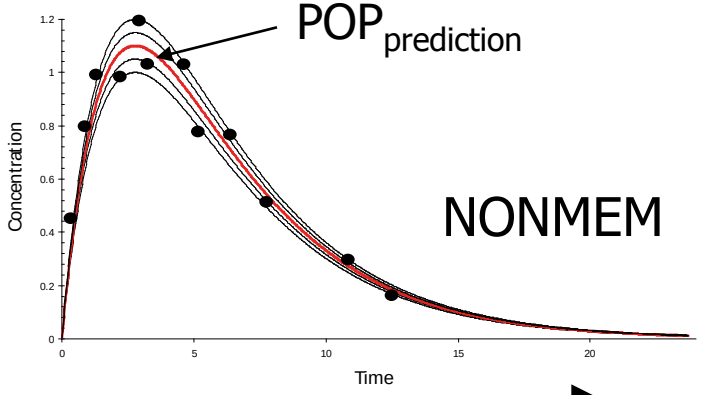


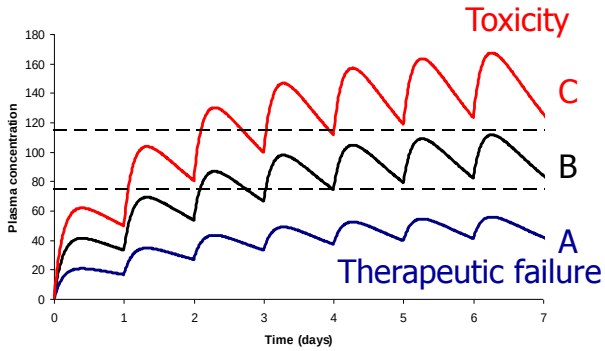
Standard two stage



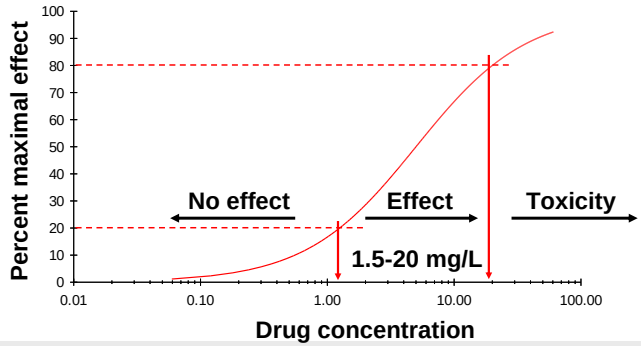
$$CL = \frac{\sum CL_i}{n}$$

Mixed effects modelling





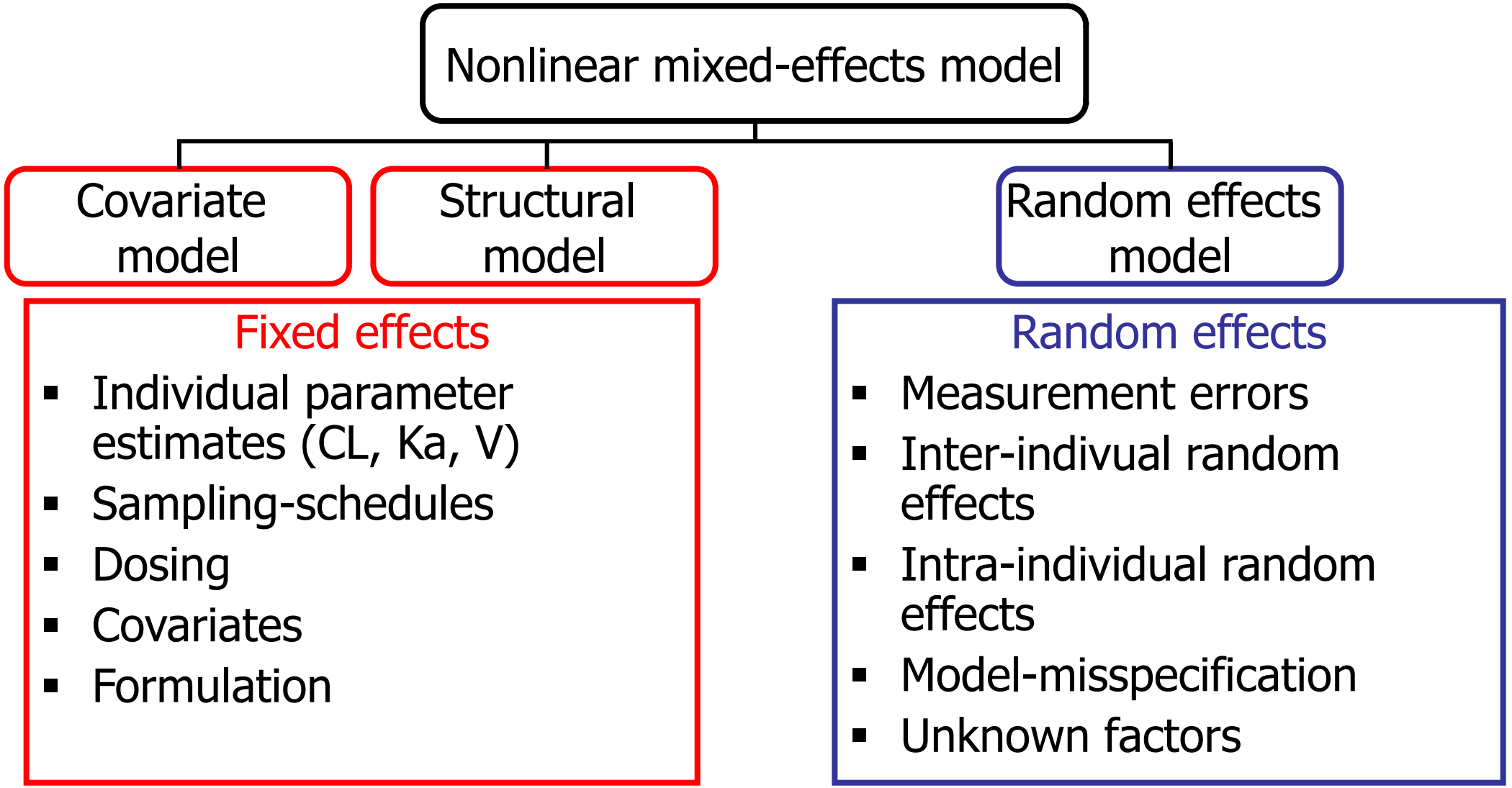
Complexity



Joel Tarning
Consensus meeting
South Africa 2011-10-18

wellcome trust MORU Mahidol Oxford
WELLCOME TRUST - MAHIDOL UNIVERSITY - OXFORD TROPICAL MEDICINE RESEARCH PROGRAMME

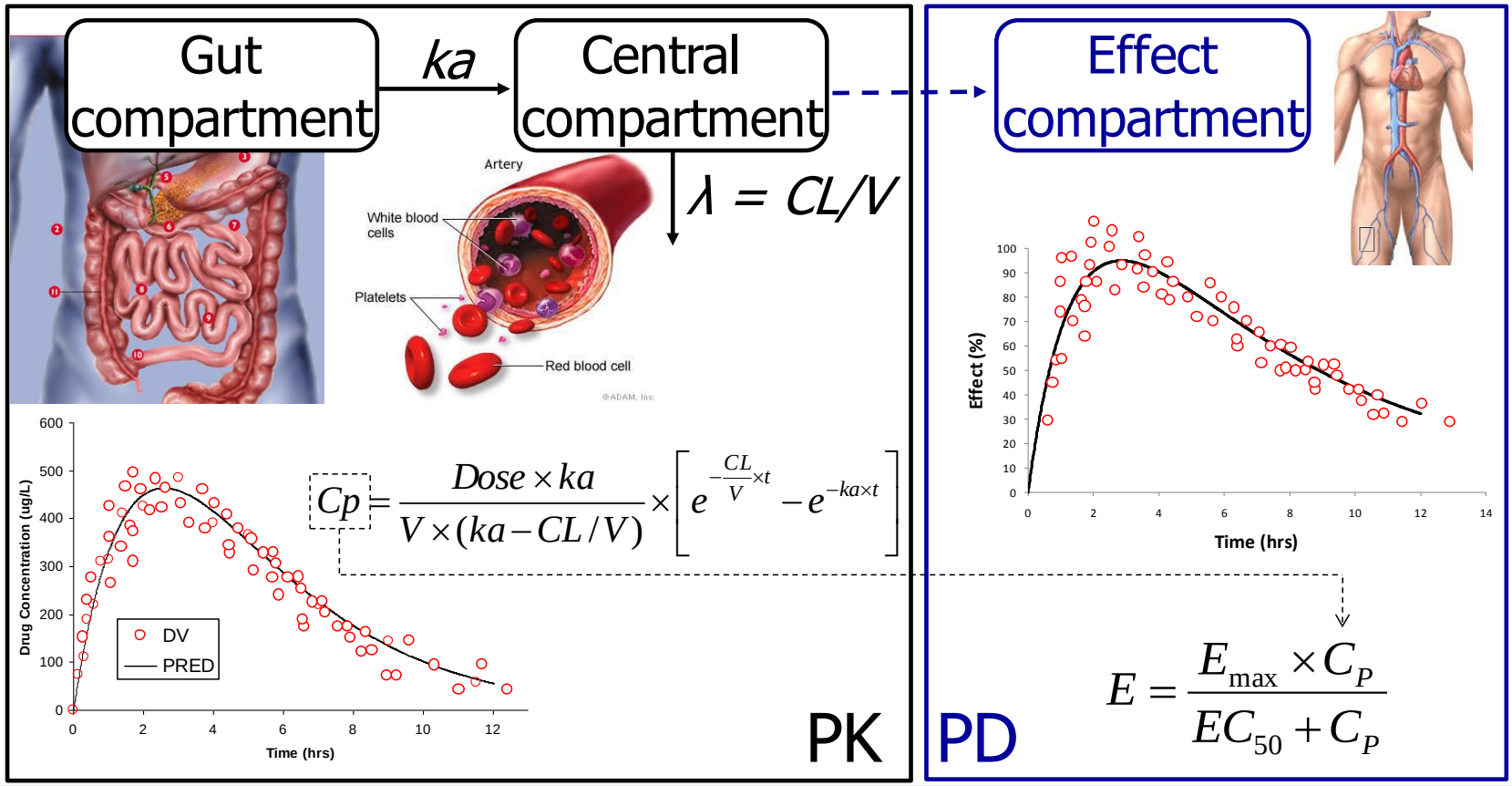
Introduction to pharmacometrics



Introduction to pharmacometrics

- Pharmacometrics (population PK/PD)

  -The aim of the pharmacometric model is to describe pharmacological responses quantitatively and qualitatively



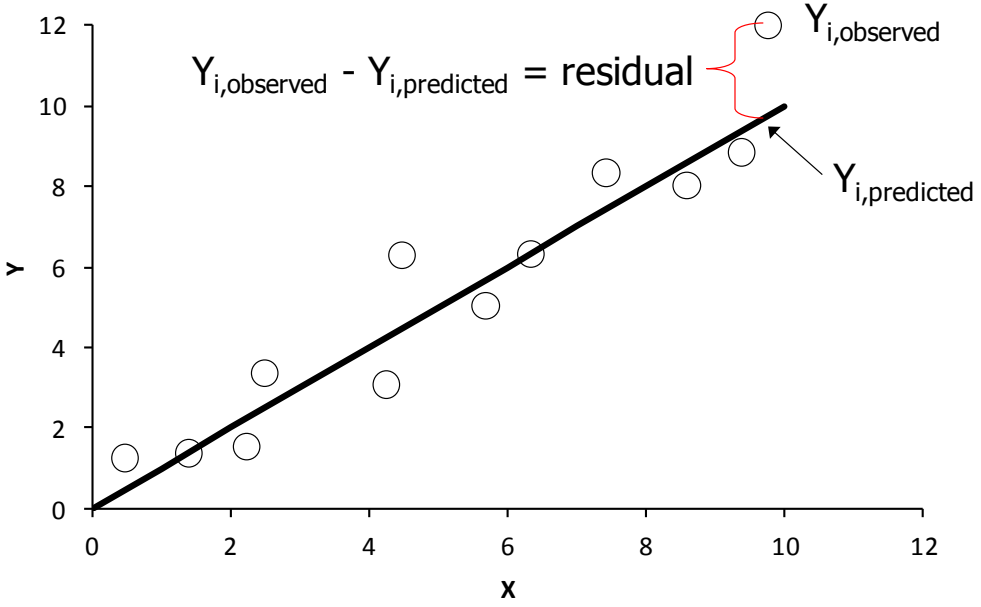
Introduction to pharmacometrics

Linear regression

$Y = a \times x + b$

Minimisation of squared residuals (SS):

$\Sigma [Y_{i,observed} - Y_{i,predicted}]^2$

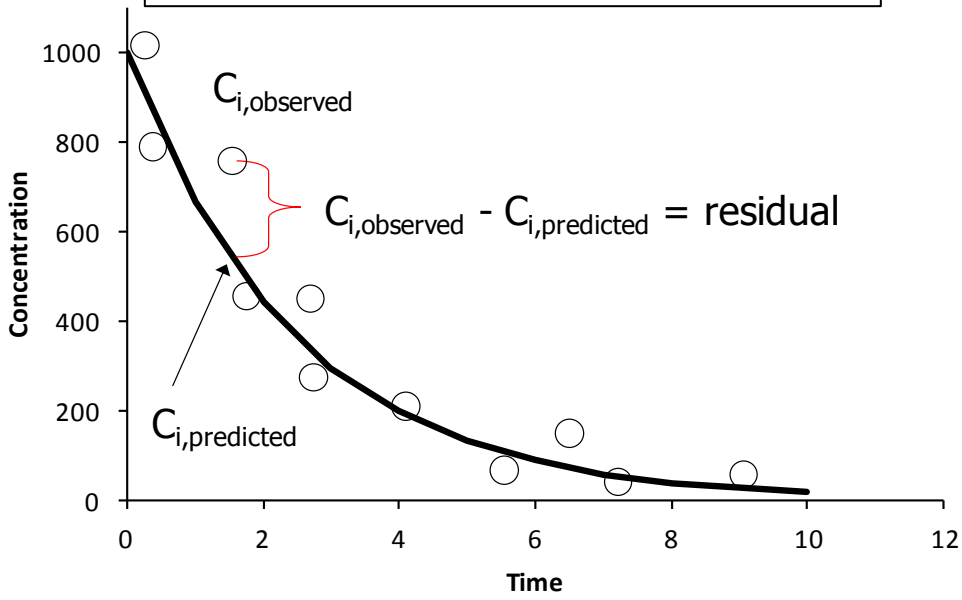


$C = C_0 \times e^{-k \times t}$

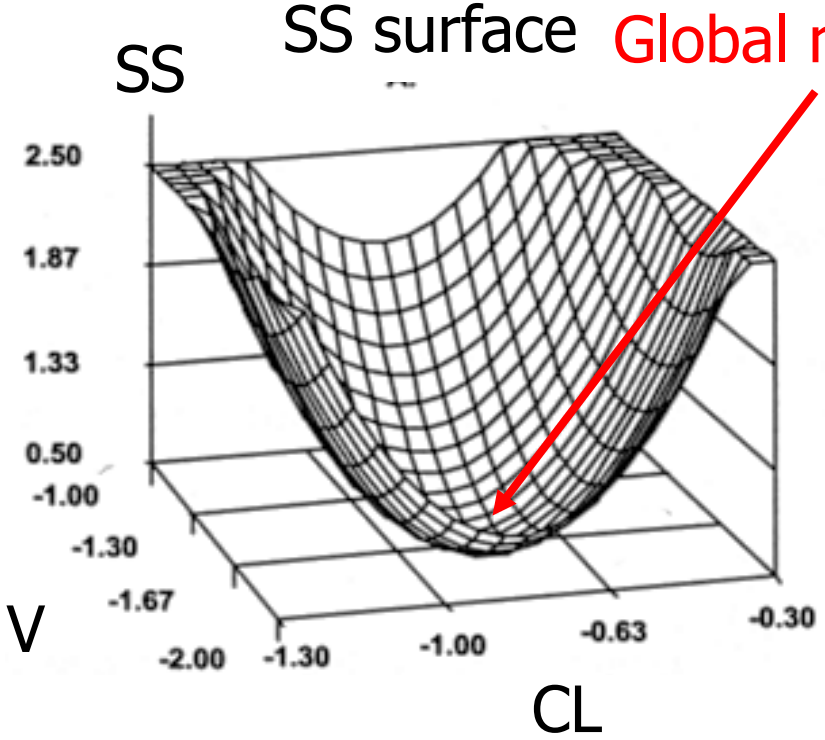
$C_0 = Dose_{IV}/V$ $\quad$ $k = CL/V$

Reparametrisation:

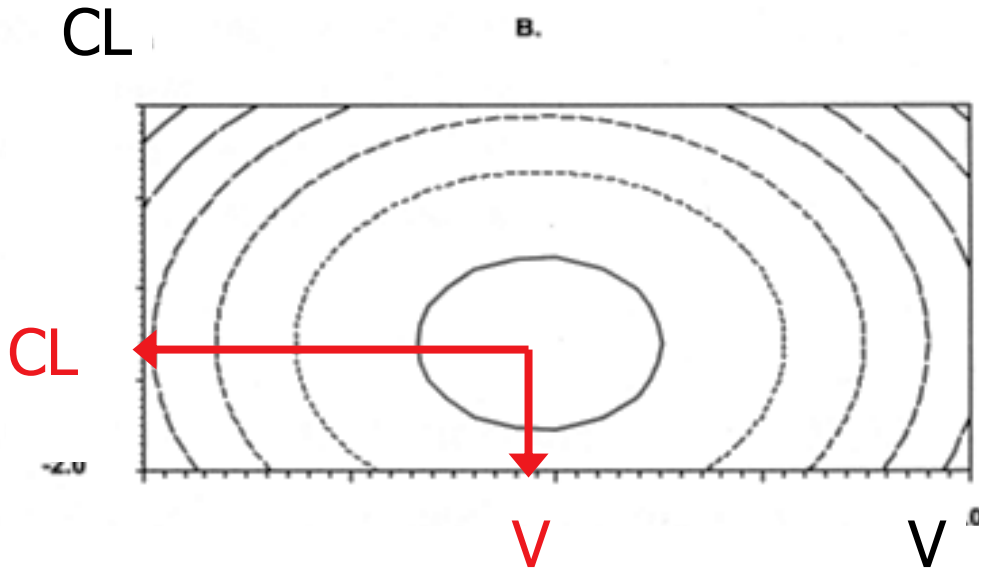
$C = [Dose_{IV}/V] \times e^{-(CL/V) \times t}$



Introduction to pharmacometrics



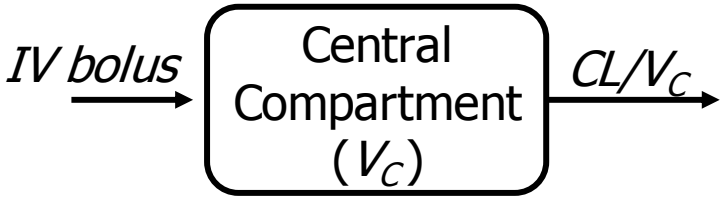
- Objective function value (OFV)
- Akaike Information Criteria (AIC)



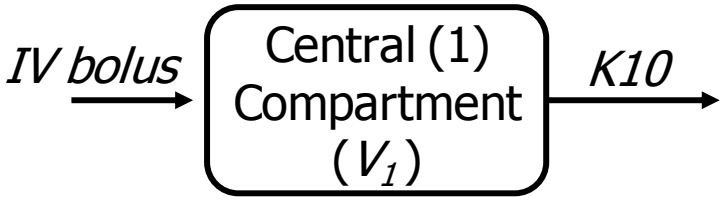
- New combinations of parameter values are tested iteratively until convergence is reached.
- The best model parameters are those that correspond to the lowest SS (logliklihood in nonlinear mixed-effects modelling)

Structural modelling

1-compartment disposition model (IV administration)

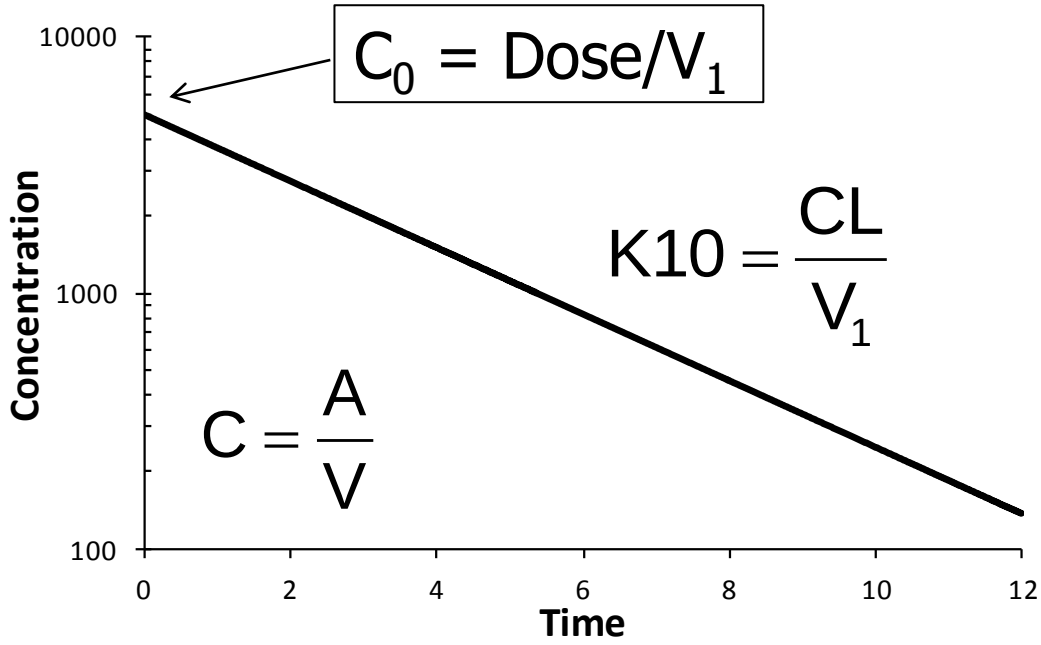


$$\frac{dA}{dT} = -\frac{CL}{Vc} \times A$$



$$\frac{dA}{dT} = -K10 \times A$$

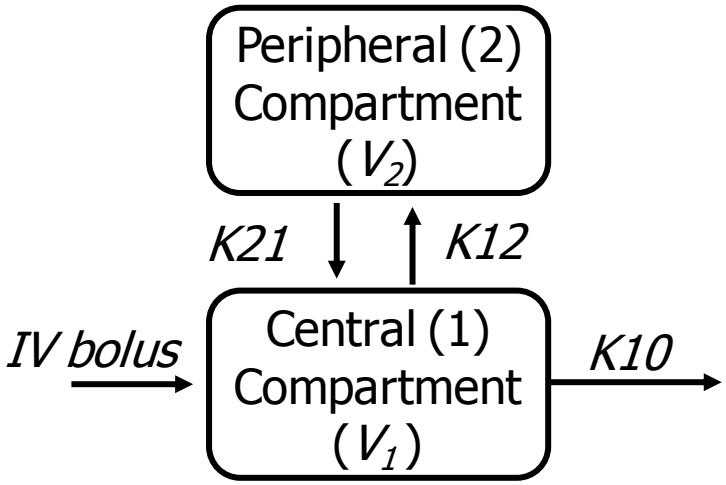
$$A(0) = Dose$$

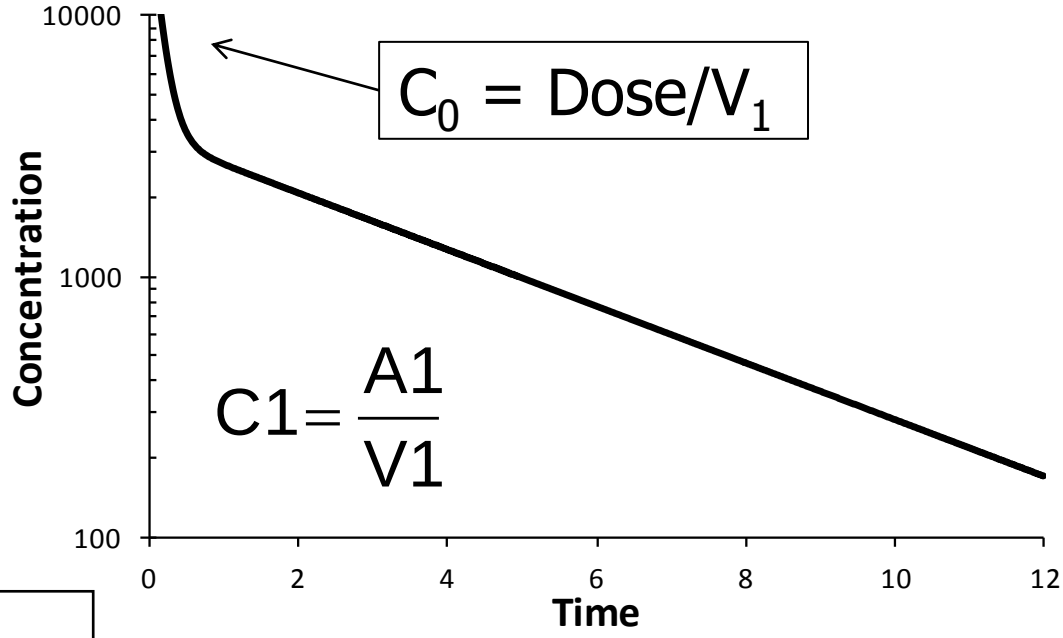


$$t_{1/2} = \frac{\ln 2}{K10} = \frac{\ln 2 \times V_1}{CL}$$

Structural modelling

2-compartment disposition model (IV administration)





$$\frac{dA1}{dT} = -K10 \times A1 - K12 \times A1 + K21 \times A2$$

$$A1(0) = Dose$$

$$\frac{dA2}{dT} = K12 \times A1 - K21 \times A2$$

$$A2(0) = 0$$

$$K10 = \frac{CL}{V_1}$$

$$K12 = \frac{Q}{V_1}$$

$$K21 = \frac{Q}{V_2}$$

Structural modelling

2-compartment disposition model (PO administration)

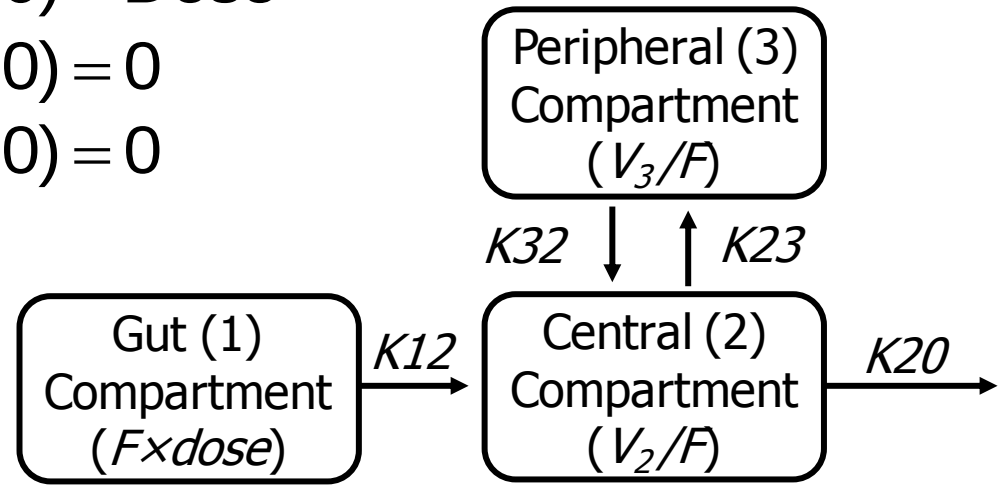
$$\frac{dA3}{dT} = K23 \times A2 - K32 \times A3$$

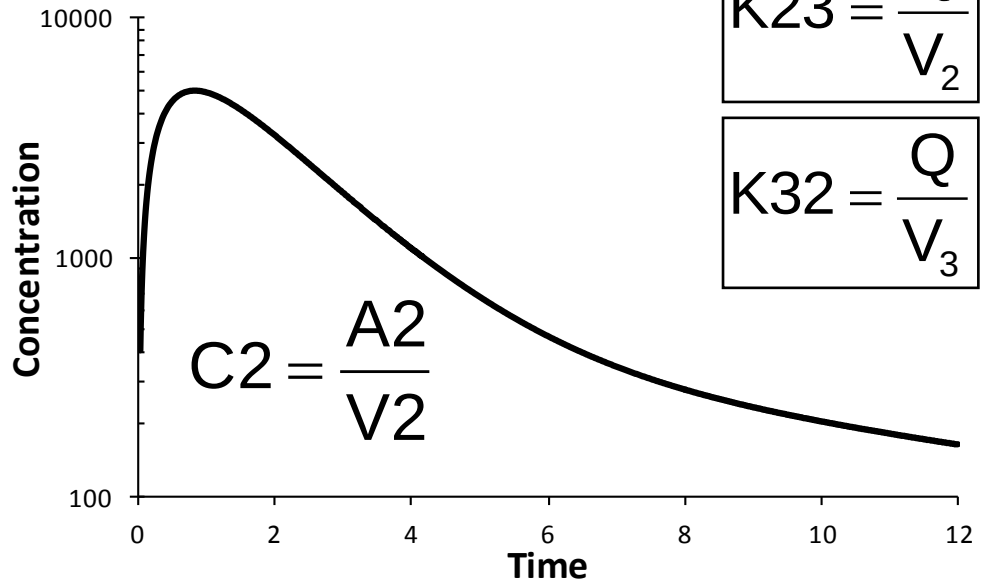
$$K20 = \frac{CL}{V_2}$$

$$K23 = \frac{Q}{V_2}$$

$$K32 = \frac{Q}{V_3}$$

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





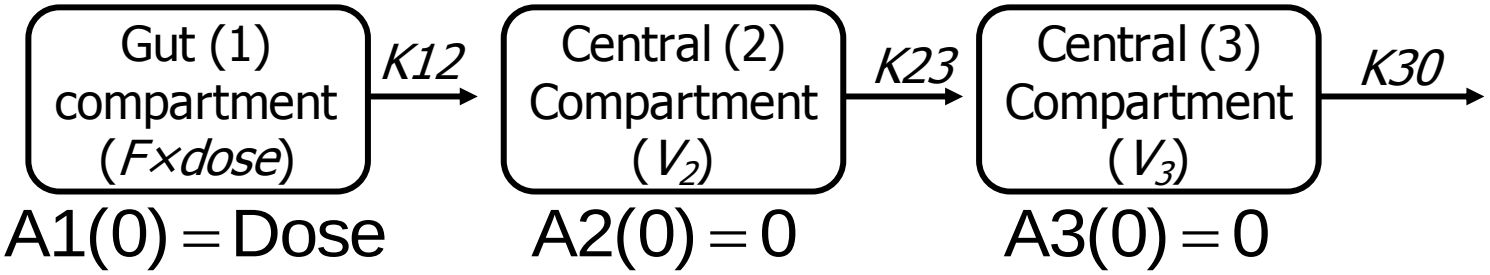
$$\frac{dA1}{dT} = -K12 \times A1$$

$$\frac{dA2}{dT} = K12 \times A1 - K23 \times A2 + K32 \times A3 - K20 \times A2$$

$$K12 = Ka$$

Structural modelling

1-compartment disposition metabolite model (PO administration)



$$K12 = Ka$$

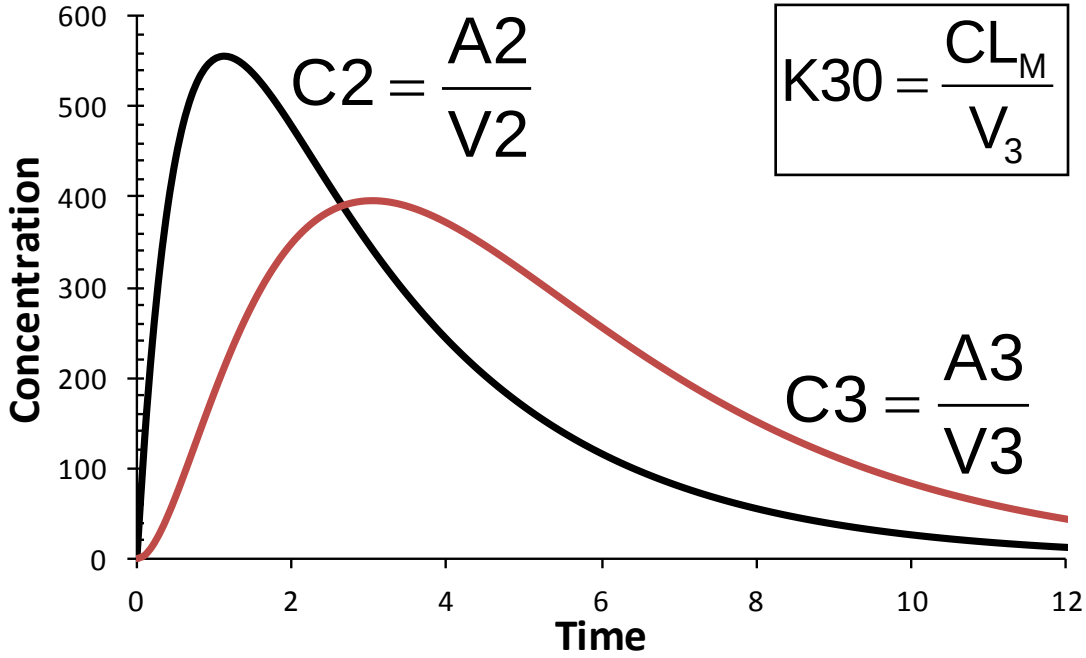
$$K23 = \frac{CL_P}{V_2}$$

$$K30 = \frac{CL_M}{V_3}$$

$$\frac{dA1}{dT} = -K12 \times A1$$

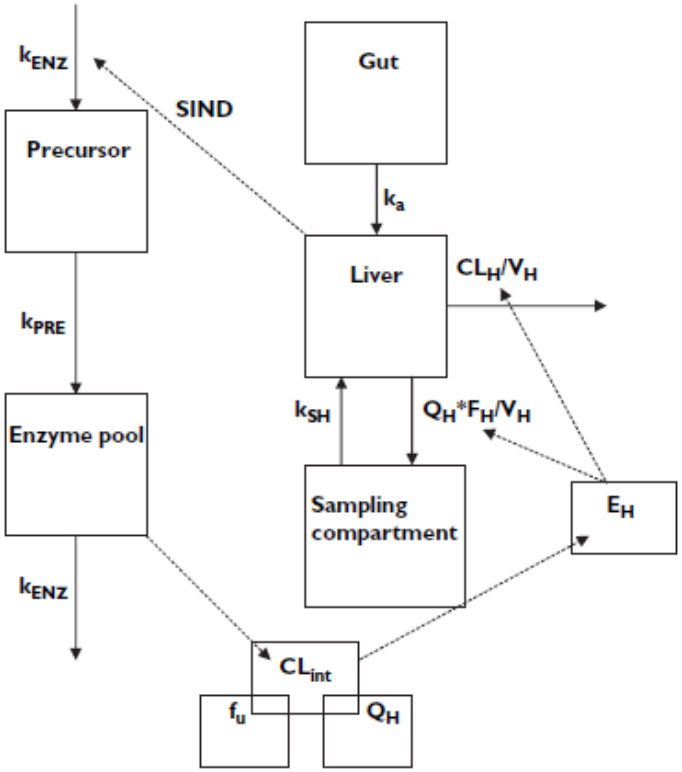
$$\frac{dA2}{dT} = K12 \times A1 - K23 \times A2$$

$$\frac{dA3}{dT} = K23 \times A2 - K30 \times A3$$



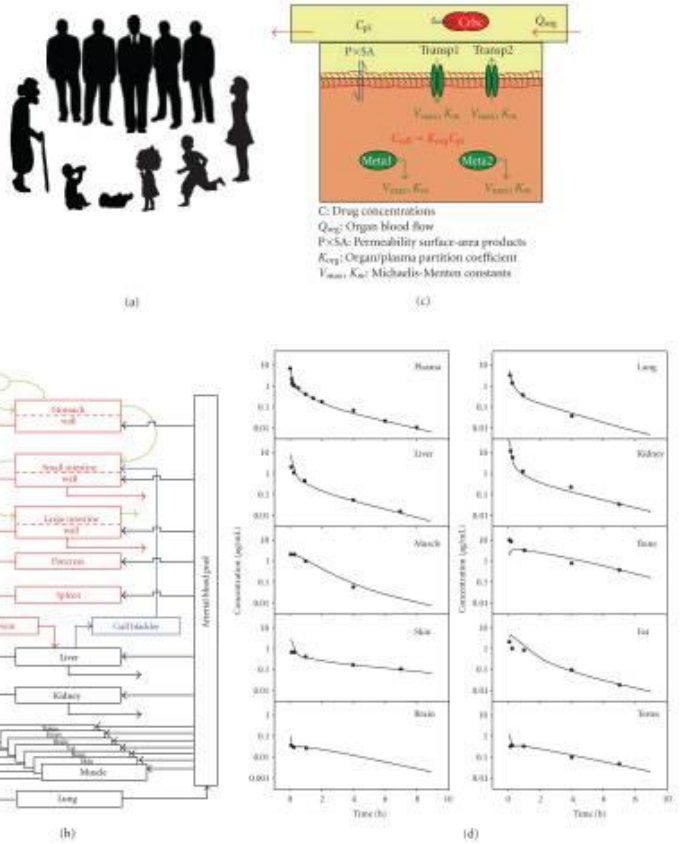
Structural modelling

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



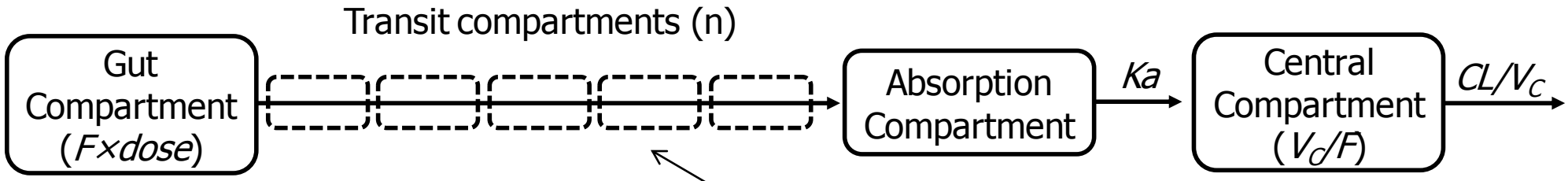
[1] Gordi T., et al, Br J Clin Pharmacol. 2005

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

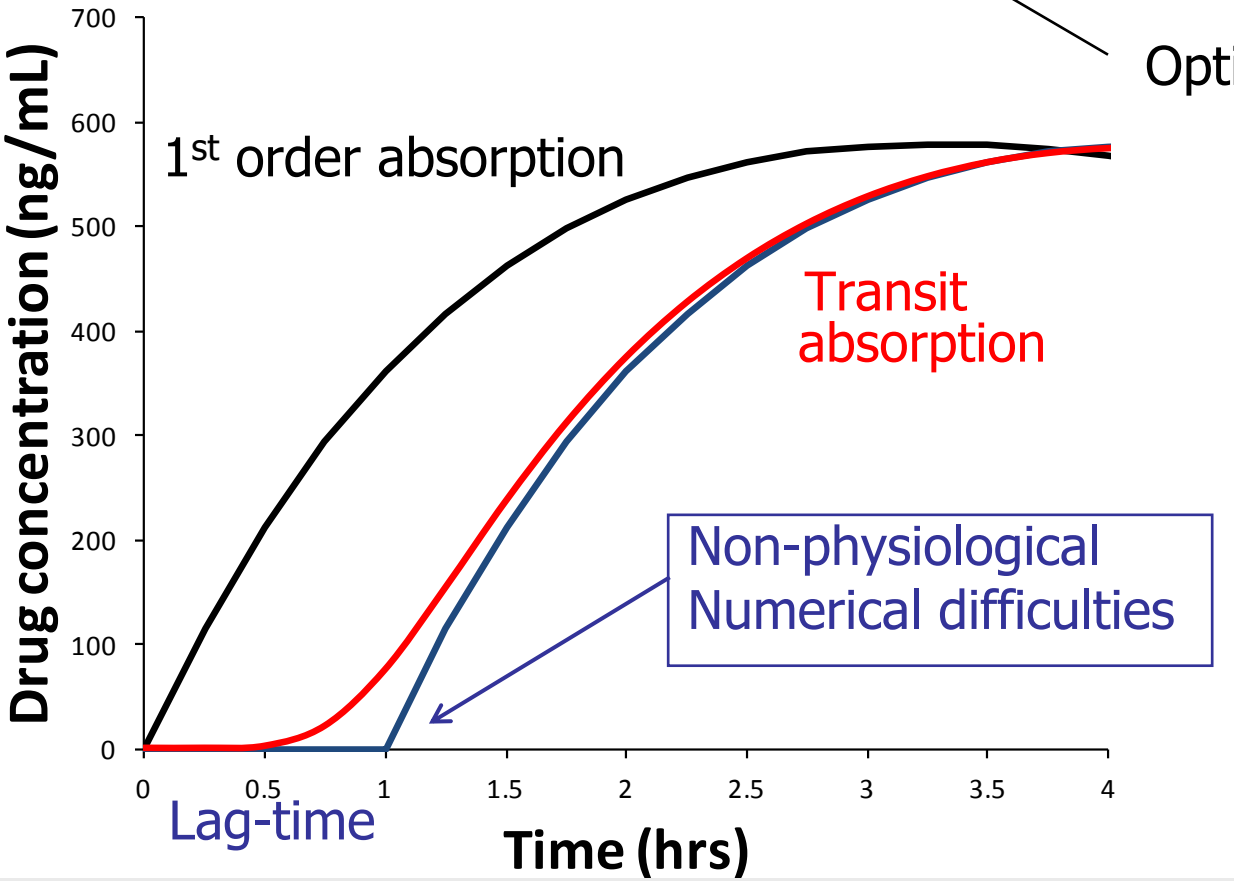


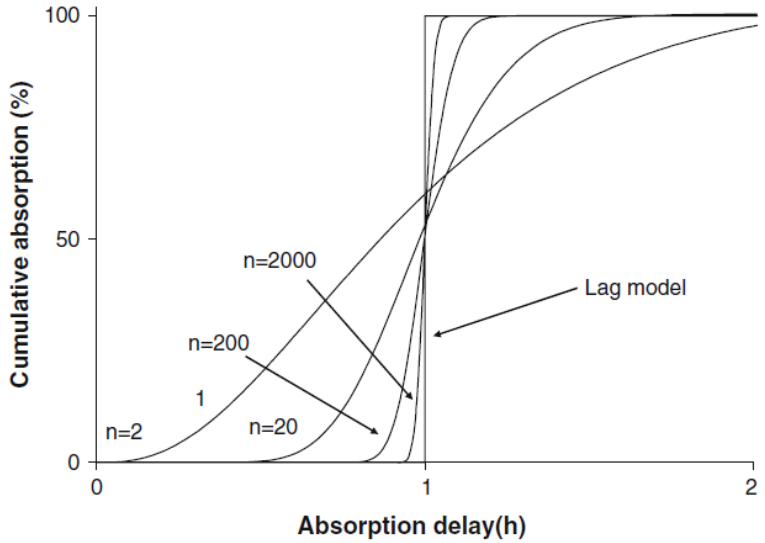
[2] Khalil F. & Laer S., J Biomed Biotechnol 2011

Structural modelling



Optimal number of transit compartments



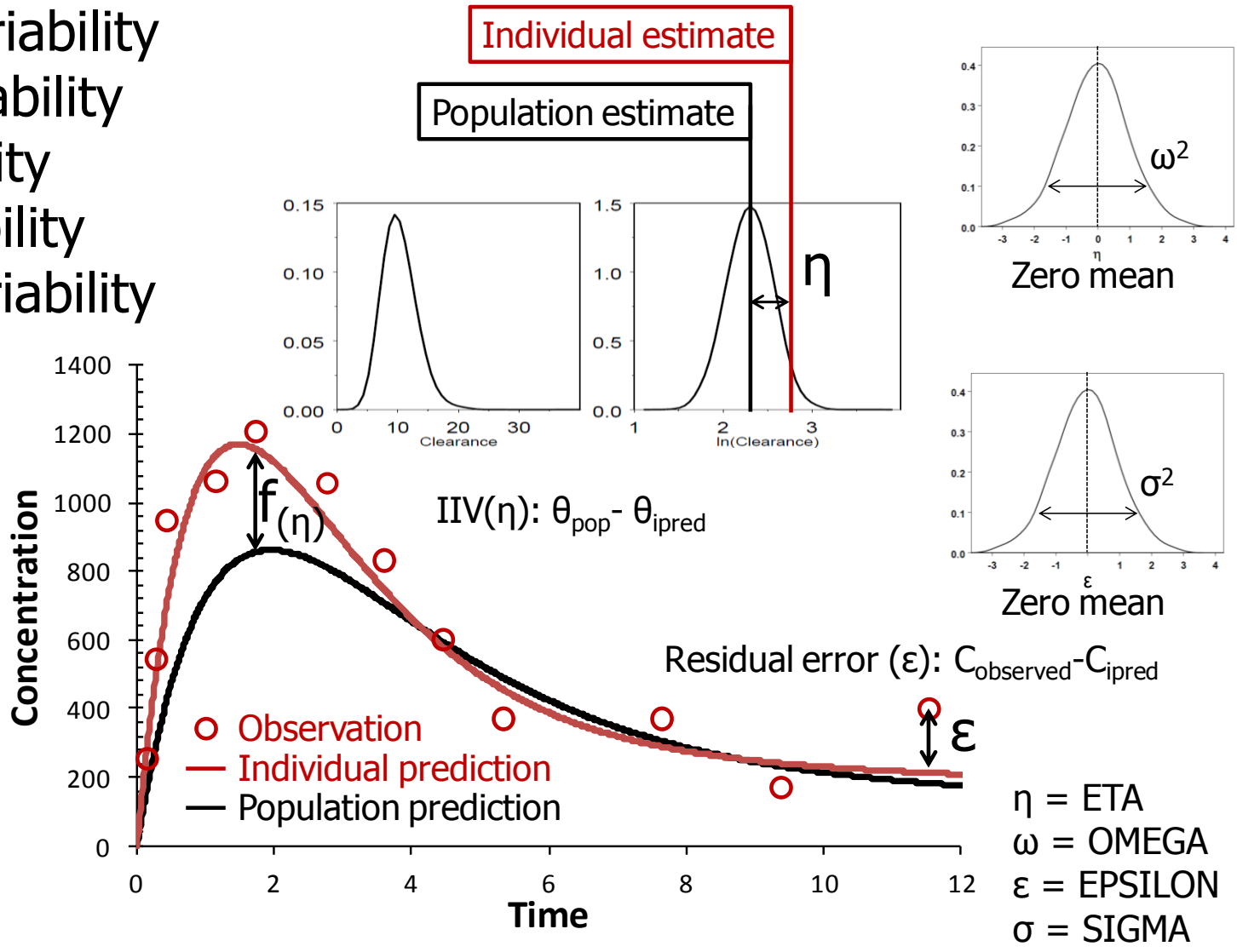


Savic R., et al,
J Pharmacokinet Pharmacodyn. 2007

Variability

Two main sources of variability

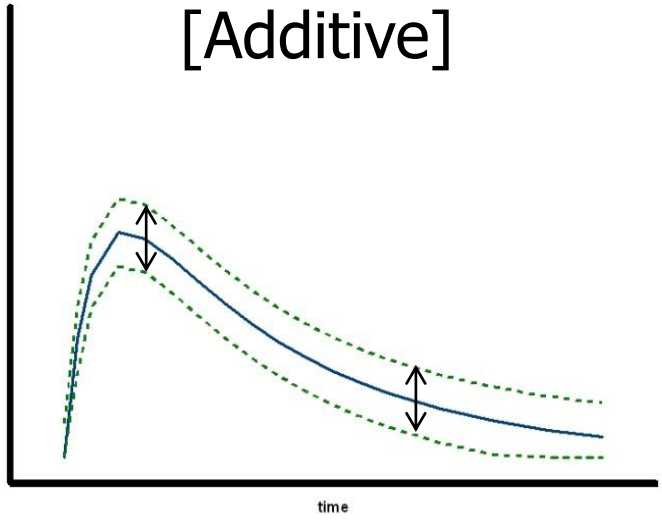
- Residual random variability
  -unexplained variability
- Inter-individual variability
  -between subject variability



Variability

$y_{ij} = f_i + \varepsilon_{ij}$

[Additive]

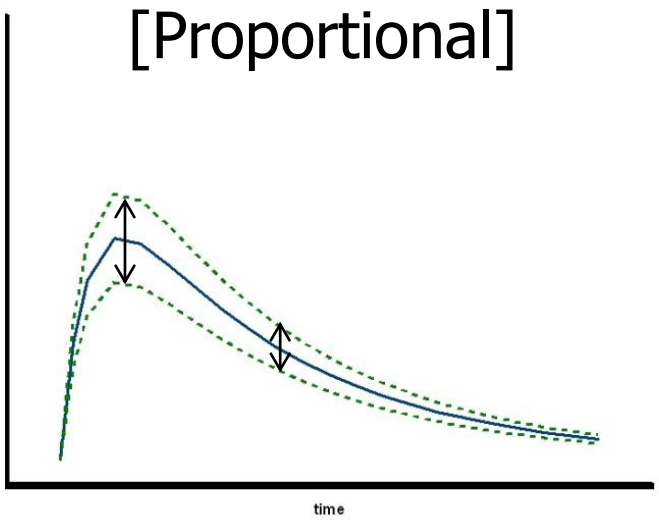


Homoscedastic error

-the residual variability is constant

$y_{ij} = f_i \times (1 + \varepsilon_{ij})$

[Proportional]

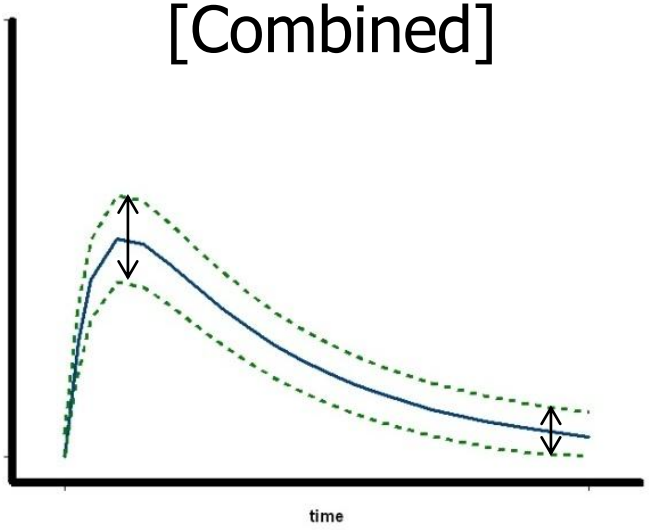


Heteroscedastic error

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

$y_{ij} = f_i \times (1 + \varepsilon_{1ij}) + \varepsilon_{2ij}$

[Combined]



Slope-intercept model

-the residual variability is proportional at high predictions and constant at low

Covariate modelling

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)

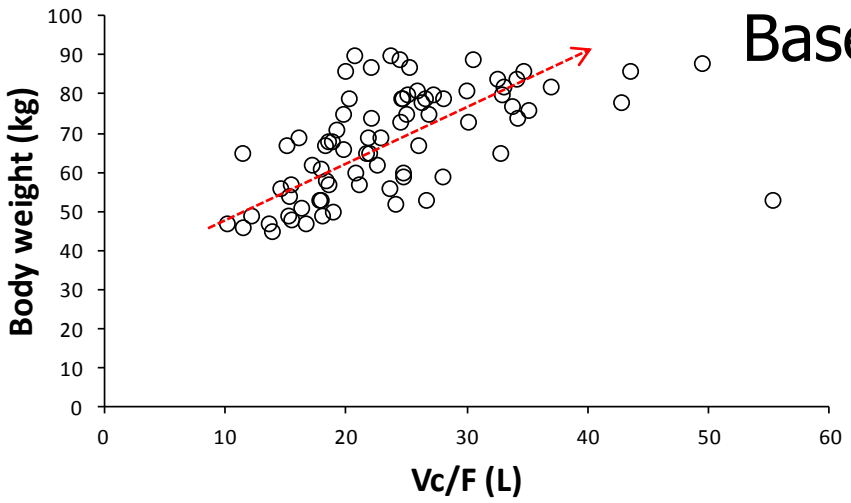
Covariate modelling: Stepwise forward addition and backward elimination

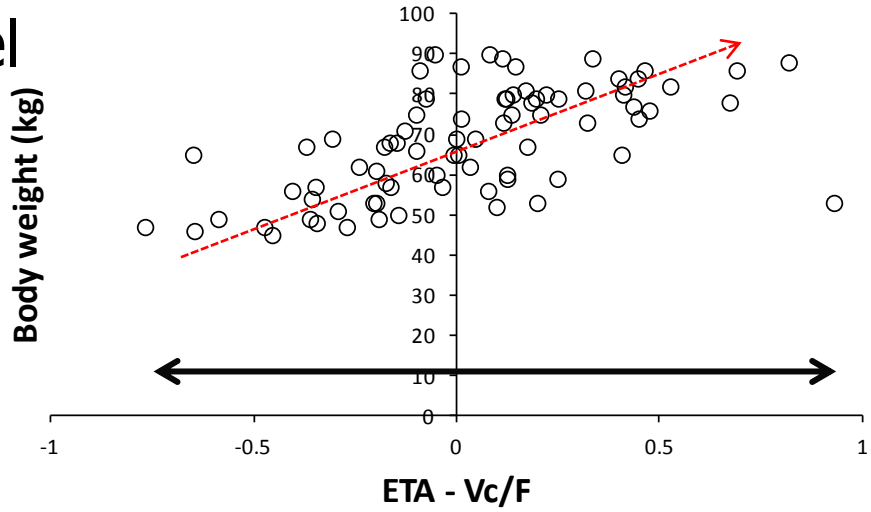
(automated functionality in Pearl-speaks-NONMEM: SCM)

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

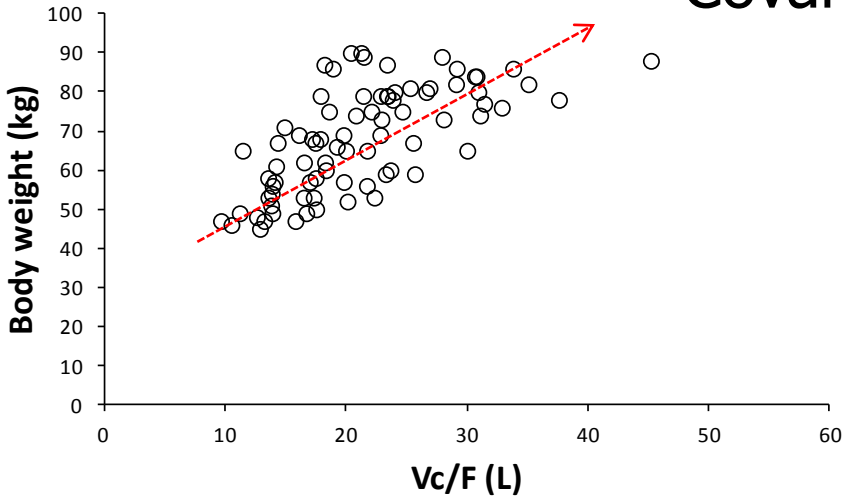
Covariate modelling

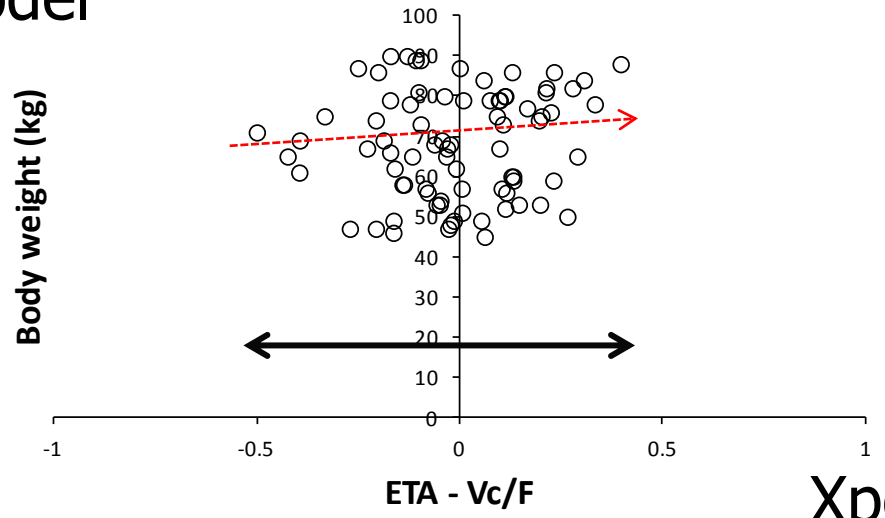
Base model





Covariate model

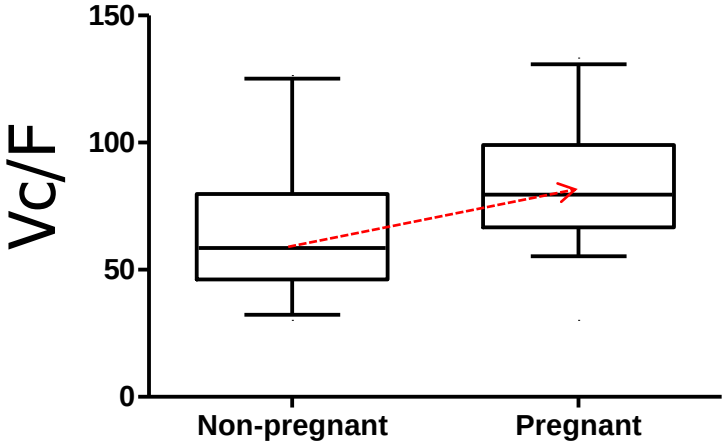


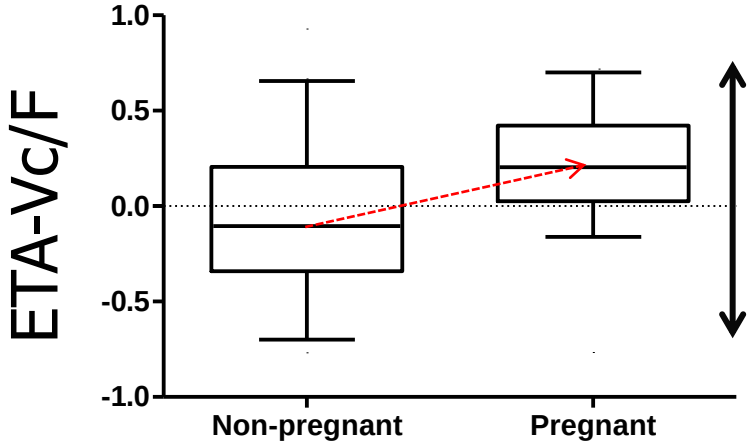


Xpose

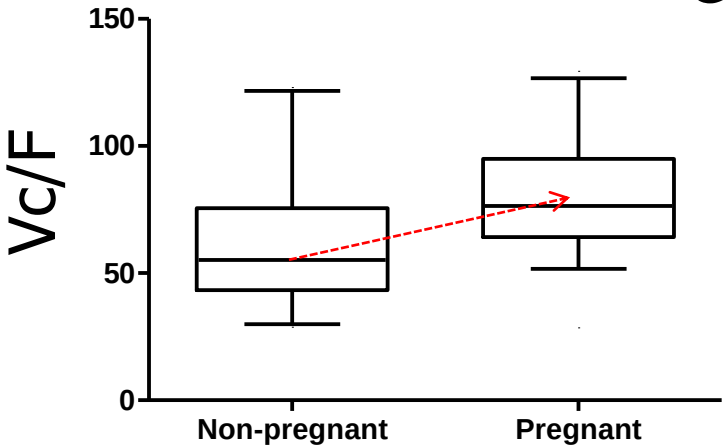
Covariate modelling

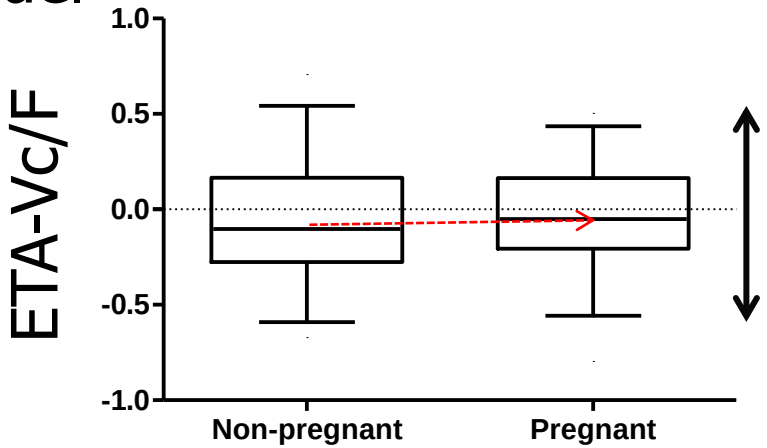
Base model





Covariate model

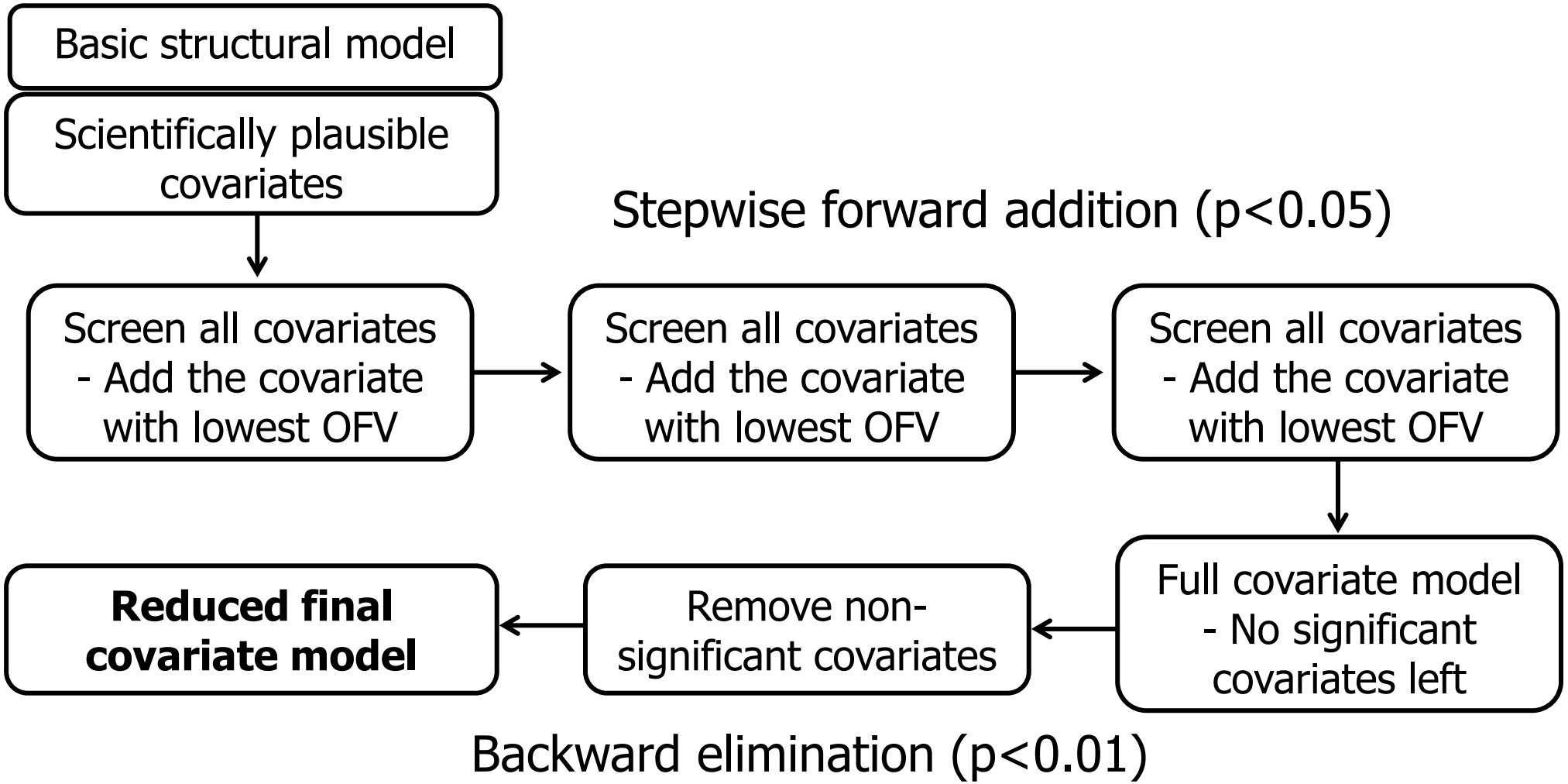




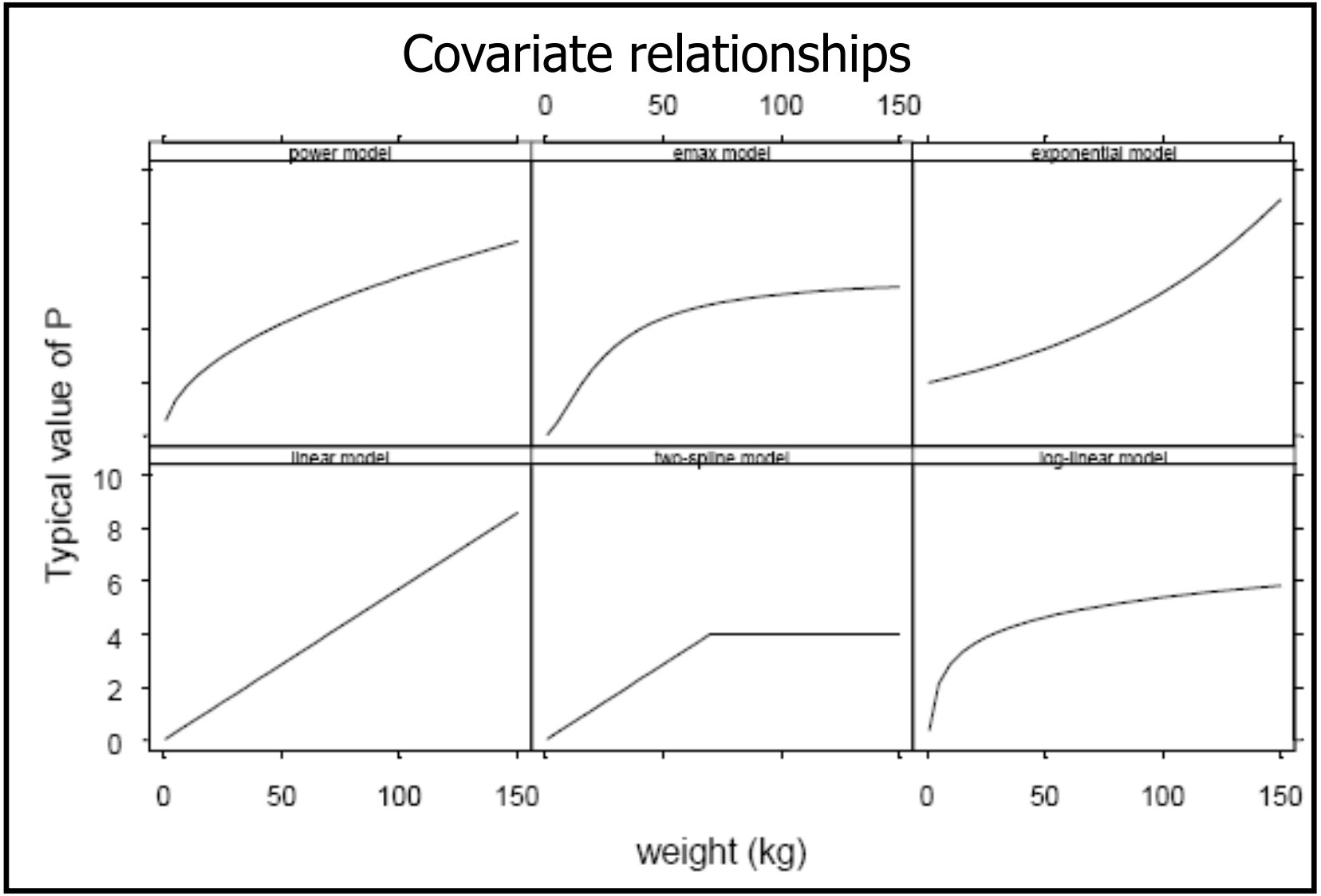
Xpose

Covariate modelling

Covariate modelling: Stepwise forward addition and backward elimination



Covariate modelling



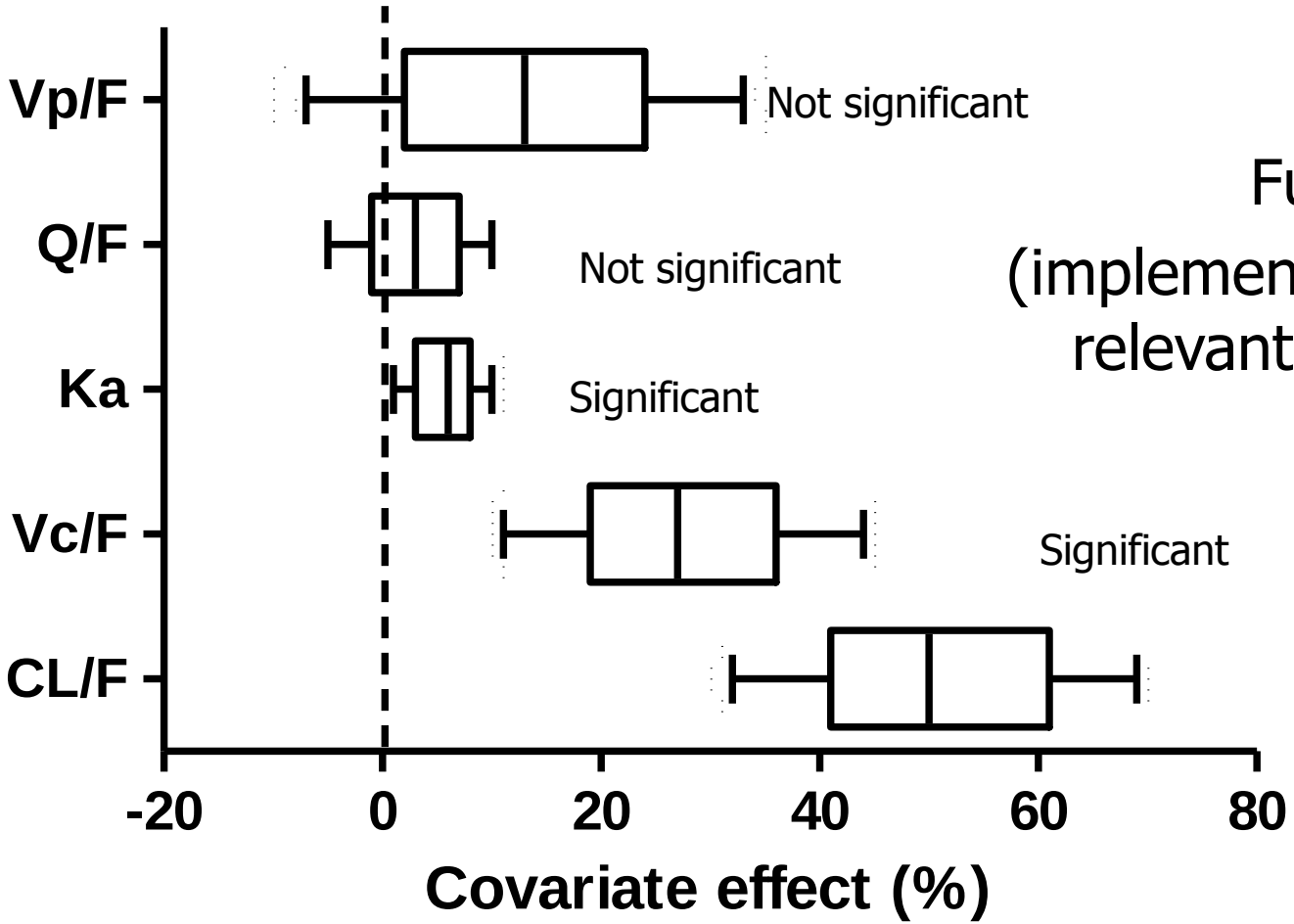
Can be implemented automatically in PsN

Covariate modelling

Covariate modelling										
	Population estimate (% RSE) [IIV]									ΔOFV
Model	CL/F (L/h)	V_C/F (L)	Q_1/F (L/h)	V_{P1}/F (L)	Ka (h^{-1})	RUV	Cov 1	Cov 2	Cov 3	
Base model	70.1 (12.5) [31.5]	32.1 (19.5) [59.5]	10.8 (14.9) [-]	108 (14.8) [-]	0.763 (4.97) [45.8]	0.295 (5.47) [-]	X	X	X	
Forward addition										
Covariate 1-CL	60.3 (10.7) [21.5]	32.6 (19.5) [59.5]	10.4 (14.9) [-]	111 (14.8) [-]	0.763 (4.97) [45.8]	0.296 (5.47) [-]	33.0 (24.5)			-25.6
Covariate 2-Vc	60.5 (10.5) [21.5]	22.1 (12.5) [39.5]	10.7 (14.9) [-]	112 (14.8) [-]	0.761 (4.97) [45.8]	0.283 (5.47) [-]	32.0 (24.5)	46.8 (35.6)		-20.2
Covariate 3-CL	60.1 (10.3) [20.5]	22.2 (12.5) [39.5]	10.9 (14.9) [-]	110 (14.8) [-]	0.761 (4.97) [45.8]	0.285 (5.47) [-]	32.0 (24.5)	46.8 (35.6)	5.8 (55.6)	-5.3
...										
Backward elimination										
Covariate 1	70.2 (13.5) [30.5]	22.2 (12.5) [39.5]	10.9 (14.9) [-]	110 (14.8) [-]	0.761 (4.97) [45.8]	0.285 (5.47) [-]	X	46.8 (35.6)	15.8 (55.6)	24.5
Covariate 2	60.2 (10.5) [20.5]	29.2 (14.5) [59.5]	10.9 (14.9) [-]	110 (14.8) [-]	0.761 (4.97) [45.8]	0.285 (5.47) [-]	32.0 (24.5)	X	15.8 (55.6)	20.4
Covariate 3	60.2 (10.5) [21.5]	22.2 (12.5) [39.5]	10.9 (14.9) [-]	110 (14.8) [-]	0.761 (4.97) [45.8]	0.285 (5.47) [-]	32.0 (24.5)	46.8 (35.6)	X	5.3
Final model	60.2 (10.5) [21.5]	22.2 (12.5) [39.5]	10.9 (14.9) [-]	110 (14.8) [-]	0.761 (4.97) [45.8]	0.285 (5.47) [-]	32.0 (24.5)	46.8 (35.6)		

Covariate modelling

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

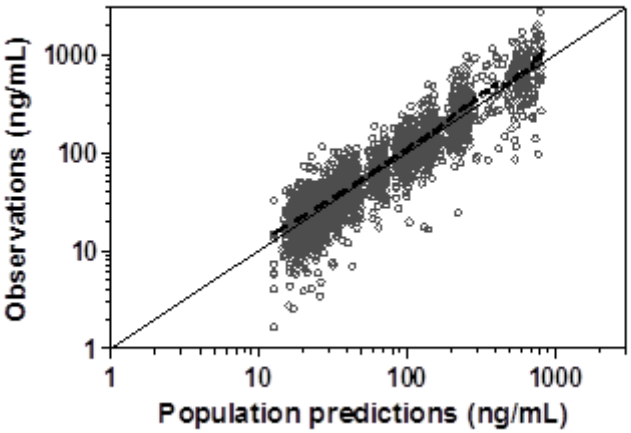


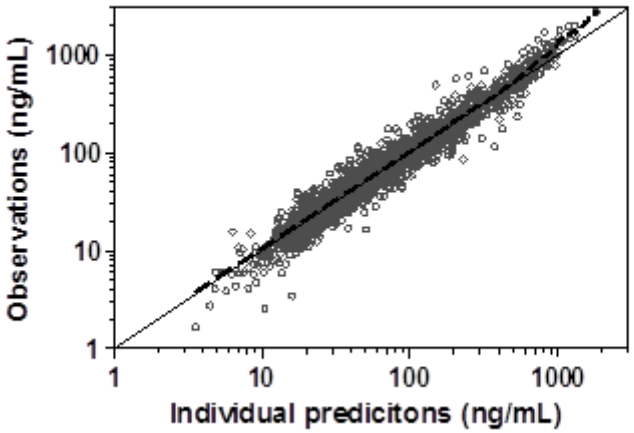
Full covariate model

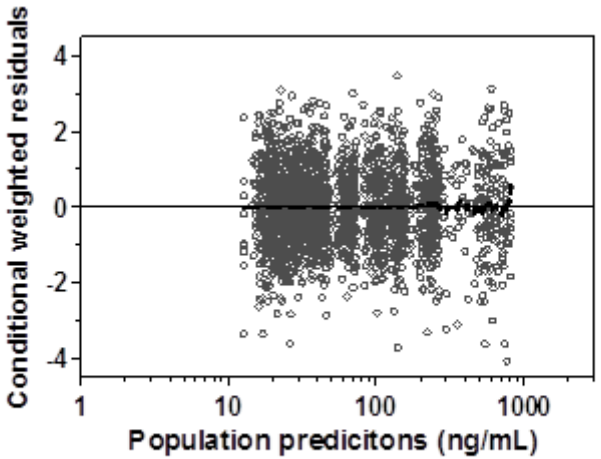
(implement the group covariate on all relevant parameters and bootstrap)

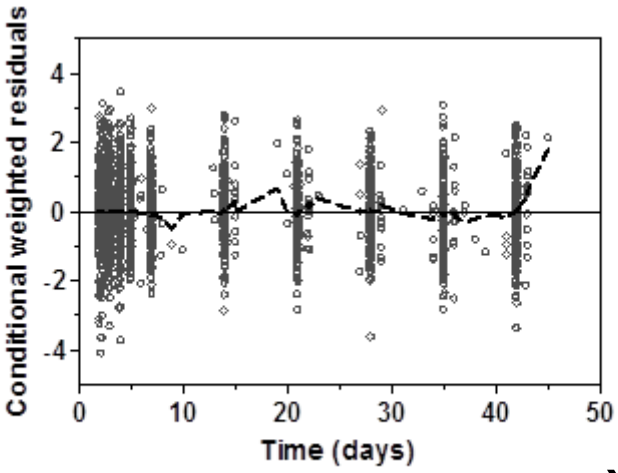
Model diagnostics

Basic Goodness-of-fit diagnostics

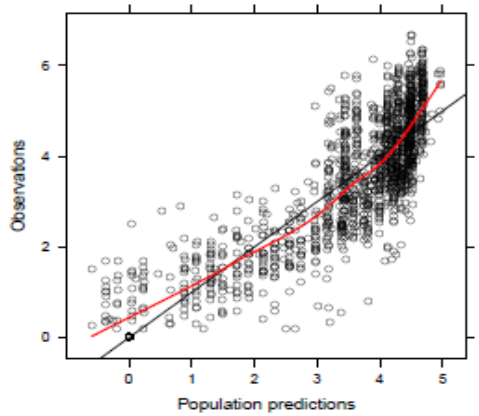


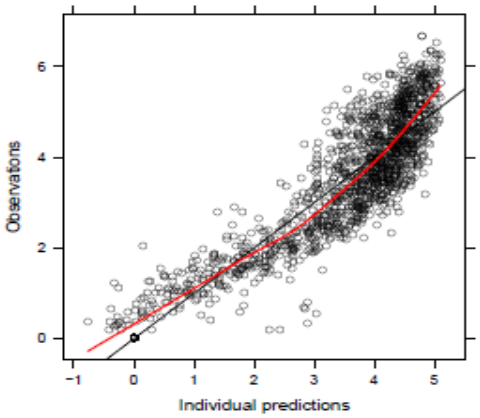






Substantial and systemic deviations/trends indicate model-misspecification





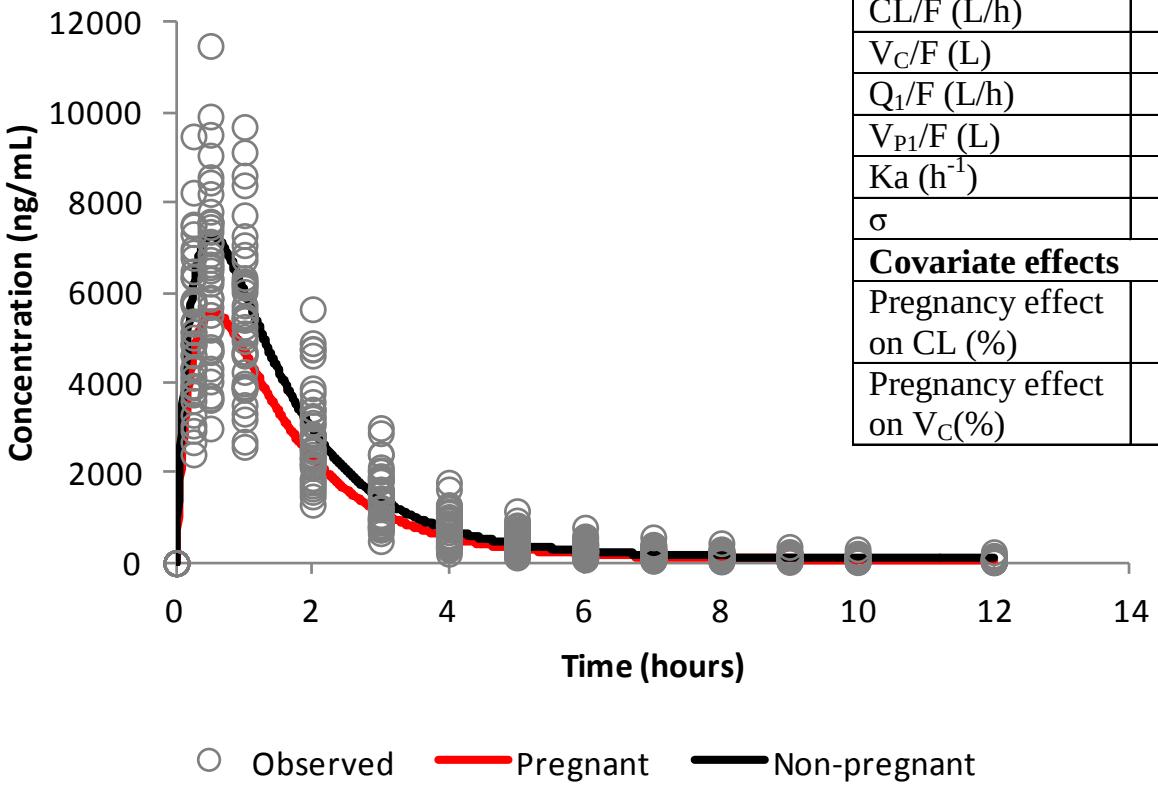
Xpose

Model diagnostics

Numerical diagnostics
- Parameter values
- Parameter certainty

NONMEM Bootstrap

Parameter estimates of the final model				
	Population estimate [a] (% RSE [b])	**95% CI. [b]**	**IIV [%CV] [a] (% RSE [b])**	**95% CI. [b]**
Typical parameters				
CL/F (L/h)	60.2 (10.5)	49.6-74.2	21.5 (27.0)	14.5-26.2
V_C/F (L)	22.2 (12.5)	18.2-25.6	39.5 (35.7)	21.7-50.7
Q_1/F (L/h)	10.9 (14.9)	6.31-13.4	-	-
V_{P1}/F (L)	110 (14.8)	80.3-131	-	-
Ka (h^{-1})	0.761 (4.97)	0.592-0.891	45.8 (22.1)	35.4-56.1
σ	0.285 (5.47)	0.255-0.314	-	-
Covariate effects				
Pregnancy effect on CL (%)	32.0 (24.5)	25.1-69.1	-	-
Pregnancy effect on V_C(%)	46.8 (35.6)	18.2-86.0	-	-

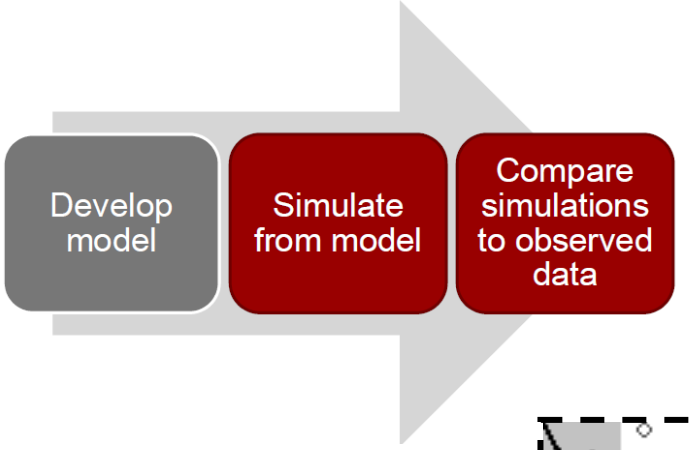


- Sample data randomly and re-fit the model for bootstrap diagnostics
- Stratify on important covariates

Bootstrap runX.mod -samples=2000

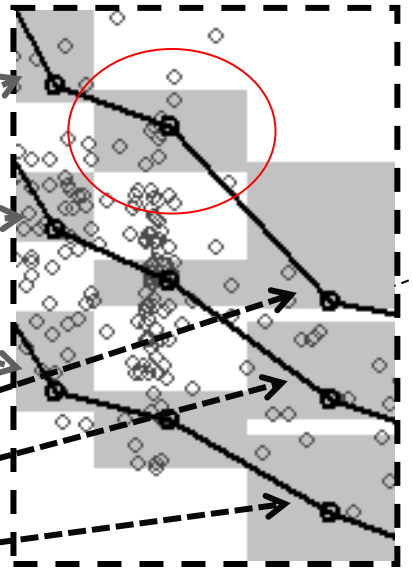
Model diagnostics

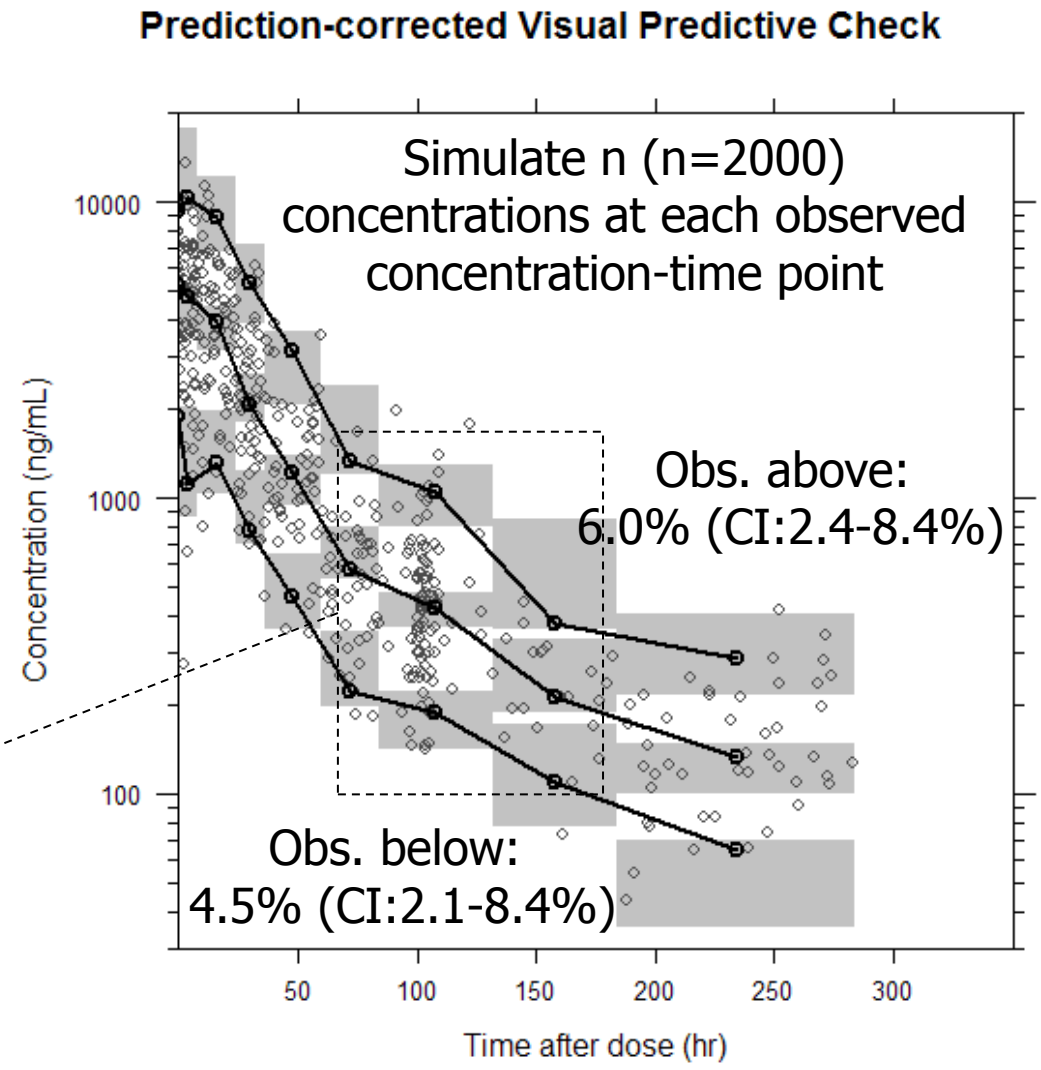
Simulation-based diagnostics



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

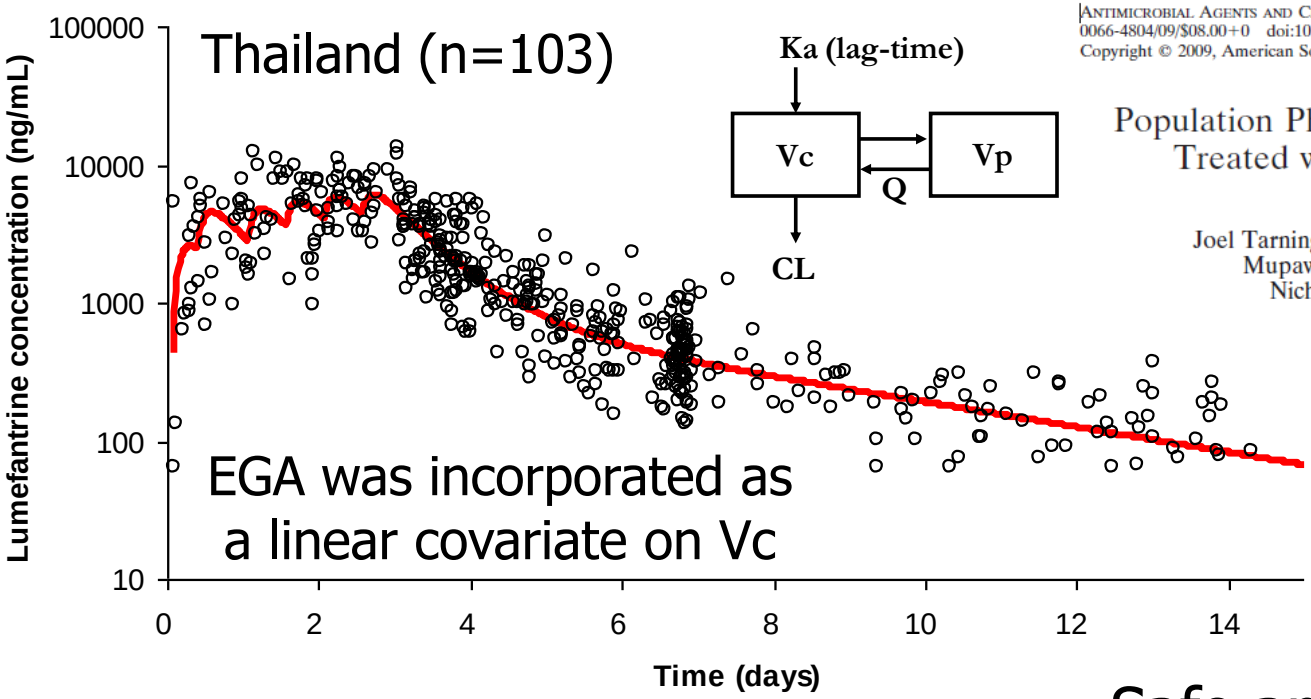
Observed
95th percentile
50th percentile
5th percentile





vpc runX.mod -samples=2000

Antimalarial examples

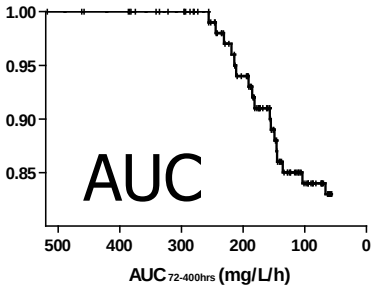


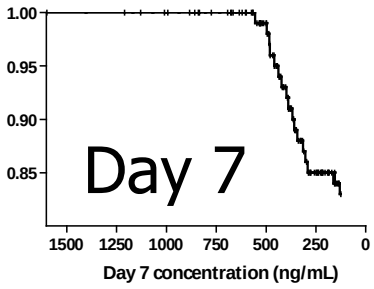
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2009, p. 3837–3846 Vol. 53, No. 9
0066-4804/09/$08.00+0 doi:10.1128/AAC.00195-09

Population Pharmacokinetics of Lumefantrine in Pregnant Women Treated with Artemether-Lumefantrine for Uncomplicated *Plasmodium falciparum* Malaria[▽]

Joel Tarning,[1,2]* Rose McGready,[1,2,3] Niklas Lindegardh,[1,2] Elizabeth A. Ashley,[3] Mupawjay Pimanpanarak,[3] Benjamas Kamanikom,[1] Anna Annerberg,[1] Nicholas P. J. Day,[1,2] Kasia Stepniewska,[1,2] Pratap Singhasivanon,[4] Nicholas J. White,[1,2] and François Nosten[1,2,3]

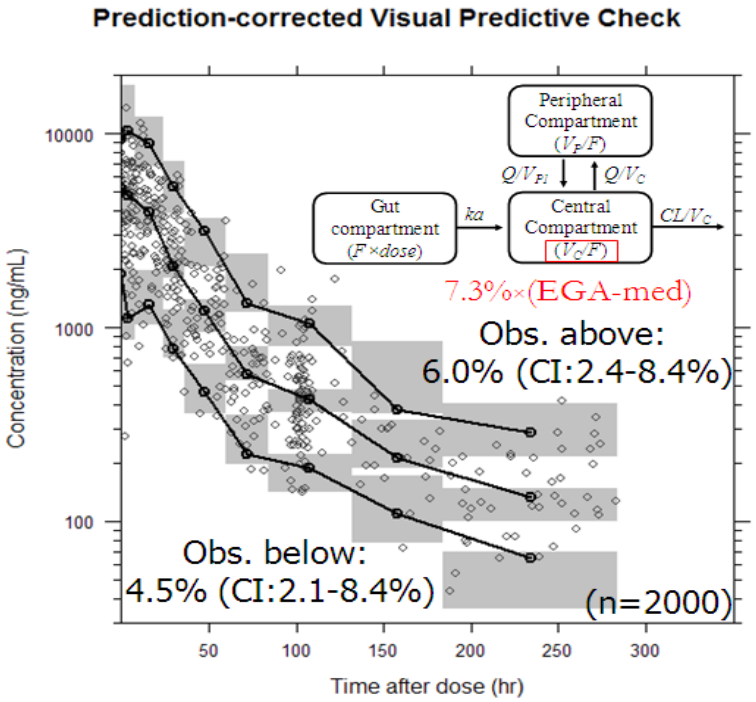
Cumulative risk of recrudescence

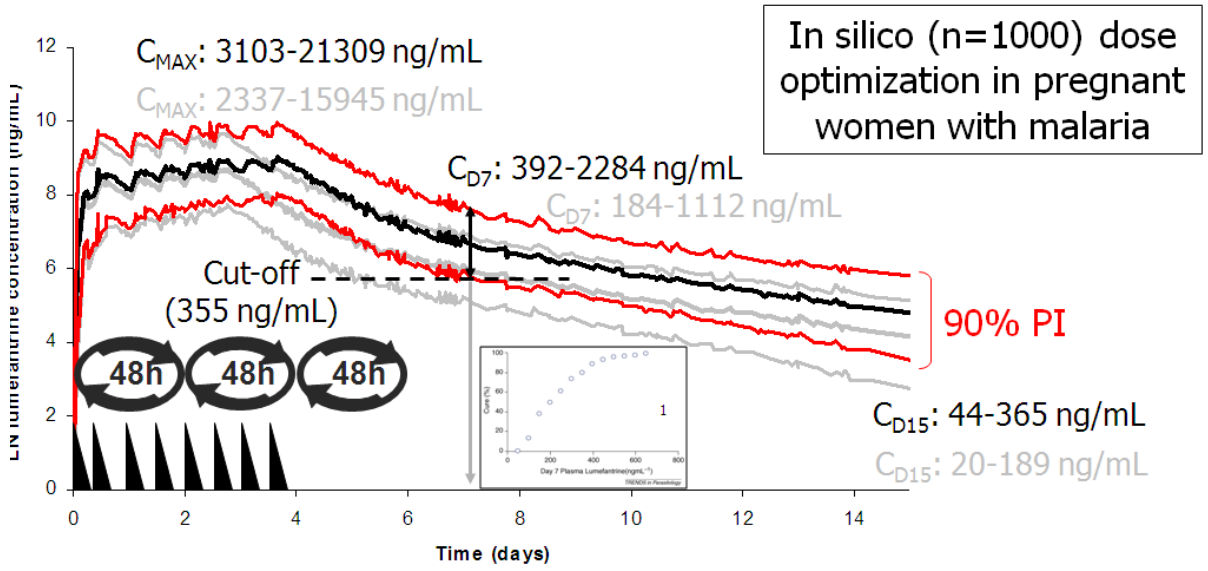




- Safe and effective artemether-lumefantrine treatment in adults
- Specific problem of low cure rates (84%) in pregnant women
- What dose is the right dose → M&S

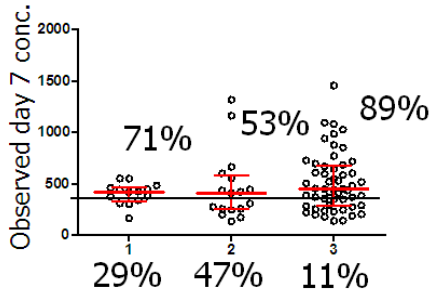
Antimalarial examples

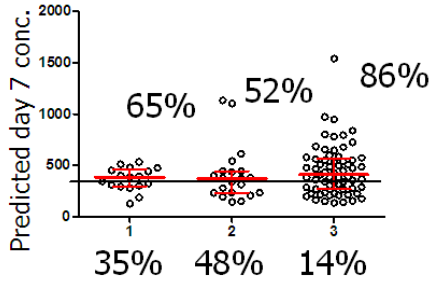


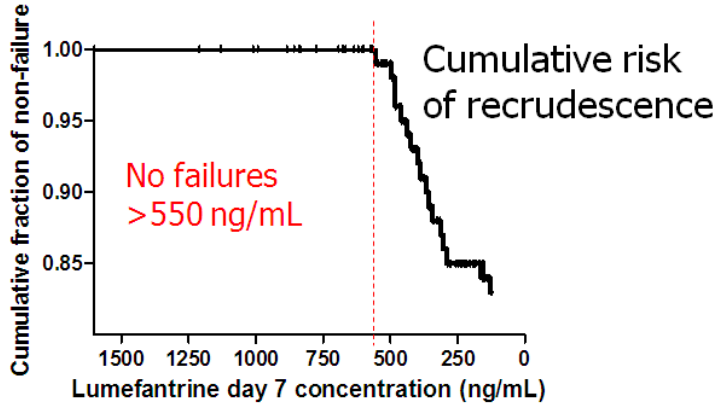


In silico (n=1000) dose optimization in pregnant women with malaria

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







Antimalarial examples

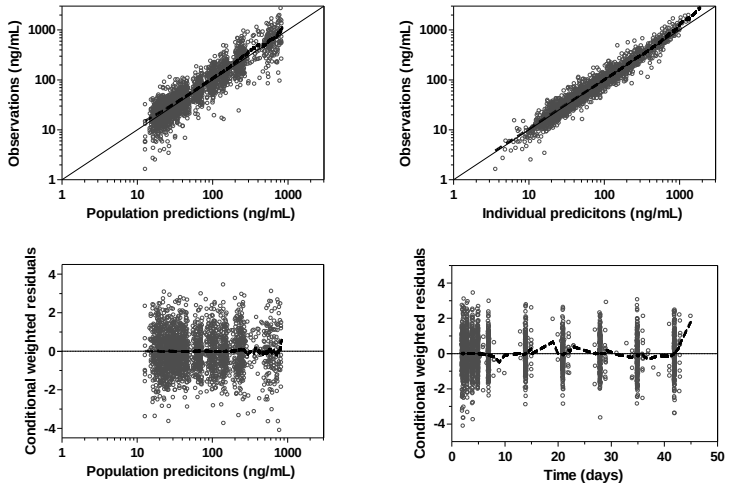
Population pharmacokinetics and pharmacodynamics of piperaquine in children with uncomplicated falciparum malaria

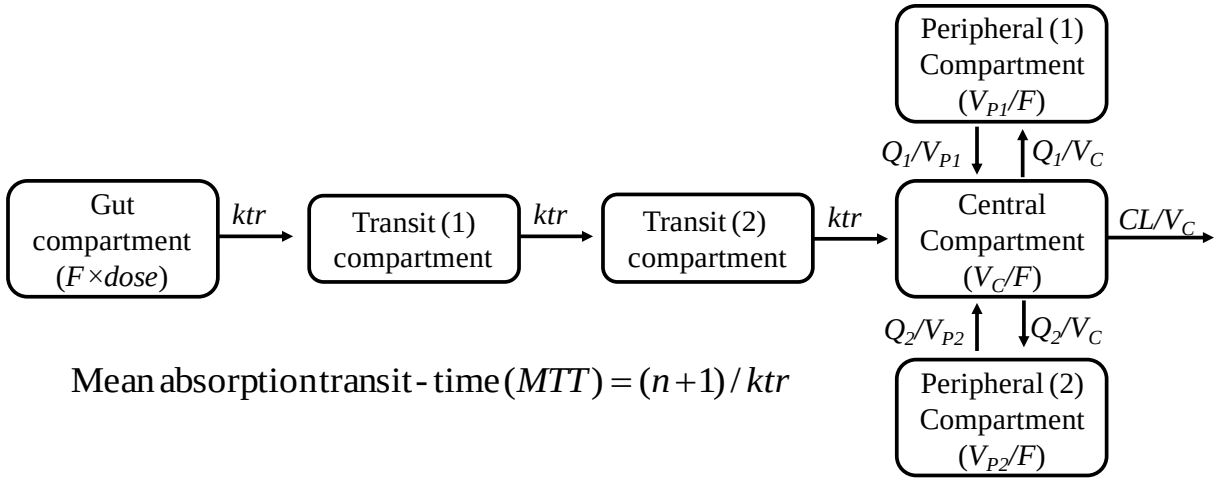
Joel Tarning[1,2*], Issaka Zongo[3], Fabrice A. Somé[3], Noel Rouamba[3], Parikh Sunil[4], Philip J. Rosenthal[4], Warunee Hanpithakpong[1], Natthapong Jongrak[1], Nicholas P. J. Day[1,2], Nicholas J. White[1,2], Francois Nosten[1,2,5], Jean-Bosco Ouedraogo[3], Niklas Lindegardh[1,2]

- 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

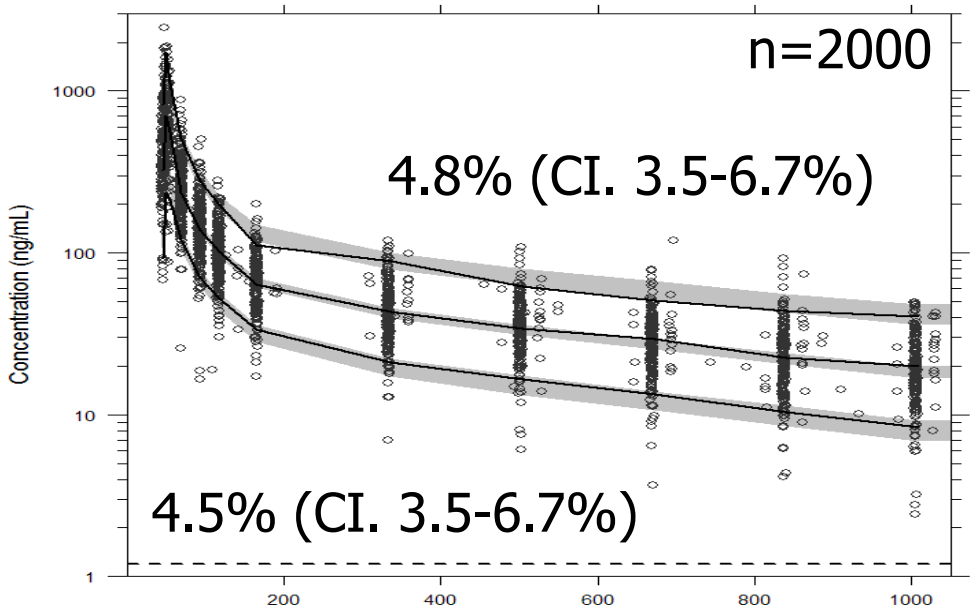
To define the population pharmacokinetic of piperaquine in the treatment of *falciparum* infection in children

Antimalarial examples



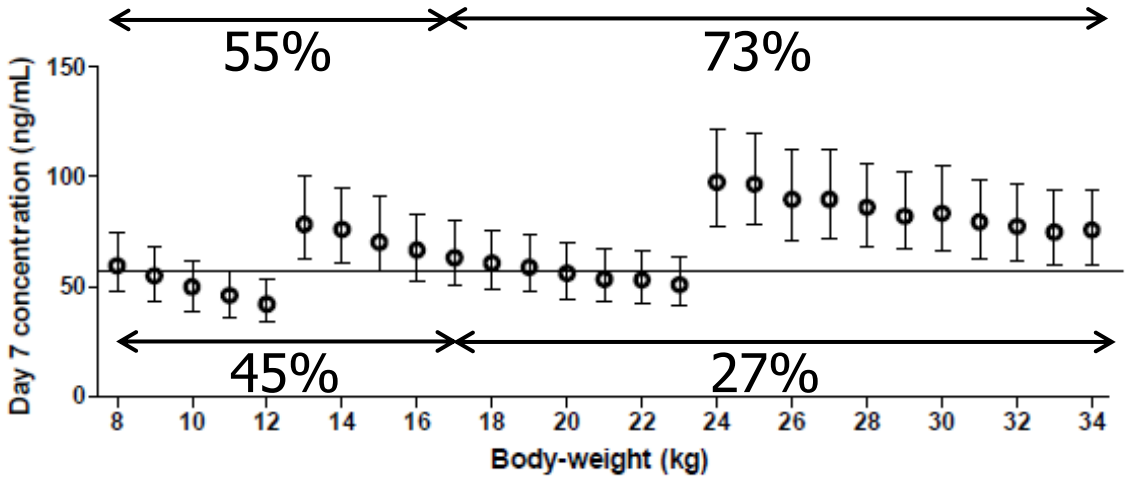


$$\text{Mean absorption transit-time}\,(MTT) = (n+1)/ktr$$

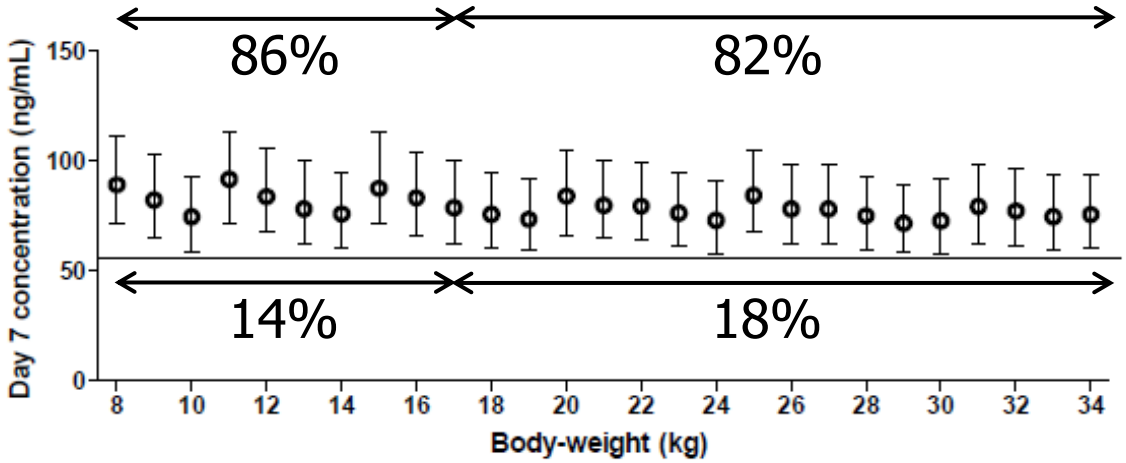


Time-to-event analysis:
The risk of a new malaria infection increased with 5.9% per 1 ng/mL decrease in day 7 concentration (HR 0.94, 95% CI 0.92 to 0.96)

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

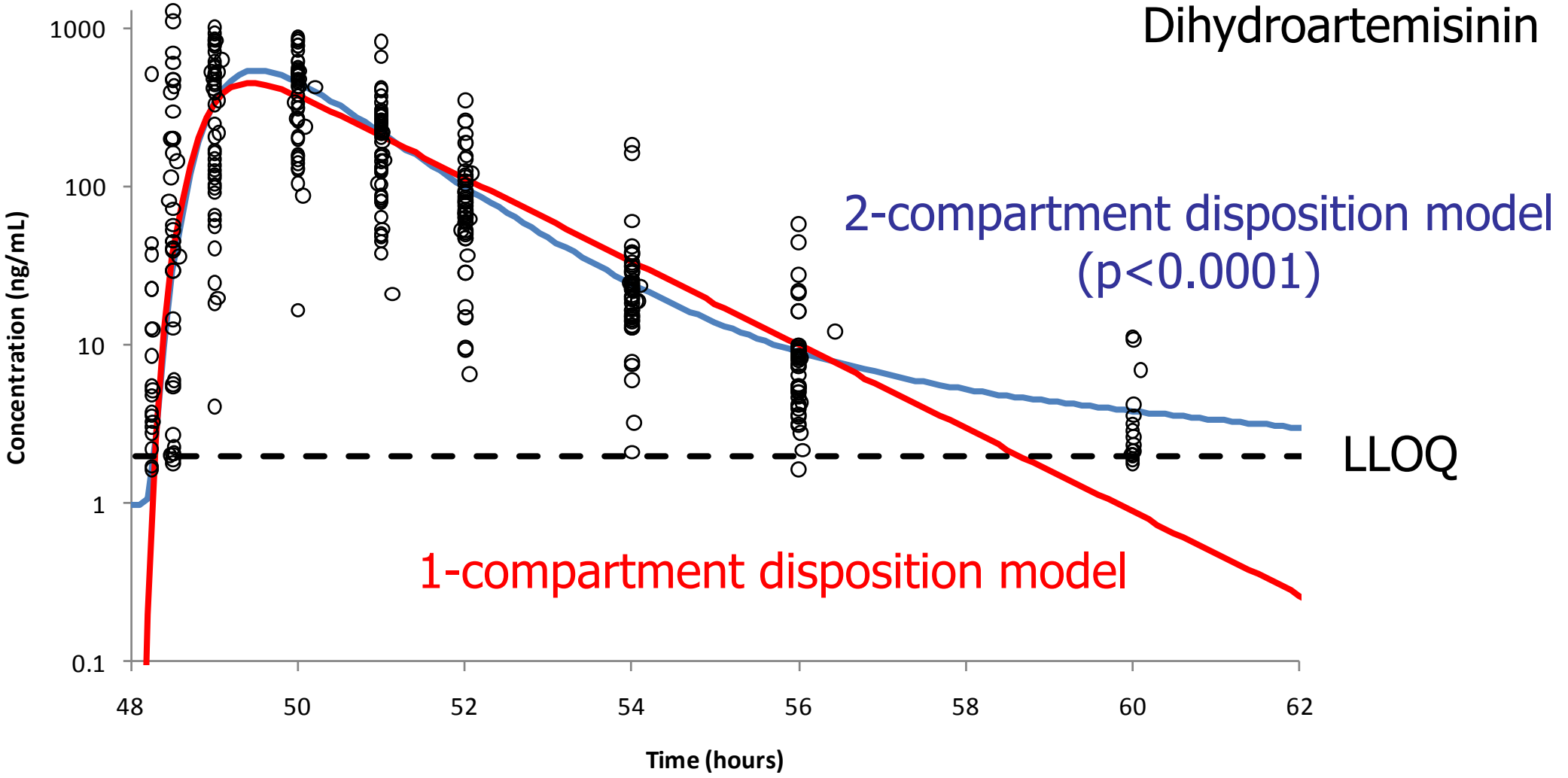
Population pharmacokinetics of dihydroartemisinin and piperaquine in pregnant and non-pregnant women with uncomplicated malaria

Joel Tarning[1,2*], Marcus J. Rijken[3], Rose McGready[1,2,3], Aung Phae Phyo[3], Warunee Hanpithakpong[1], Nicholas P. J. Day[1,2], Nicholas J. White[1,2], Francois Nosten[1,2,3], Niklas Lindegardh[1,2]

- 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

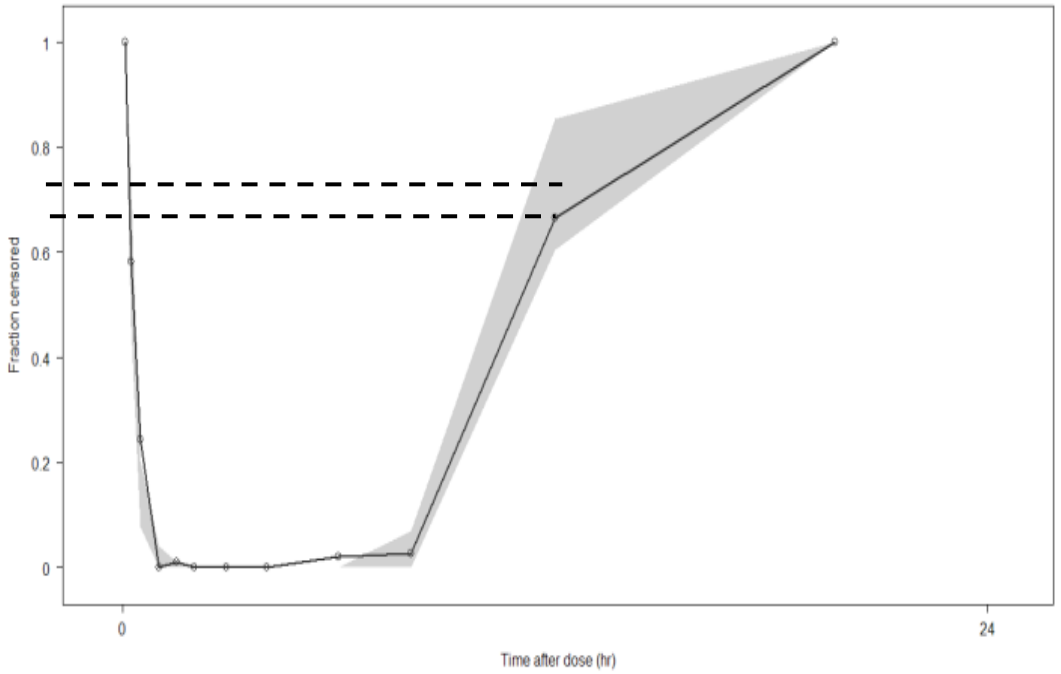
Tarning et al. Submitted AAC

Antimalarial examples



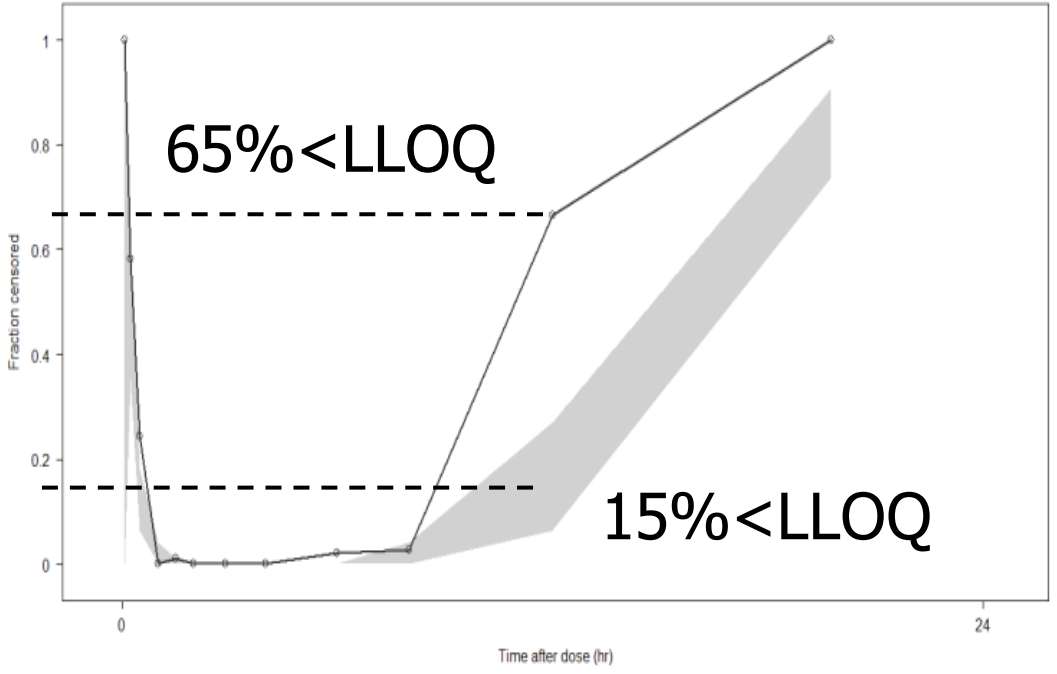
Antimalarial examples

1-compartment disposition model



— Observed Predicted

2-compartment disposition model



— Observed Predicted

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

Thank you

Department of Pharmacology - MORU

wellcome trust
MORU
Mahidol Oxford
WELLCOME TRUST - MAHIDOL UNIVERSITY - OXFORD
TROPICAL MEDICINE RESEARCH PROGRAMME