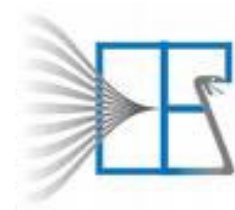


Are Children Small Adults?

***What can modeling offer to
(clinical) practice?***

***Catherijne Knibbe, PharmD, PhD
Hospital Pharmacist-Clinical Pharmacologist***

ZIEKENHUIS
ST ANTONIUS



Leiden / Amsterdam
Center for Drug Research

How are children dosed in (clinical) practice?

In practice drugs in children are mainly dosed in mg/kg

- Often **different mg/kg** per **age** group
- Even in the **absence of relevant differences** in PK or PK-PD relationships

How should children be dosed?

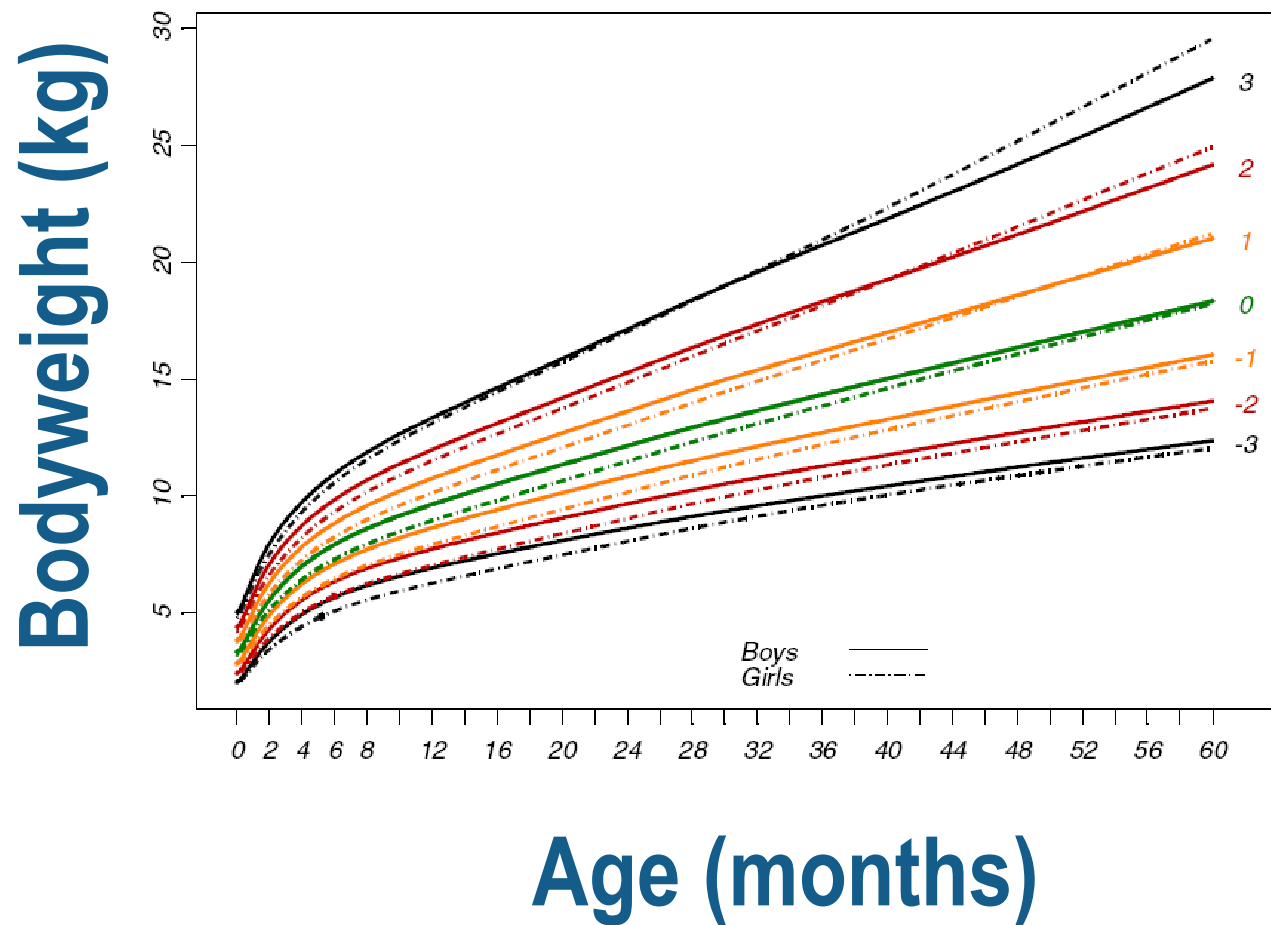
Individualised dosing in paediatrics: dosing recommendation should be based on potential differences in PK, PD or PK-PD relationships:

- **developmental growth**

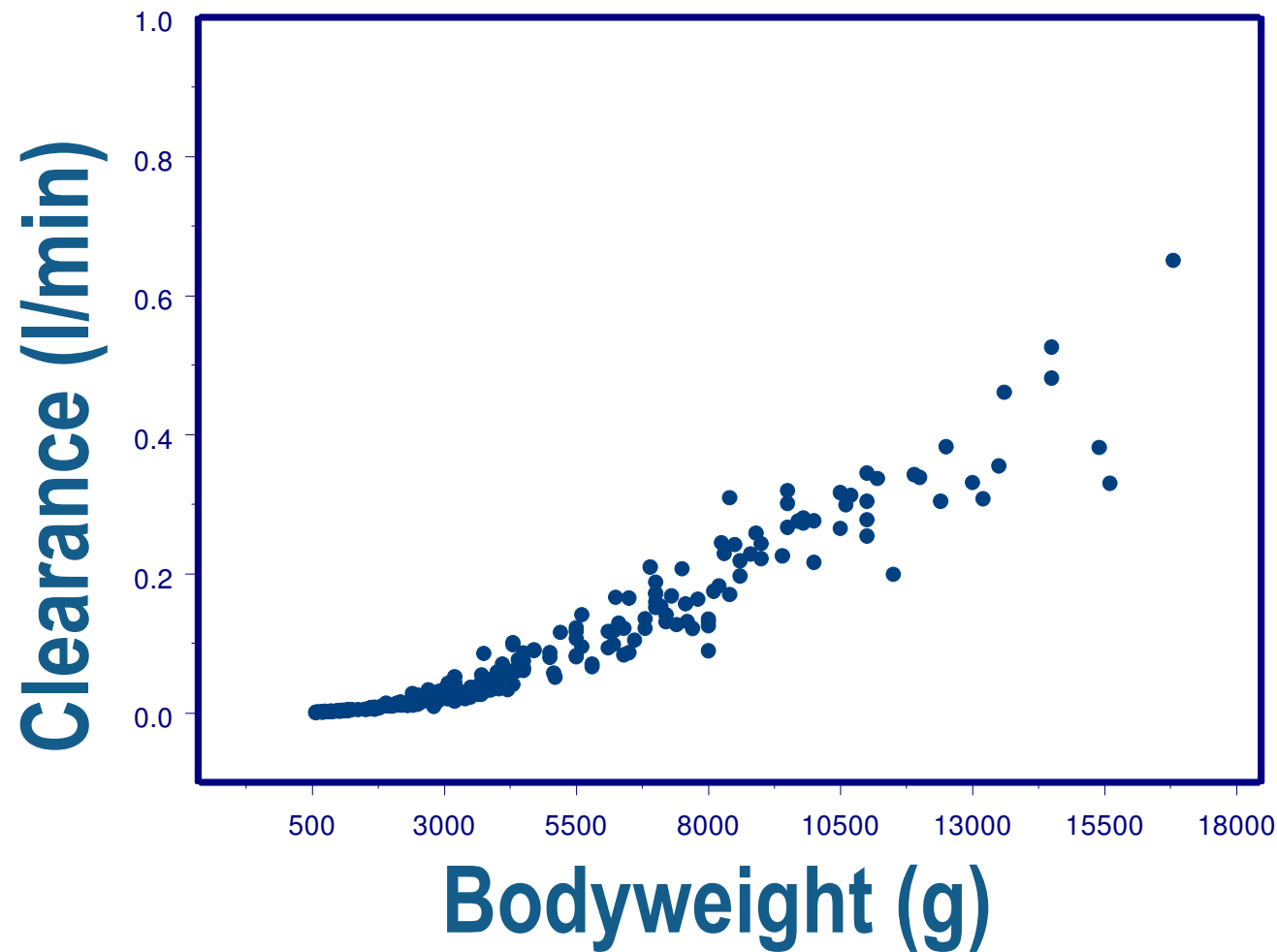
X

- **other covariates** (genetics, (critical) illness, comedication etc)

Correlation between age and bodyweight

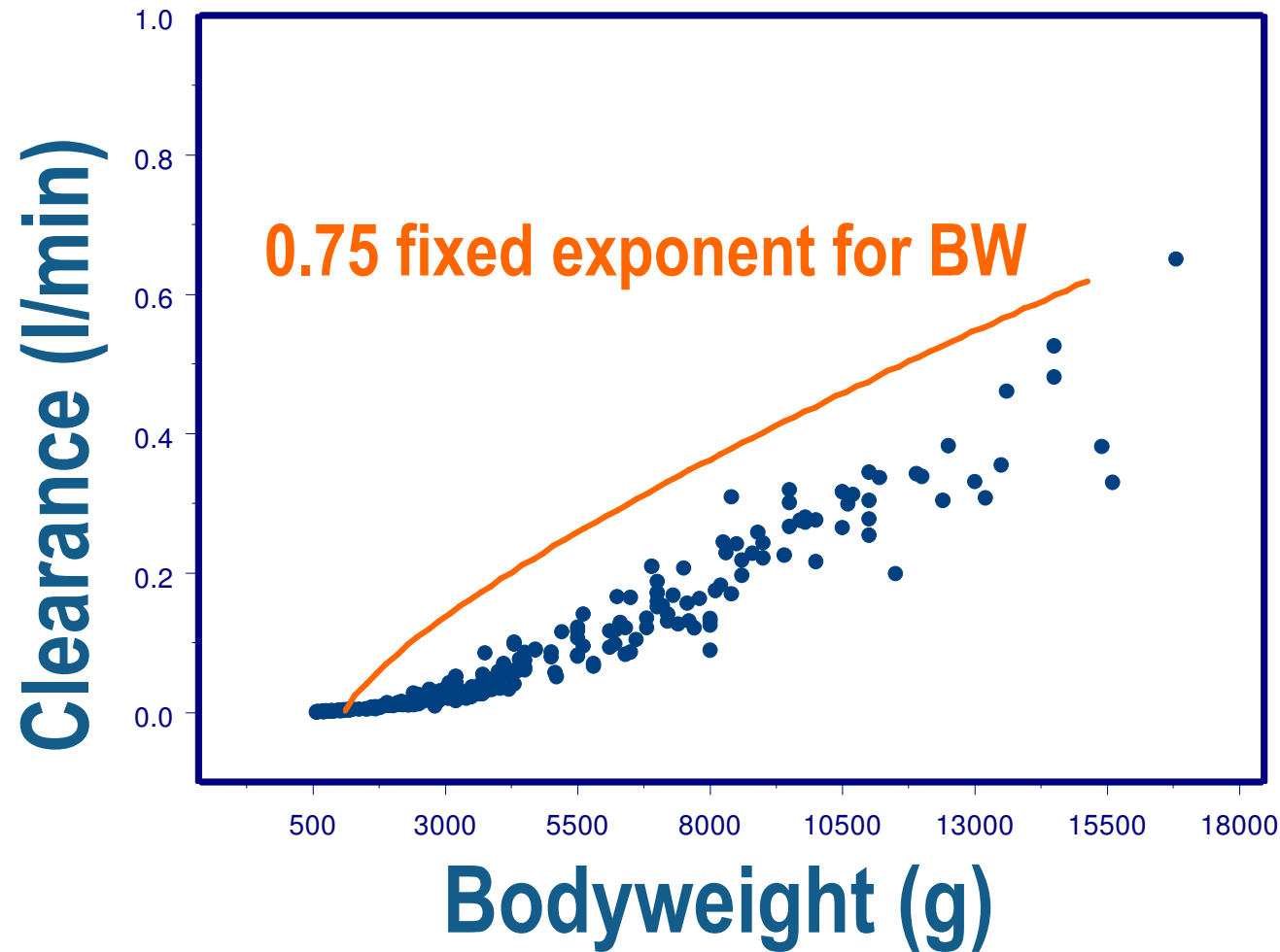


Glucuronidation of *morphine* in children

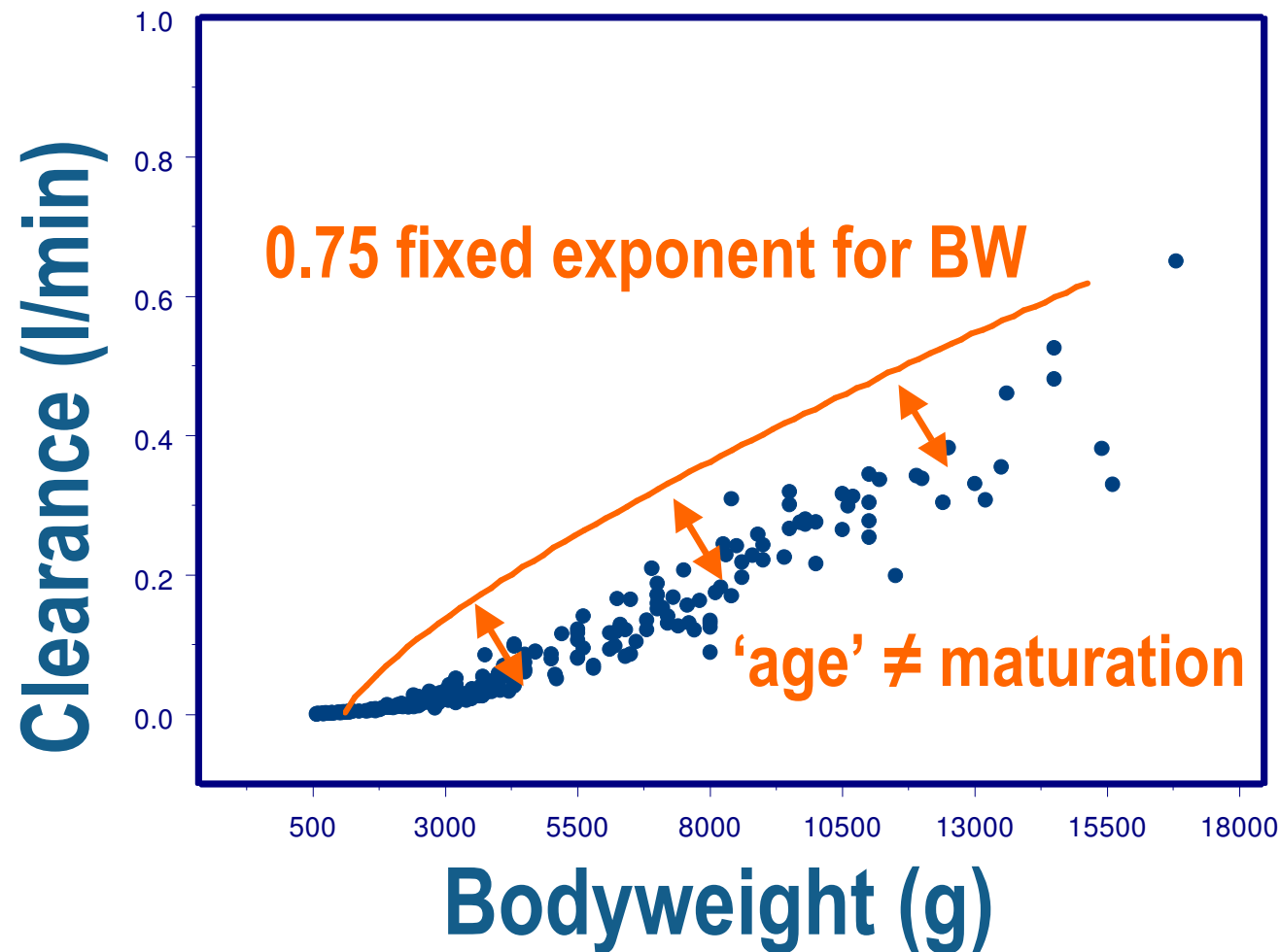


Knibbe CA, Krekels EH et al, Clin Pharmacokinet, in press

Glucuronidation of *morphine* in children



Glucuronidation of *morphine* in children



covariate analysis: correlation between age and bodyweight

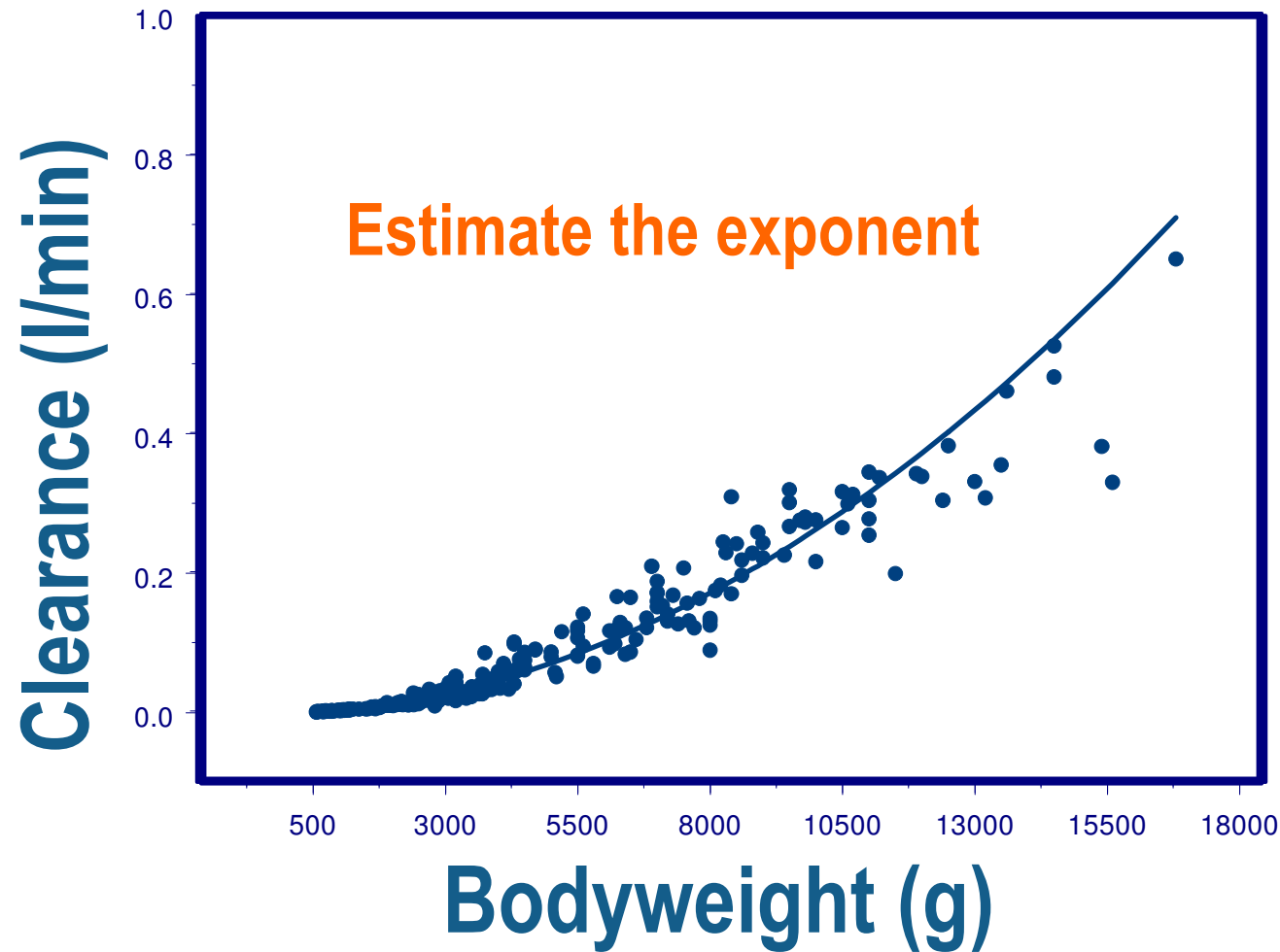
If a **fixed function for BW** is used:

- **Additional functions based on age** are needed to correct for deviations caused by fixed functions for BW (drug-specific age-functions)



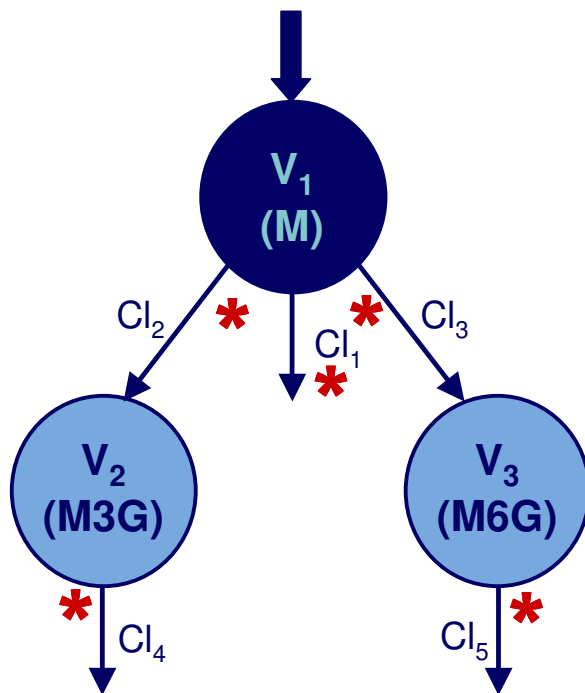
Complex and often unstable models
particularly under the age of two years

Optimize *one surrogate marker* for maturation



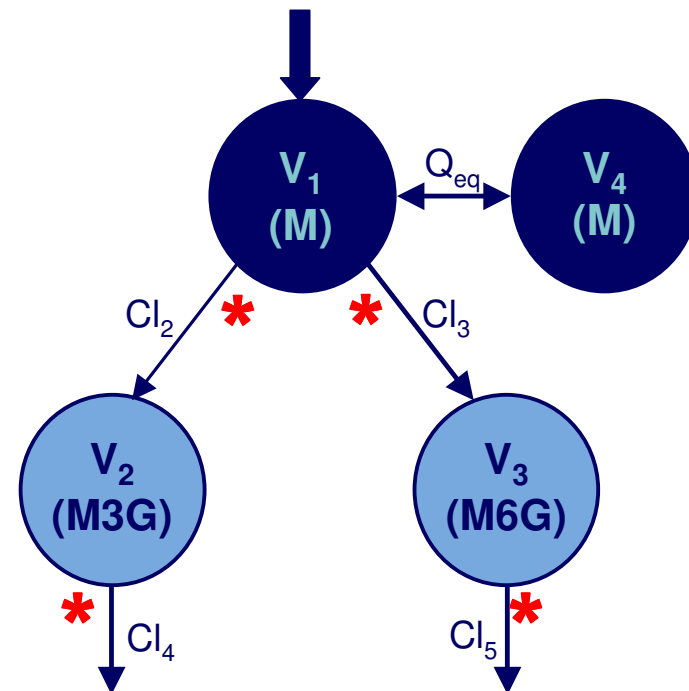
Comparison of *fixed* and *estimated* functions

* BW 0.75 **fixed**



Unstable model

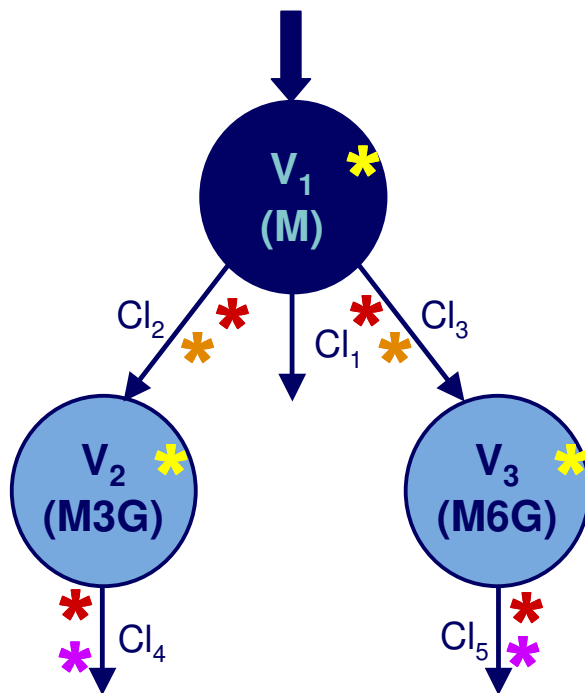
* BW 1.44 **estimated**



Stable model

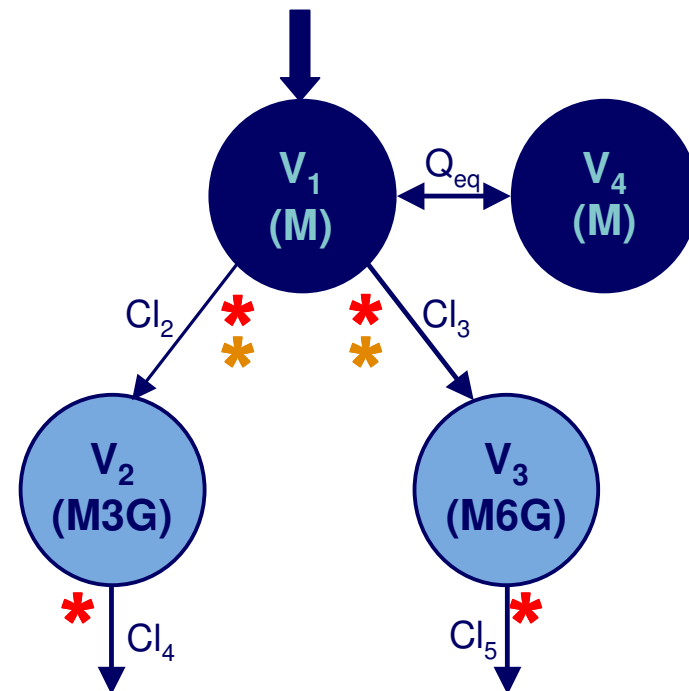
Comparison of *fixed* and *estimated* functions

* * * exp PNA



Six thetas needed

* PNA $\uparrow$ or $\downarrow$ 10 days



1-3 thetas needed

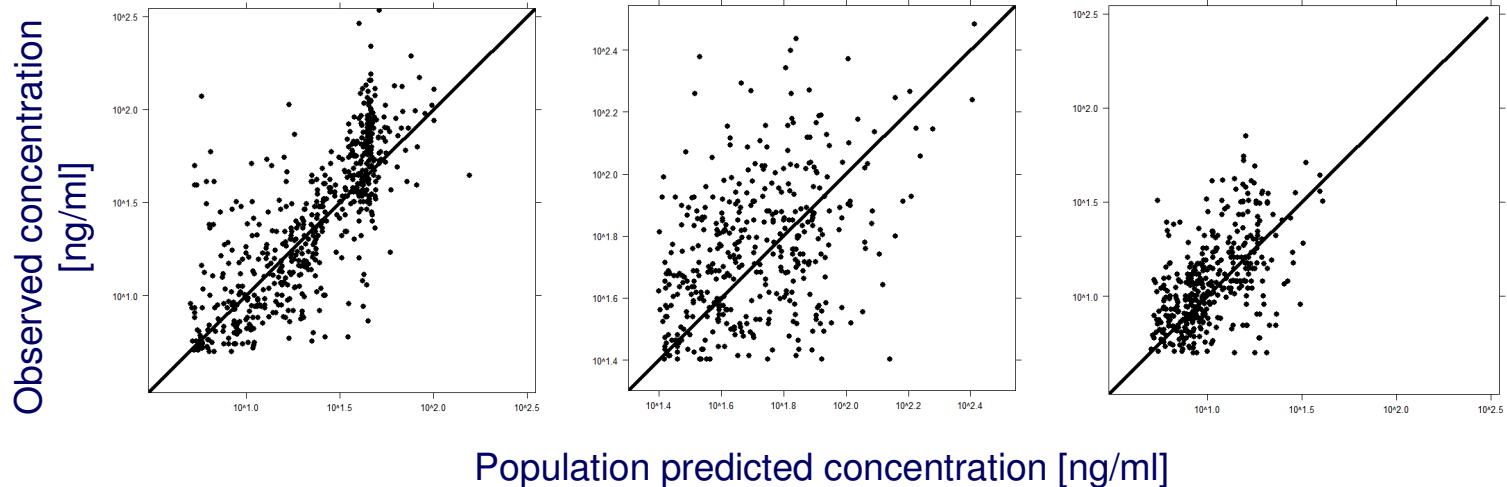
Internal validation of the *estimated* model

Morphine

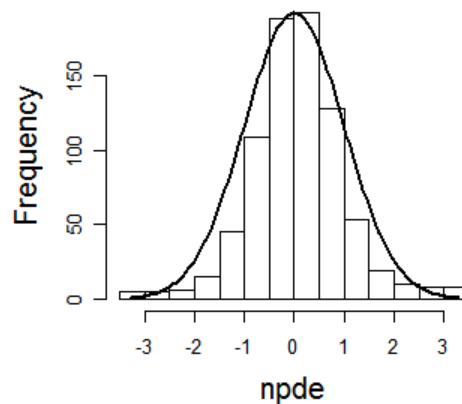
M3G

M6G

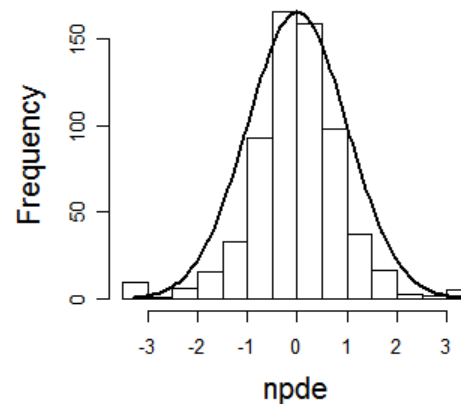
Predicted
vs
Observed



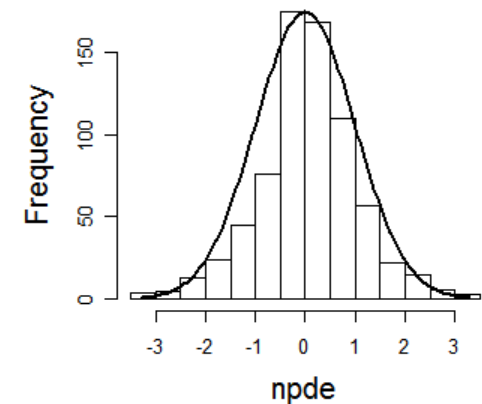
Normalized
Prediction
Distribution
Errors



Mean: 0.074*
Variance: 0.90*



Mean: -0.027
Variance: 0.86*



Mean: 0.056*
Variance: 1.00

Internal validation of the **estimated** model

<i>Parameters</i>	<i>Model fit</i>		<i>Bootstrap</i> (99 out of 100)	
	<i>value</i>	<i>CV(%)</i>	<i>mean value</i>	<i>CV(%)</i>
Fixed effects (n=10)				
k = exponential scaling factor	1.49	3.6	1.49	3.9
Cl ₁ PNA < 10 d (ml/min/kg ^k)	3.68	9.0	3.65	9.9
Cl ₁ PNA > 10d (ml/min/kg ^k)	8.04	11.0	7.93	12.7
Cl ₂ PNA < 10d (ml/min/kg ^k)	0.423	11.1	0.412	15.5
Cl ₂ PNA > 10d (ml/min/kg ^k)	0.623	10.2	0.618	13.9
Cl ₃ (ml/min/kg ^k)	1.84	9.9	1.83	11.5
Cl ₄ (ml/min/kg ^k)	0.955	9.0	0.954	14.2
Q _{eq} (ml/min)	40.8	24.1	38.9	29.3
V ₁ = V ₄ (l/kg)	1.64	8.2	1.64	8.0
V ₂ = V ₃ (fraction of V ₁)	0.157	21.2	0.156	21.5
Inter-individual variability (n=5)				
ω ² Cl ₁	0.0809	24.0	0.0754	28.0
ω ² V ₁	0.162	17.9	0.166	19.3
ω ² Cl ₃	0.256	27.1	0.250	27.8
ω ² Cl ₄	0.110	15.2	0.110	16.9
ω ² Cl ₃ -Cl ₄ interaction	0.128	18.2	0.164	18.4
Residual error (n=3)				
σ ^{2, prop} (morphine)	0.440	14.7	0.434	15.1
σ ^{2, prop} (M3G)	0.261	27.2	0.242	30.4
σ ^{2, prop} (M6G)	0.0894	15.7	0.0888	17.1

External validation of the *estimated* model

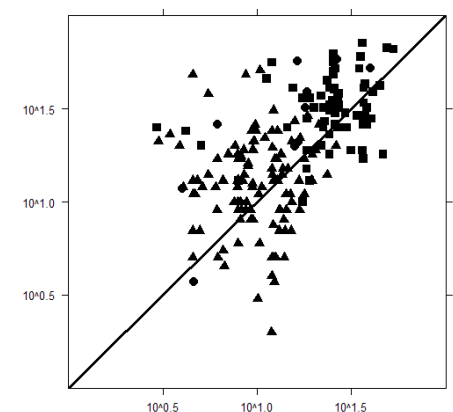
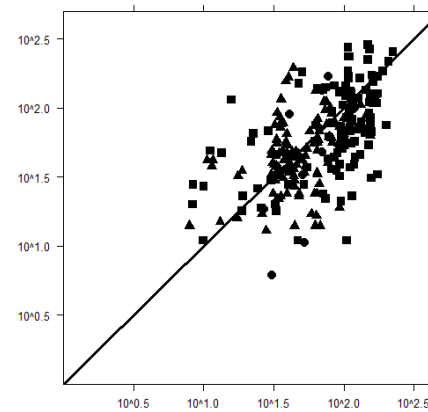
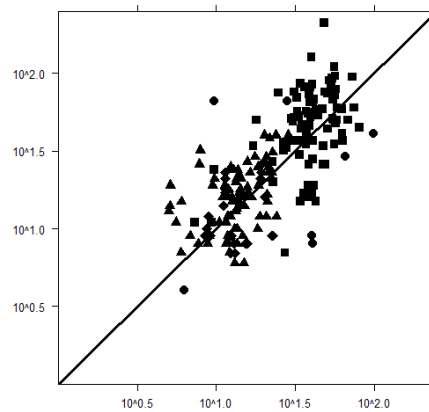
Morphine

M3G

M6G

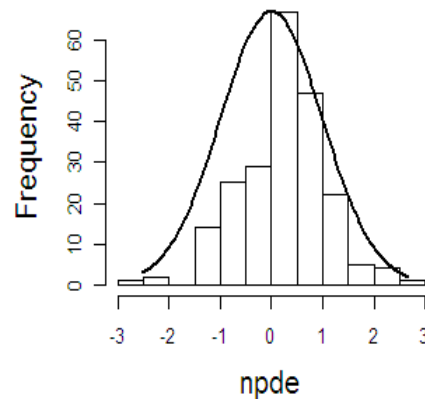
Predicted
vs
Observed

Observed concentration
[ng/ml]

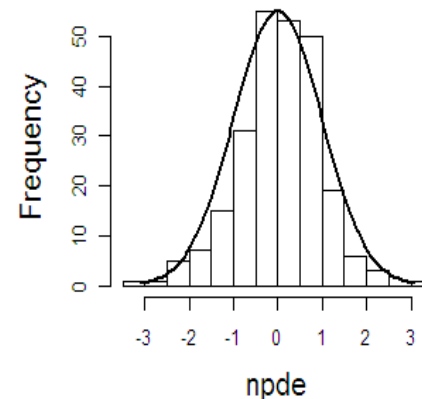


Population predicted concentration [ng/ml]

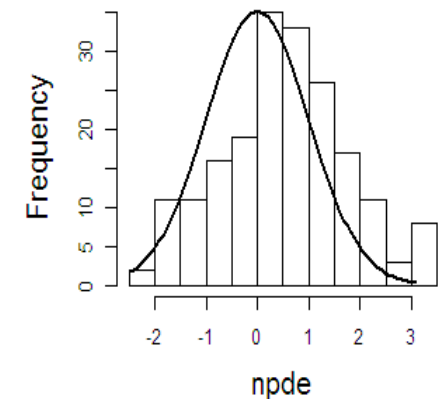
Normalized
Prediction
Distribution
Errors



Mean: 0.0025***
Variance: 0.6818***



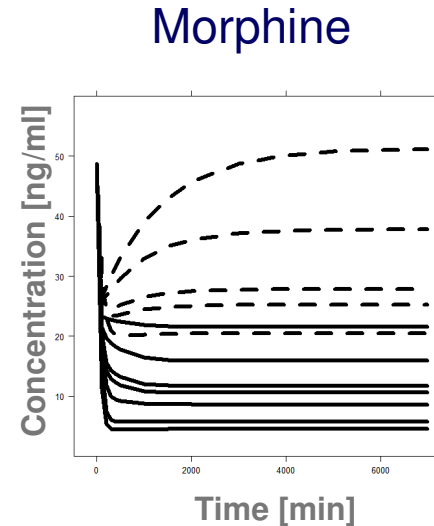
Mean: 0.03461
Variance: 0.8481



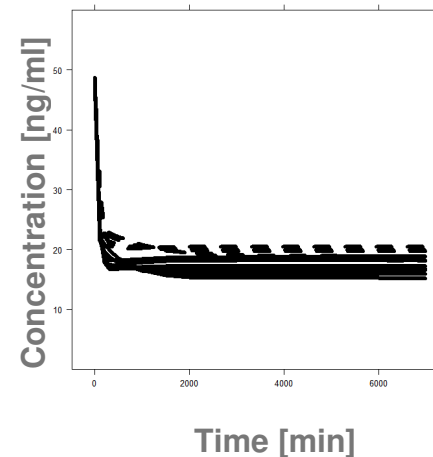
Mean: 0.5153***
Variance: 1.501***

Validation of the proposed dosing regimen in a *prospective trial* (NTR Number NTR1438)

Traditional
dosing
scheme
in $\mu\text{g/kg/h}$



Proposed
dosing
scheme
 $\mu\text{g/kg}^{1.5}/\text{h}$



Perspectives

- Apply **PB-PK modelling** concepts
- Identify **system specific properties** in the models of developmental changes
- Explore its use for **drugs sharing similar disposition pathways**
 - e.g. morphine, zidovudine

Conclusions

- Population PK and PD models are the basis for identification **dosing algorithms for individualization** of therapy that can be used in **clinical practice**
- Keep an **open mind** when analysing pediatric data
 - **Estimate** the influence of covariates bodyweight and/or age
- **Use only fully validated** models for simulations of dosing algorithms.
- Evaluate developed dosing algorithms in **prospective clinical trials**

Involved researchers in paediatrics

- **Leiden**

- Elke Krekels, Ibrahim Ince, Maurice Wang, Massimo Cella, Roosmarijn de Cock, Oscar Della Pasqua, Meindert Danhof

- **Rotterdam, Erasmus MC Sophia**

- Heleen Blusse van Oud-Albas, Saskia de Wildt, John van den Anker, Dick Tibboel

- **Leuven**

- Karel Allegaert

- **Utrecht Medical Centre**

- Imke Bartelink, Toine Egberts, Lieke Sanders, Jaap Jan Boelens

- **Nieuwegein**

- Jeroen Diepstraten, Rifka Peeters, Mathieu Tjoeng

- **Cincinatti Childrens Hospital**

- Sander Vinks