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Incorporating uncertainty and variability into PBPK based predictions of human pharmacokinetics

H. Jones, R. Gieschke

F. Hoffmann- La Roche
Preclinical and Clinical Modeling & Simulation
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Outline

- **Background**
  - PBPK models in drug development
  - Variability and uncertainty
- **Specifying variability for PBPK models**
  - Physiology related variability
  - Compound related variability
- **Model Implementation in ACSL**
  - Structural Model
  - Statistical Model (MVN Monte-Carlo)
- **Results**
  - Drug A
  - Drug B
- **Conclusion**

PBPK at Different Stages of the Pre-Clinical Process

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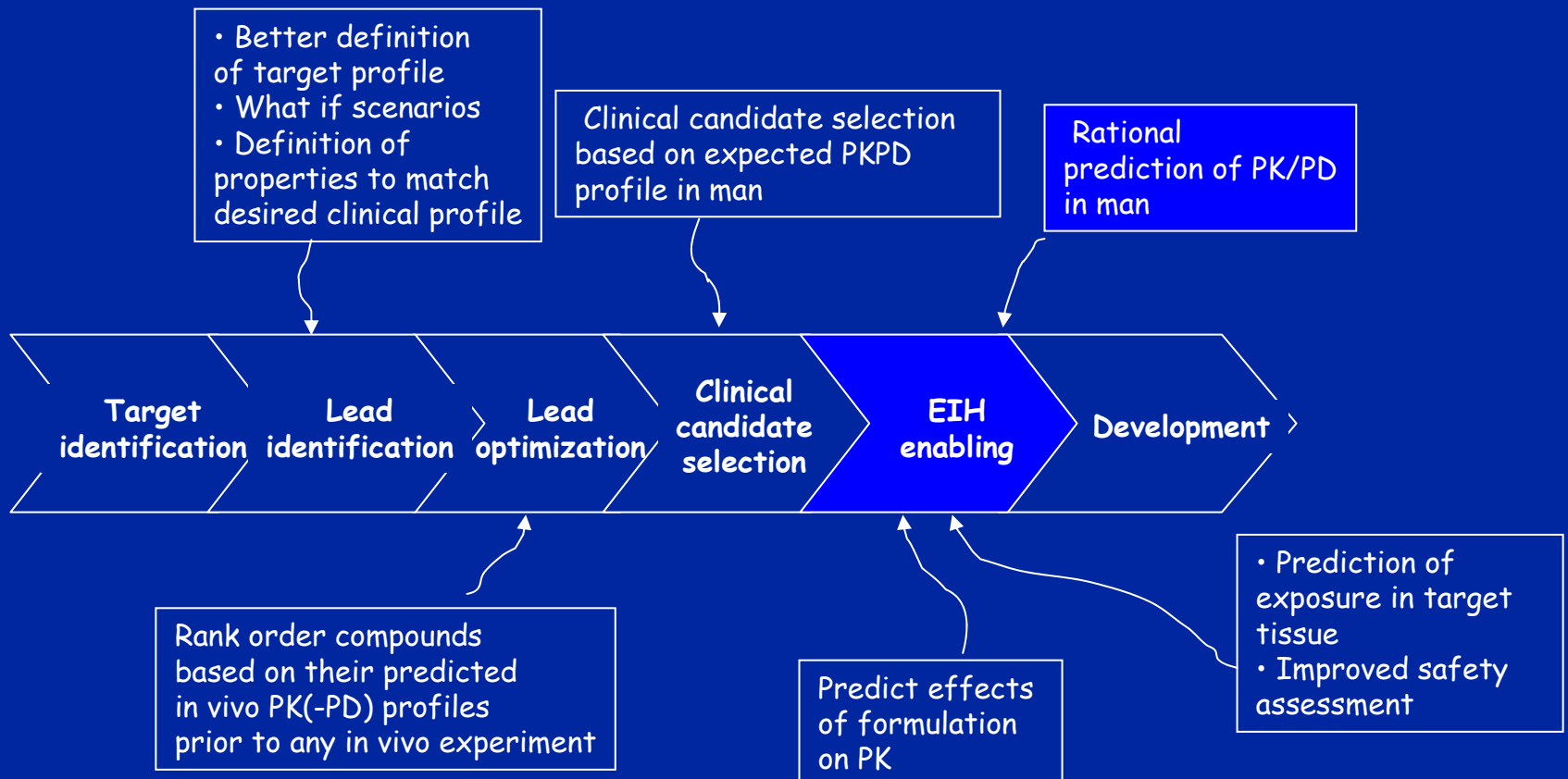
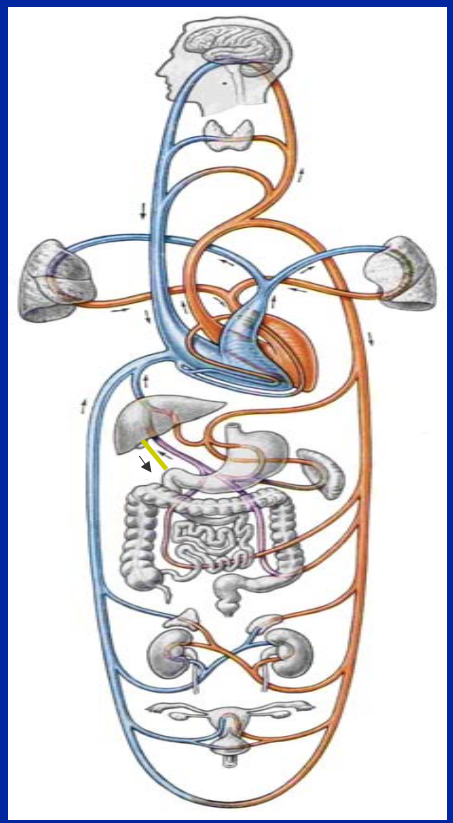
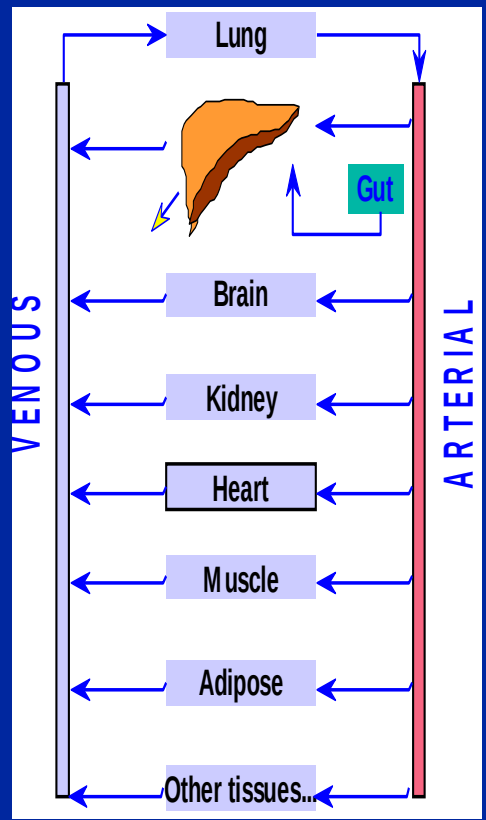


Concept of physiologically based pharmacokinetic (PBPK) Modeling



Sobotta/Becher 1972



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PBPK Model Equations

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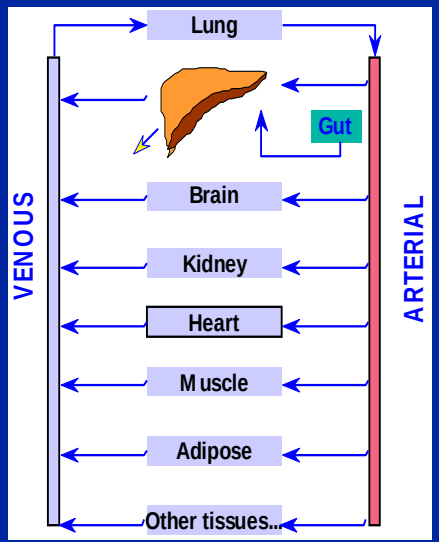

Non-eliminating Tissue

$$V_T \cdot \frac{dC_T}{dt} = Q_T \cdot (Ca - Cv_T);\ Cv_T = \frac{C_T}{P_T / R}$$

Eliminating Tissue

$$V_L \cdot \frac{dC_L}{dt} = (Q_L - Q_G) \cdot Ca + Q_G \cdot Cv_G - Q_L \cdot Cv_L - CL\,\mathrm{int}_{L(u)} \cdot Cv_{L(u)}$$

Venous Blood

$$V_{VB} \cdot \frac{dCv}{dt} = \sum Q_{T_i} \cdot Cv_{T_i} - CO \cdot Cv + input;\ C_{plasma} = \frac{Cv}{R}$$

Model Parameters

$$Physiol.: V_T s, Q_T s \qquad Compound: P_T s, R, CL\,\mathrm{int}$$

Predicting drug concentrations in man using PBPK modeling

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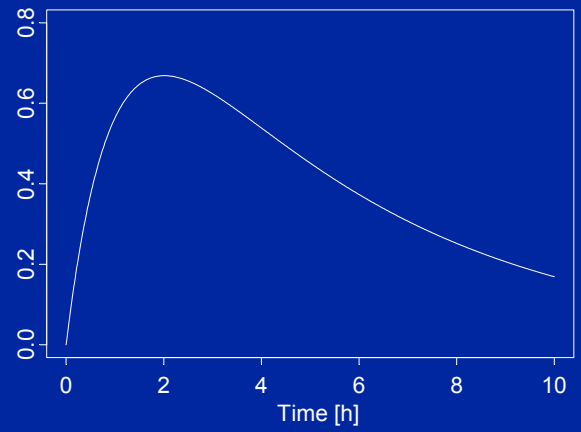
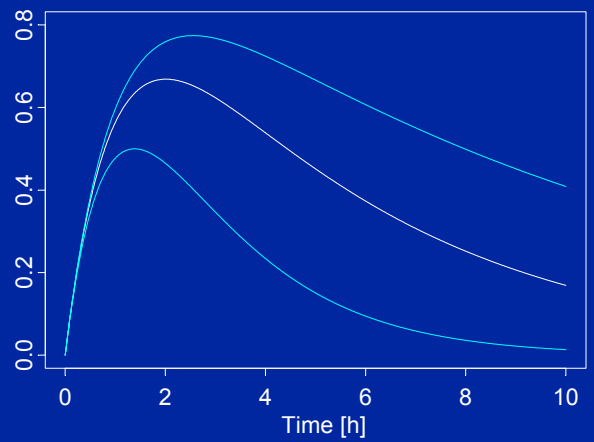
Standard Approach:
single set of PBPK parameters



Objective:

- **use information on variability of PBPK parameters and**
- **investigate contribution of physiological (PV) and compound related variability (CV) on predictions**



PBPK model parameters
Variability and Uncertainty

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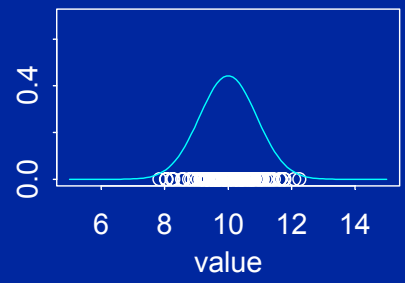
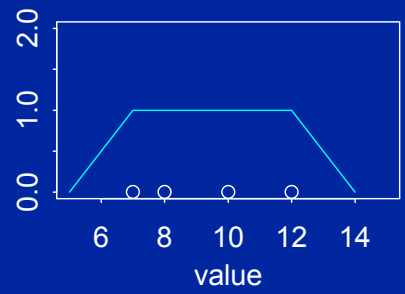
Distribution “known”

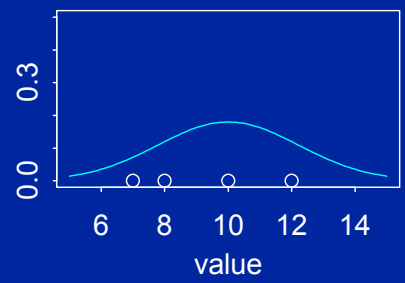


Distribution “unknown”
Uncertainty:

Fuzzy Number



Probability Density Function



Physiology related variability (PV)

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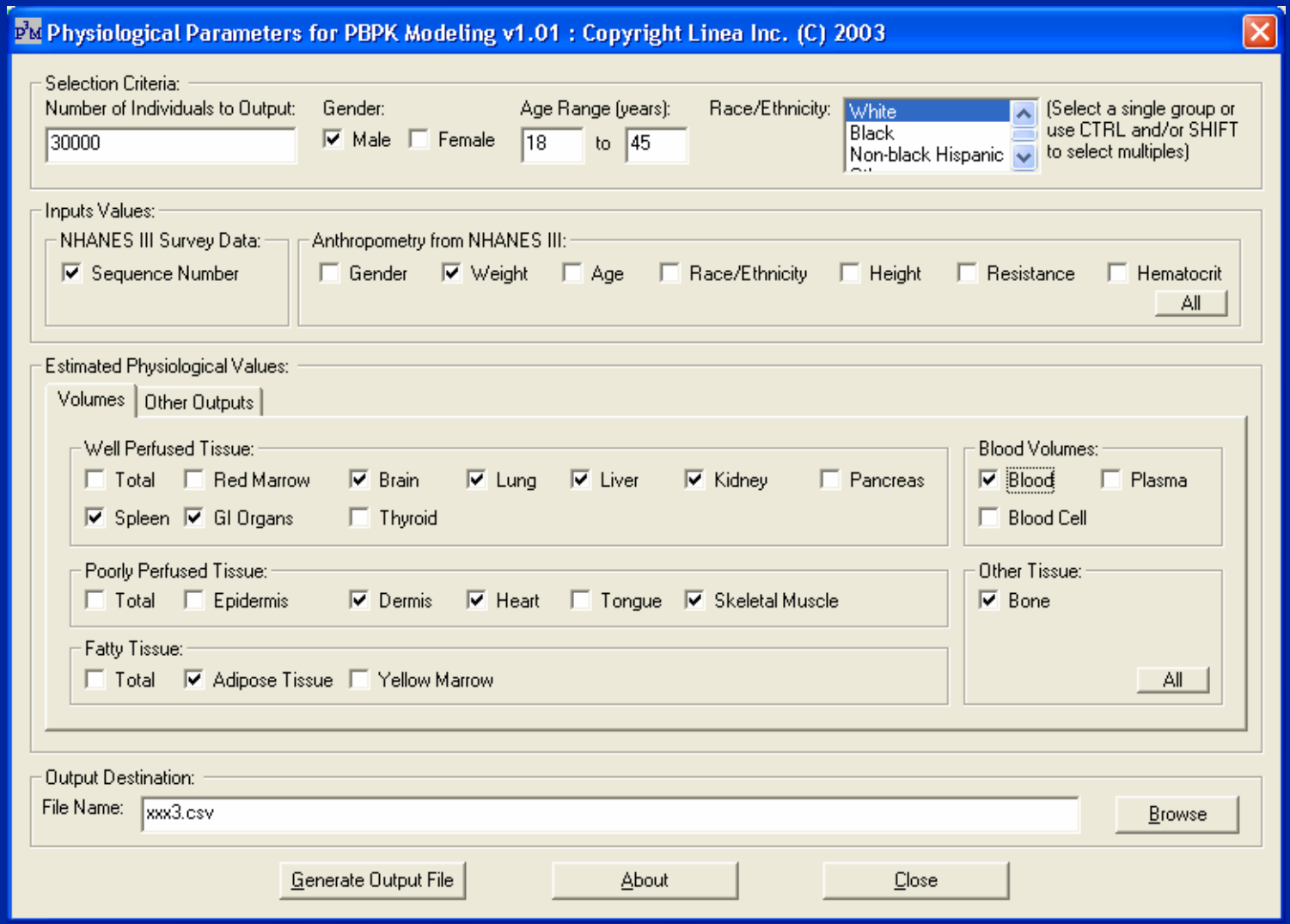

P³M, Price CRT 2003

Distribution of physiological model parameters

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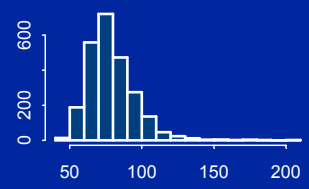
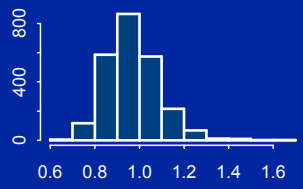
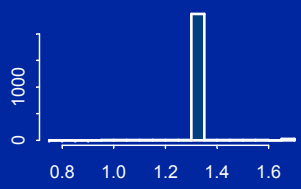
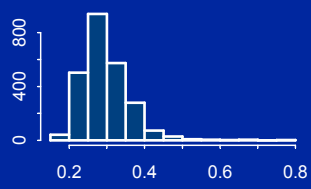
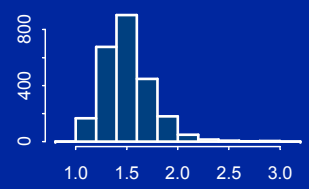
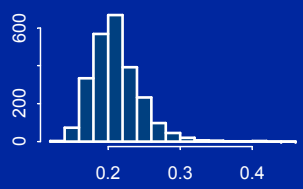


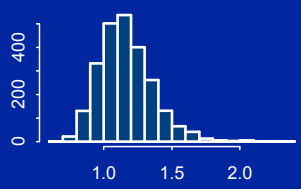


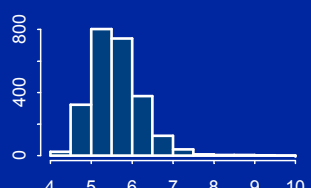


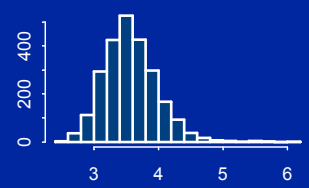


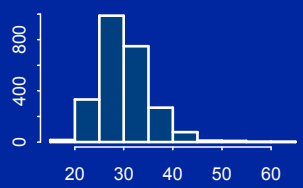


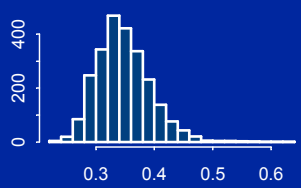


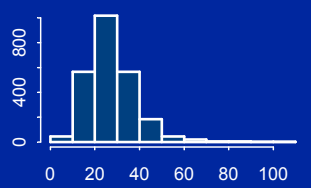


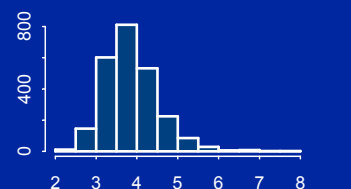


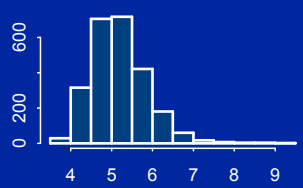






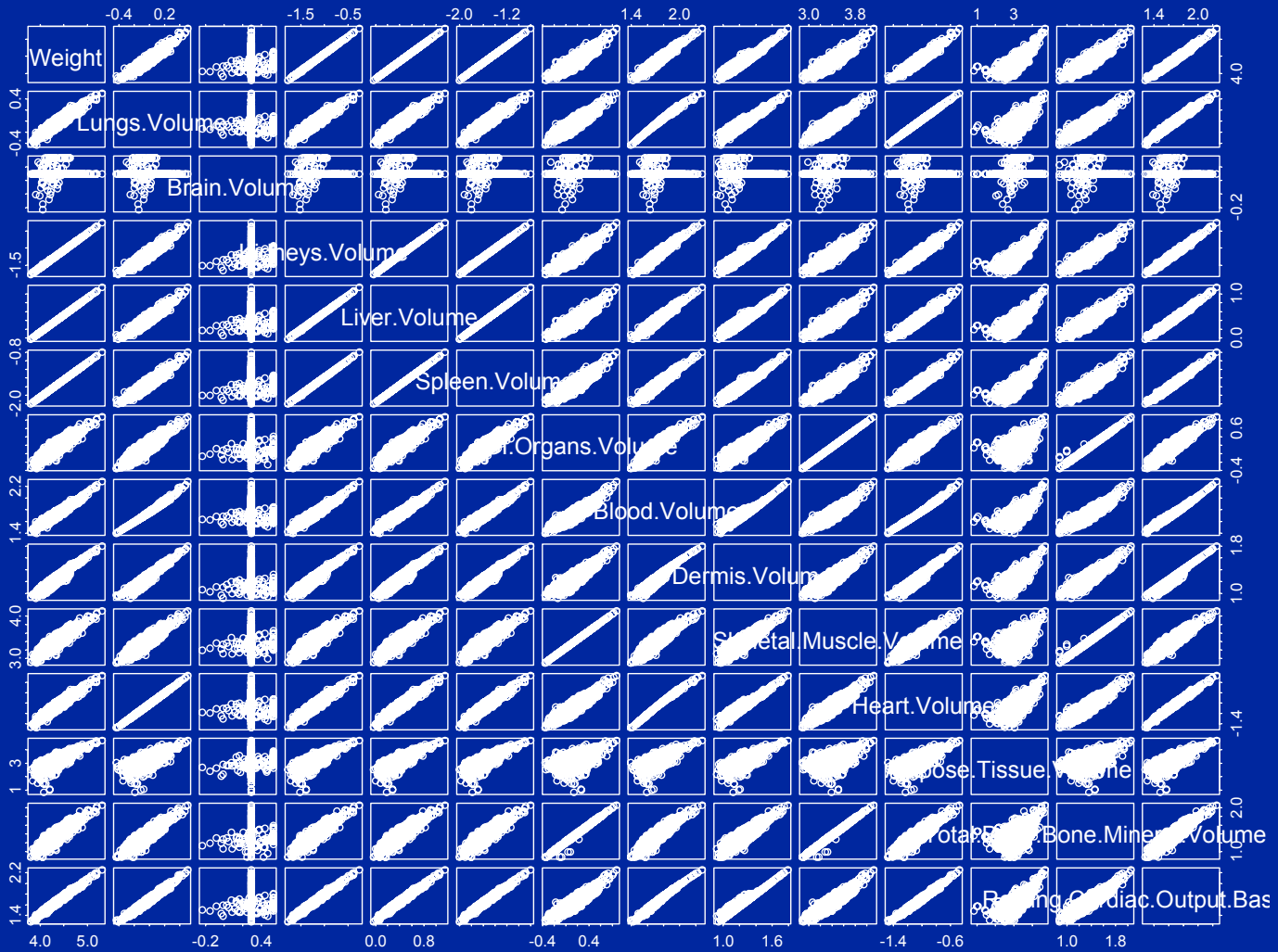






Correlation pattern of physiological parameters

0.90<r<0.99, brain vol. uncorrelated, adipose vol. 0.5<r<0.8



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Compound related variability (CV)
P_Ts, fu, R, CLint

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Tissue:plasma partition coefficients (P_T)
(Poulin & Theil JPS 2000, 2002)

Fraction unbound in tissue (fuT)
Fraction unbound in plasma (fuP)
n-octanol:buffer partition ratio (LogP)
Tissue composition (lipids, water)
pKa
Blood:Plasma ratio R

In vivo intrinsic clearance in liver ($CL_{int\ L(u)}$)
(Houston, 1994)

- In vitro intrinsic clearance (CL_{int}) (hepatocytes, microsomes)
- Scaling factors (hepatocellularity, microsomal recovery)
  (Wilson et al. BJCP, 2003)
- *Liver weight*

Model Implementation
Structural Model

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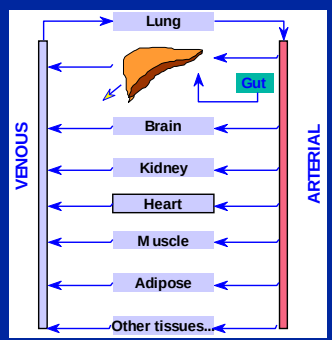
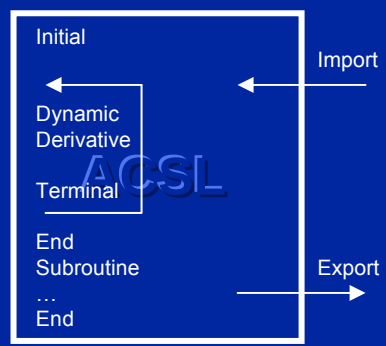
ACSL – Advanced Continuous Simulation Language

- Fortran based simulation language, ~ 1970
- Automobile and Aircraft Industry
- Ordinary differential equation systems

- Parameter import and export
- Macro language
- Fortran subroutines (user defined)





Model Implementation
Variability

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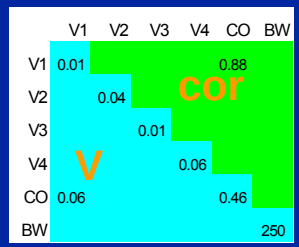


18 < Age < 40
Gender = F

S-PLUS

Cholesky Decomposition (correlations)

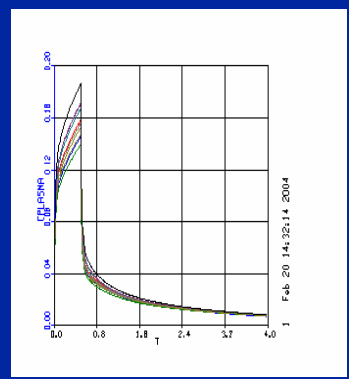
$V \rightarrow A$

$V=A \cdot A^T$

A

ACSL

Compound related variability
P_Ts, CLint



“Experimental” Conditions

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Compound Variability (CV) / Physiol. Variability (PV)	None	in vitro CLint	P_Ts	in vitro CLint, P_Ts
None	(X)	X	X	X
Variability with correlations (PV correlated)	X			X
Variability without correlations (PV uncorrelated)	X			(X)

Drug Characteristics

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Drug A

In vitro CLint(u)	3034.8 uL/min/mg	30%CV
SF	33.0 mg/g liver	39%CV
VLiver	0.026 BW	
BW	70 kg	19%CV
R	0.69	5%CV
Fup	0.0016	9%CV
P_Ts		6-91%CV (observed)

Drug B

In vitro Clint(u)	1.99 uL/min/Mcells	59%CV
SF	107 Mcells/g liver	52%CV
VLiver	0.026 BW	
BW	76 kg	19%CV
R	0.65	3%CV
Fup	0.00095	10%CV
P_Ts		26-57%CV (predictions)

Drug A (0-10 h)

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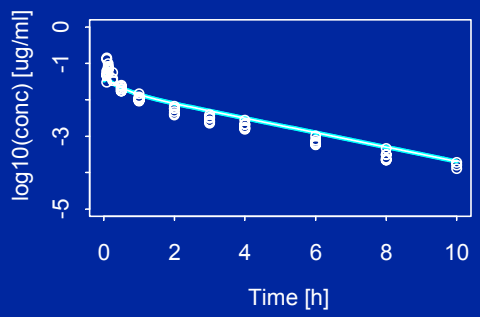
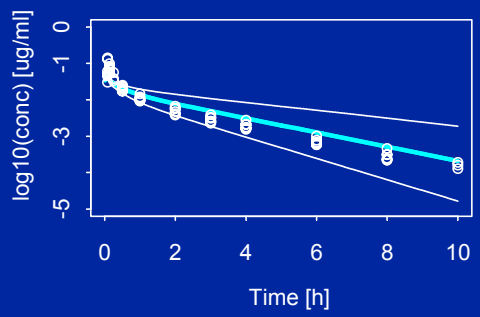
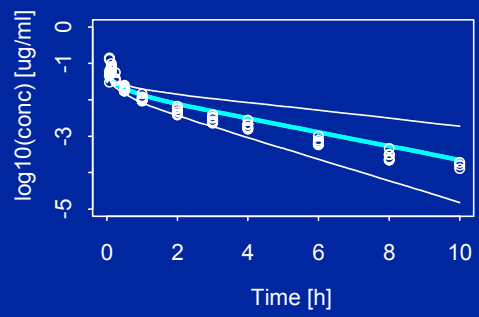
no variability



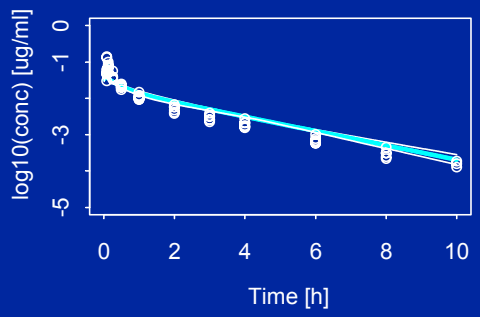
CV: PT+CL



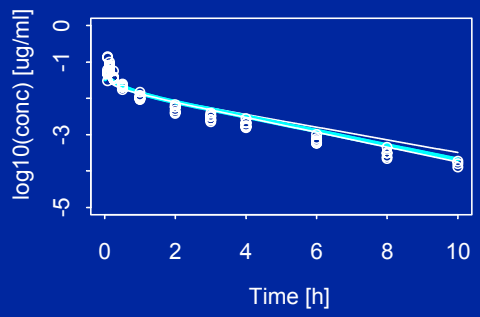
CV: PT+CL / PV correlated



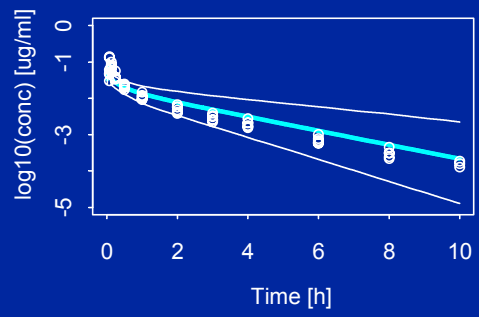
PV correlated



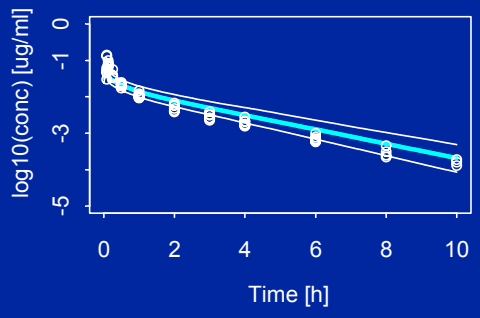
CV: PT



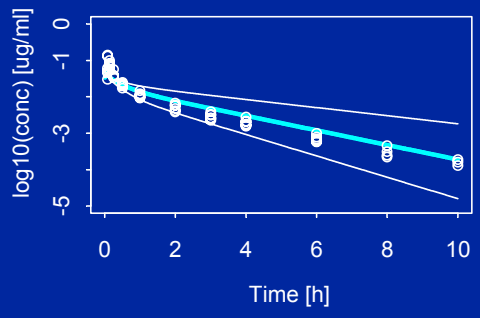
CV: PT+CL / PV uncorrelated



PV uncorrelated



CV: CL



Legend
CV: compound related variability
PT – partition coefficient
CL – in vitro intrinsic clearance
PV: Physiology related variability

Drug A (0-0.5 h)

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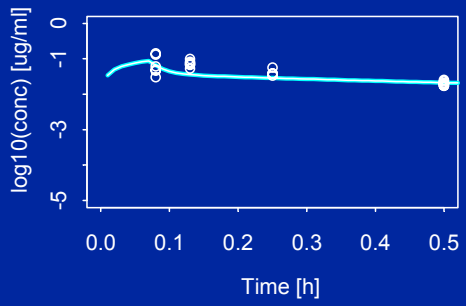
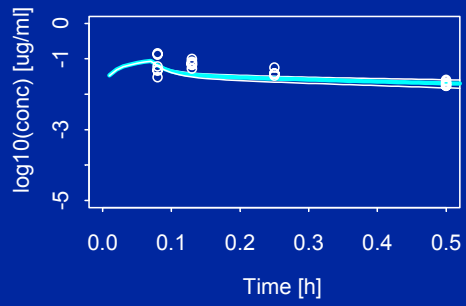
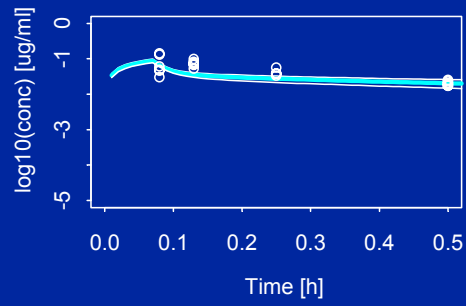
no variability



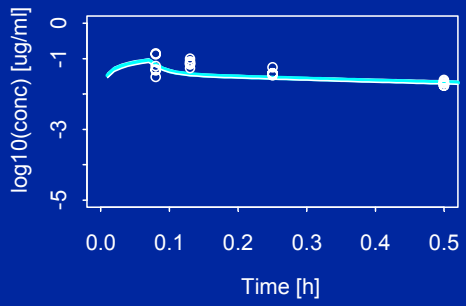
CV: PT+CL



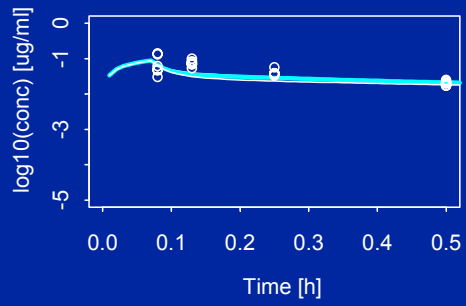
CV: PT+CL / PV correlated



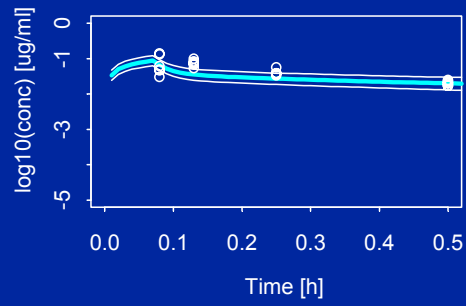
PV correlated



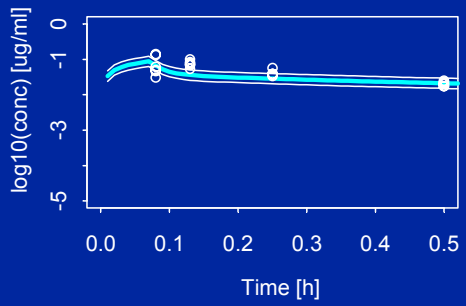
CV: PT



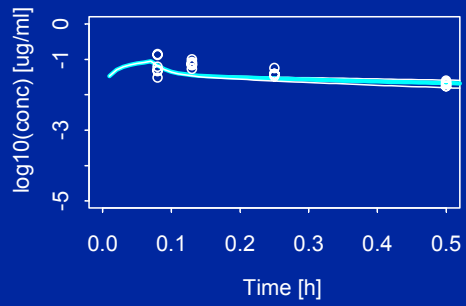
CV: PT+CL / PV uncorrelated



PV uncorrelated



CV: CL



Legend
CV: compound related variability
PT – partition coefficient
CL – in vitro intrinsic clearance
PV: Physiology related variability

Drug B (0-24 h)

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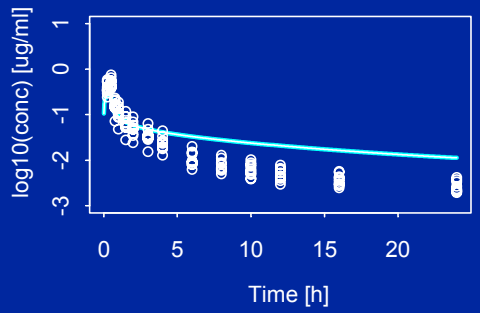
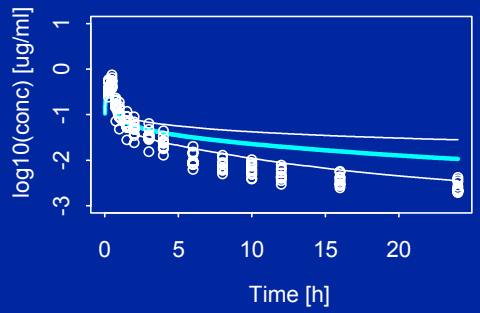
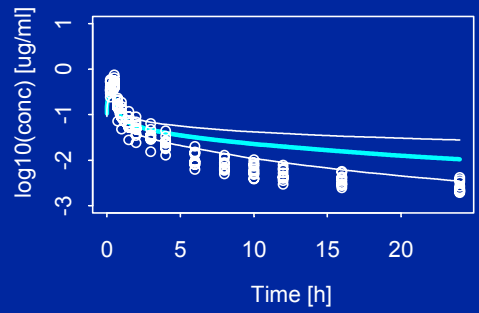
no variability



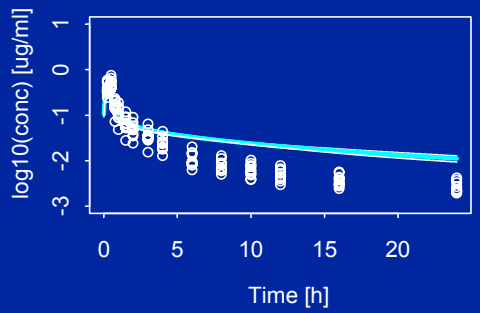
CV: PT+CL



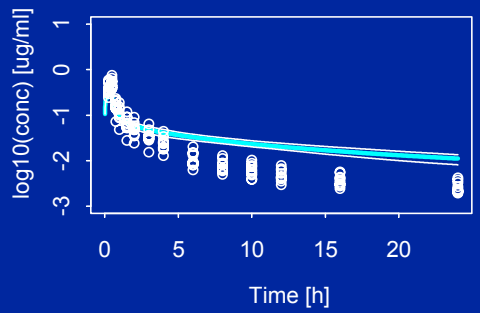
CV: PT+CL / PV correlated



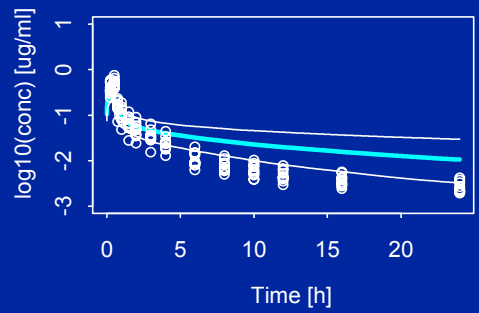
PV correlated



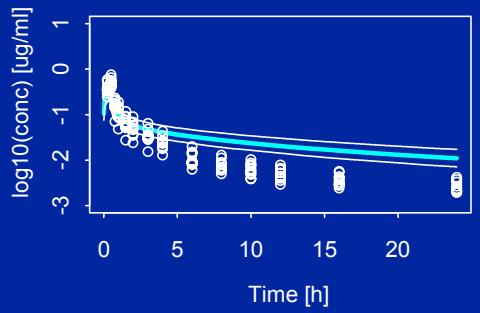
CV: PT



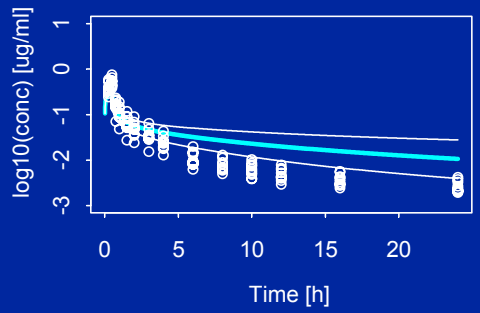
CV: PT+CL / PV uncorrelated



PV uncorrelated



CV: CL



Legend
CV: compound related variability
PT – partition coefficient
CL – in vitro intrinsic clearance
PV: Physiology related variability

Drug B (0-2 h)

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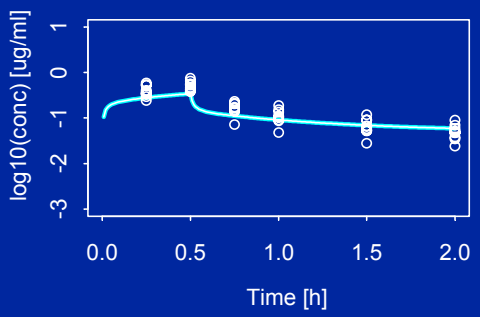
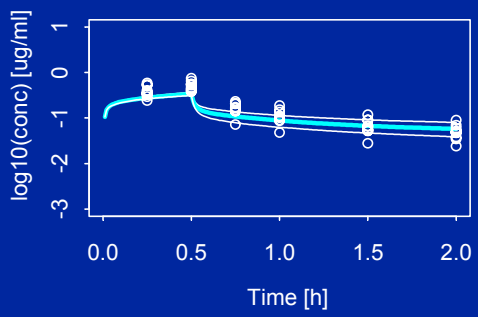
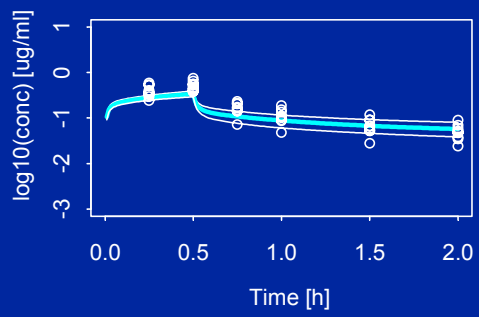
no variability



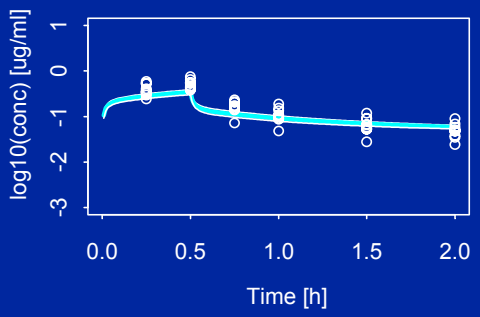
CV: PT+CL



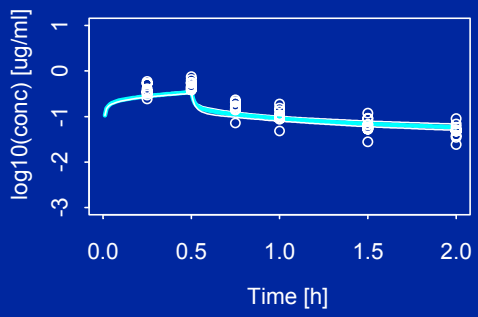
CV: PT+CL / PV correlated



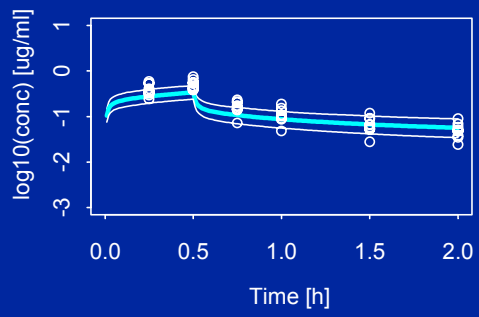
PV correlated



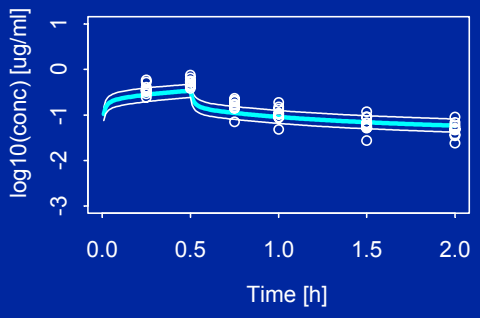
CV: PT



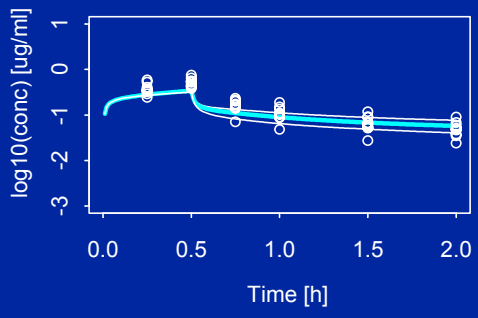
CV: PT+CL / PV uncorrelated



PV uncorrelated



CV: CL



Legend
CV: compound related variability
PT – partition coefficient
CL – in vitro intrinsic clearance
PV: Physiology related variability

Conclusion

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- Compound related variability contributed (much) more than physiological related variability to variability of predicted drug concentrations.
- Physiological variability appears to be more relevant during drug absorption.
- Respecting reported correlations from Linea Inc. in physiological parameters reduces (nearly all) variability in predicted concentrations.
- Compound related variability is mainly due to variability in CLint
- ACSL proved to be an appropriate tool for the present investigation (but lacks statistical routines).

Acknowledgements

- Neil Parrott, Preclinical M&S
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- Eric Luedin, Clinical Statistics
- Karin Jorga, Clinical M&S

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Table 46 Weight in kilograms for men 18 to 74 years of age: number examined, mean, standard deviation, and selected percentiles by race and age, United States, 1976 to 1980*

Race and age (years)	Number of examined persons	Mean	Standard deviation	Percentile 5th	10th	15th	25th	50th<	75th	85th	90th	95th
All races†												
18-74	5,916	78.1	13.5	58.6	62.3	64.9	68.7	76.9	85.6	91.3	95.7	102.7
18-24	988	73.8	12.7	56.8	60.4	61.9	64.8	72.0	80.3	85.1	90.4	99.5
25-34	1,067	78.7	13.7	59.5	62.9	65.4	69.3	77.5	85.6	91.1	95.1	102.7
35-44	745	80.9	13.4	59.7	65.1	67.7	72.1	79.9	88.1	94.8	98.8	104.3
45-54	690	80.9	13.6	60.8	65.2	67.2	71.7	79.0	89.4	94.5	99.5	105.3
55-64	1,227	78.8	12.8	59.9	63.8	66.4	70.2	77.7	85.6	90.5	94.7	102.3
65-74	1,199	74.8	12.8	54.4	58.5	61.2	66.1	74.2	82.7	87.9	91.2	96.6
White												
18-74	5,148	78.5	13.1	59.3	62.8	65.5	69.4	77.3	85.6	91.4	95.5	102.3
18-24	846	74.2	12.8	56.8	60.5	62.0	65.0	72.4	80.6	85.5	91.0	100.0
25-34	901	79.0	13.1	59.9	63.7	65.9	69.8	78.0	85.6	91.3	95.3	102.7
35-44	653	81.4	12.8	62.3	66.6	68.8	72.9	80.1	88.2	94.6	98.7	104.1
45-54	617	81.0	13.4	62.0	66.1	67.3	71.9	79.0	89.4	94.2	99.0	104.5
55-64	1,086	78.9	12.4	60.5	64.5	66.6	70.6	78.2	85.6	90.4	94.5	101.7
65-74	1,045	75.4	12.4	55.5	59.5	62.5	67.0	74.7	83.0	87.9	91.2	96.0
Black												
18-74	649	77.9	15.2	58.0	61.1	63.6	67.2	75.3	85.4	92.9	98.3	105.4
18-24	121	72.2	12.0	58.3	60.9	62.3	64.9	70.8	77.1	81.8	83.7	93.6
25-34	139	78.2	16.3	58.7	63.4	64.9	68.4	75.3	84.4	90.6	92.2	106.3
35-44	70	82.5	15.4	*	61.7	65.2	69.7	83.1	94.8	100.4	104.2	*
45-54	62	82.4	14.5	*	64.7	67.0	73.2	81.8	93.0	100.0	102.5	*
55-64	129	78.6	14.7	56.8	61.4	64.3	68.0	77.0	86.5	93.8	98.6	104.7
65-74	128	73.3	15.3	52.5	56.7	58.0	61.0	71.2	81.1	90.8	97.3	105.1

*Includes clothing weight, estimated as ranging from 0.09 to 0.28 kilogram.

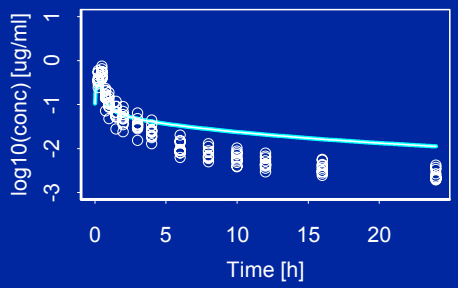
† Includes all other races not shown as separate categories.

(From National Center for Health Statistics (1987) *Anthropometric Reference Data and Prevalence of Overweight, United States 1976-1980*, DHHS Publication No. 87-1688, U.S. Department of Health and Human Services, Public Health Service, Hyattsville, MD.)

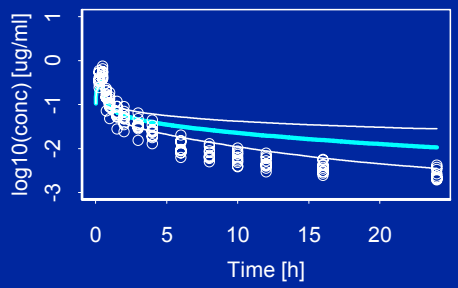
Backup

Drug B - variance in PV * 4

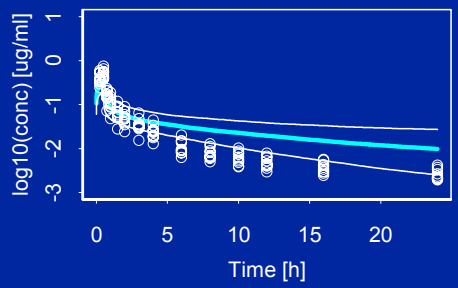
no variability



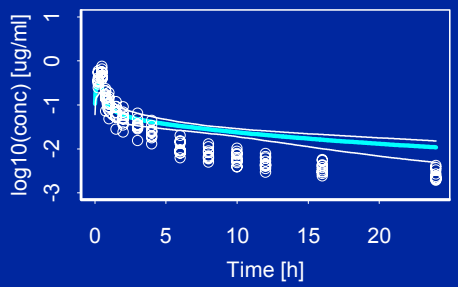
CV: PT+CL



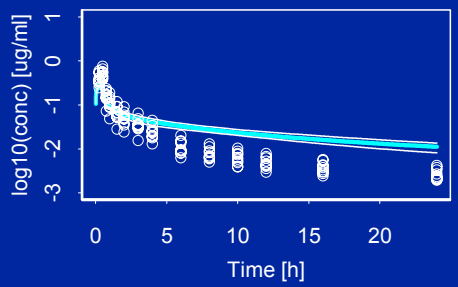
CV: PT+CL / PV correlated



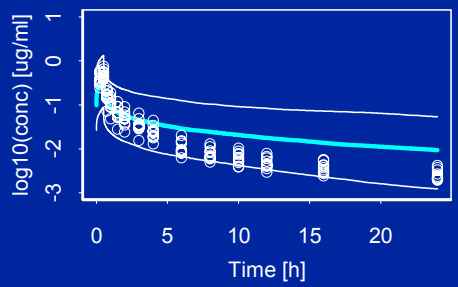
PV correlated



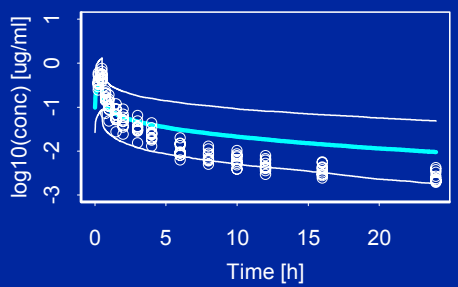
CV: PT



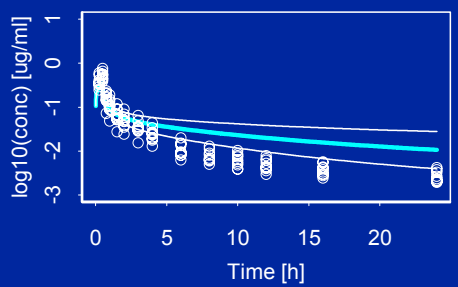
CV: PT+CL / PV uncorrelated



PV uncorrelated



CV: CL



Legend
CV: compound related variability
PT – partition coefficient
CL – in vitro intrinsic clearance
PV: Physiology related variability