Application of a Bayesian population approach to physiologically-based modelling and simulation of mavoglurant pharmacokinetics

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Mavoglurant

- **Mavoglurant** (MVG) is a structurally novel **antagonist** at the **metabotropic glutamate receptor 5**, currently under clinical development at Novartis Pharma AG for the treatment of **CNS diseases.**

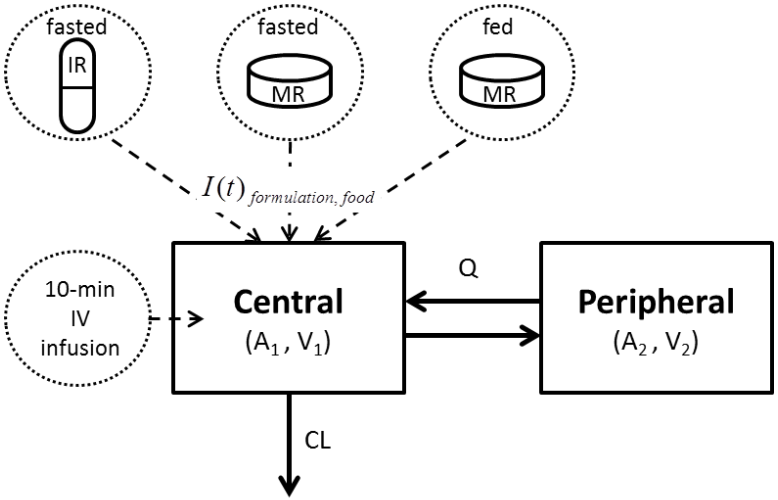
- MVG **pharmacokinetics** (PK) were previously investigated in **healthy adults**[1]:
  - **Lipophilic** drug **extensively distributed** to organs and tissues
  - **Elimination** thought to be mediated by **hepatic oxidative metabolism** involving mainly **cytochrome P450** (CYP) **3A4**, **2C8**, **2C9** and **2C19** enzymes

- The **drug-drug interaction** (DDI) with **ketoconazole** (strong CYP3A4 inhibitor) was evaluated in **adults → 3-fold increase** in **systemic exposure** (unpublished results).

- PK of MVG was also evaluated in **children** aged from **3 to 11 years** (unpublished results).

[1] Walles M *et al*. DMD. 2013

Population PK model for adults



V_{ss} = 172 l (CV of 30%)

CL = 29 l/h (CV of 32%)

Bodyweight (BW) as **covariate** for V_1 and V_2

Advantages

- Easy implementation and fast analysis
- **Disposition** model **mechanistic enough** to evaluate the **impact of covariates**
- **Flexible input model** that can capture complex profiles with multiple peaks

Disadvantages

- No thorough understanding of the **absorption**, **distribution** and **elimination** mechanisms
- Can't predict concentrations in **clinically relevant tissues** (*i.e.* target site)
- Can't **extrapolate** beyond the studied population and experimental conditions

Wendling T *et al*. Pharm Res. 2014

Objectives

1. To **develop** and **optimise** a **population whole-body physiologically-based PK** (WBPBPK) **model** for MVG to gain mechanistic understanding of its **disposition** in a **healthy adult population**.

2. To evaluate the ability of the model to **extrapolate** across **experimental conditions** and **sub-populations**:

   - From **IV administration** to **oral administration** in **adults**
   - From oral administration of **MVG alone** to **co-administration with ketoconazole** in **adults**
   - From oral administration in **adults** to oral administration in **children**

Clinical PK data

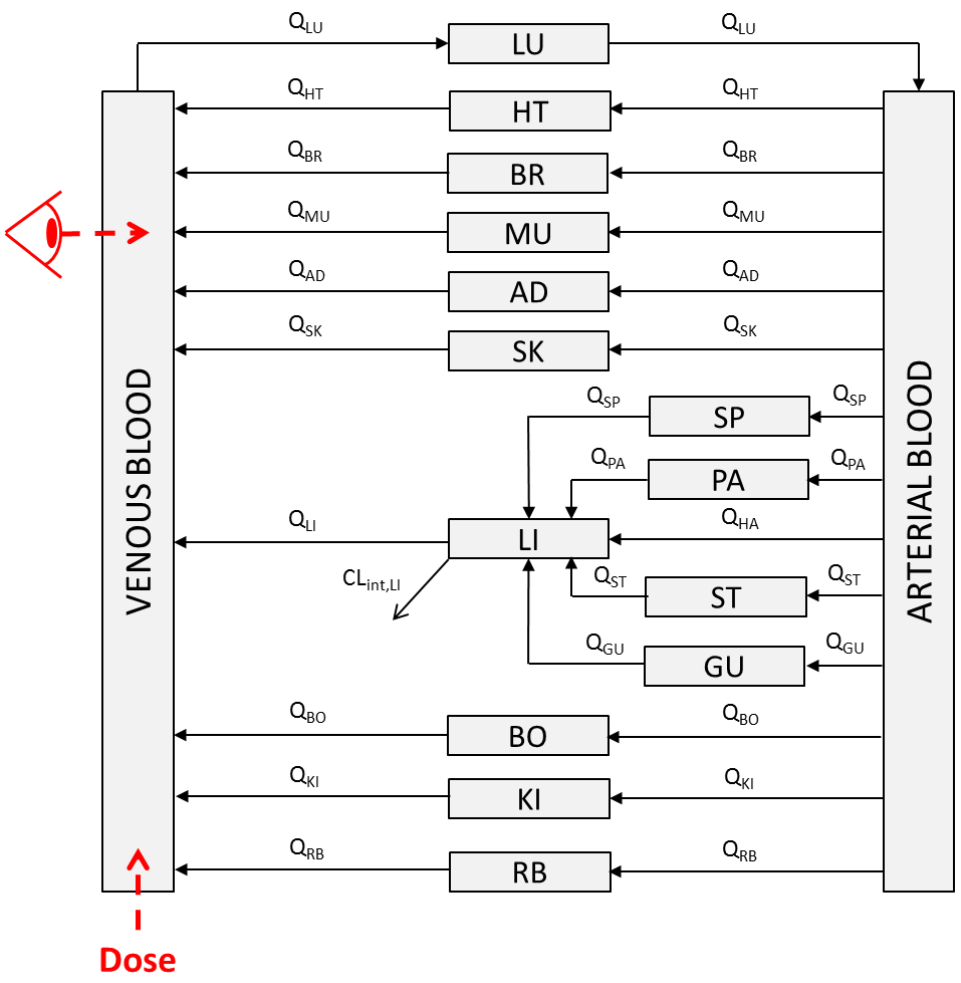
- **Study 1**: single **IV** administration of either 25, 37.5 or 50 mg of MVG in **adults** (n=120).

Fitting

- **Study 2** (cross-over): single **oral** administration of an immediate-release **capsule** formulation of MVG (25 mg) in **adults** (n=16):
  - 1st period: alone
  - 2nd period: on Day 5 of a repeated daily 400-mg dose of **ketoconazole**
- **Study 3**: single **oral** administration of a **suspension** (POS) formulation of MVG (50 mg) in **adults** (n=28).
- **Study 4**: single **oral** administration of the **POS** formulation of MVG (15 mg) in **children** aged from 3 to 11 years (n=21).

Predictive performance

Structure of the WBPBPK model for MVG



- **14 tissue compartments** and **2 blood compartment** (16 ODEs).
- **Elimination** occurs only in the **liver**.
- Drug **uptake** by tissues is **perfusion-limited** (well-stirred compartments).

- **Physiological parameters**:
  - Blood flows
  - Organ volumes

Literature

- **Drug-specific parameters** (n=15):
  - $CL_{int,LI}$
  - K_bs

Pre-clinical experiments

Fitting PBPK models to clinical data

- Although **generic WBPBPK models** are structurally identifiable[2], the **absence of tissue data** in human typically yields **numerically unstable analyses:**

  → **prior information** on the parameters using **Bayesian statistics**

- **PBPK models** are especially suited to **separate** the **physiologic variability** from the overall variability in the system

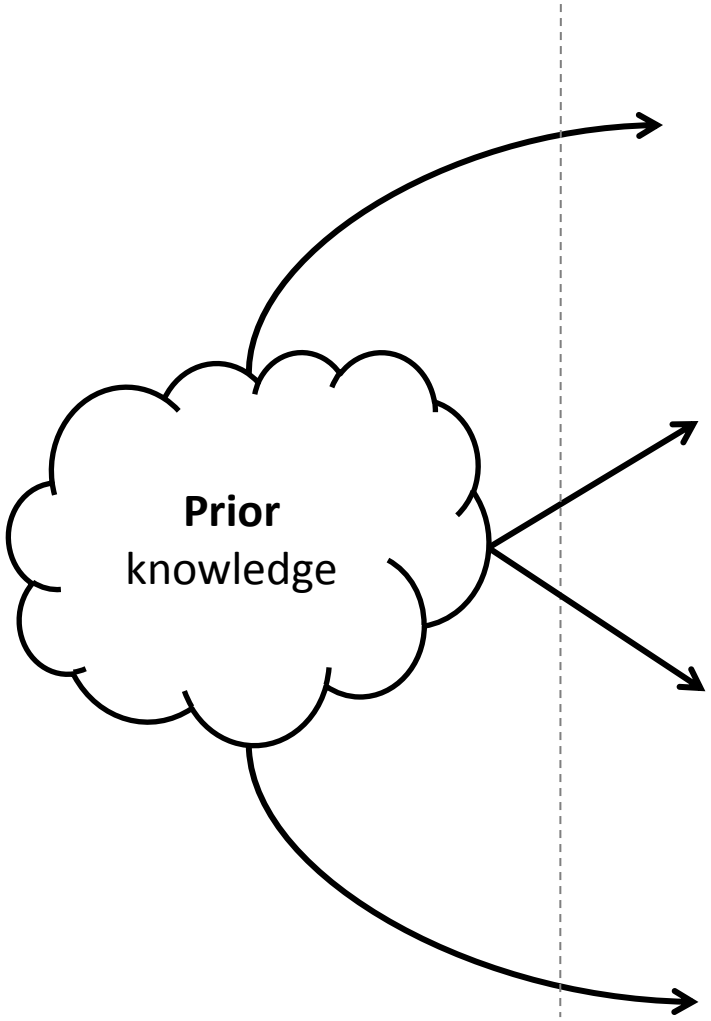
  → relationships between **physiological parameters** and **individual covariates**[3,4]

- In addition, analyses based on **hierarchical models** allow **random variability** in the parameters to be quantified

  → **posterior distributions** for both **individual** and **population parameters**

[2] Yates JW. J PKPD. 2006 [3] Nestorov I. Expert Opin Drug Metab Toxicol. 2007 [4] Willmann S *et al*. J PKPD. 2007

Modelling and simulation workflow



Development a WBPBPK structure model

Sensitivity analysis

Bayesian analysis of clinical data

Extrapolations

→ Identify parameters that can be estimated based on plasma data

→ Improve population and individual parameter estimates

Pre-clinical studies → **Clinical** studies

Sensitivity analysis of the model

Method

- To identify the drug-specific parameters that have a **significant influence** on the **plasma response**.

- **1000 parameter sets** were randomly drawn from a **multivariate log-normal distribution** (30% CV) → **uncertainty** in prior values

- For each set, a **relative sensitivity coefficient** was calculated for the **venous blood compartment** as follows:

$$RS_{pj} = \frac{\partial A_j}{\partial \theta_p} \cdot \frac{\theta_p}{A_j}$$

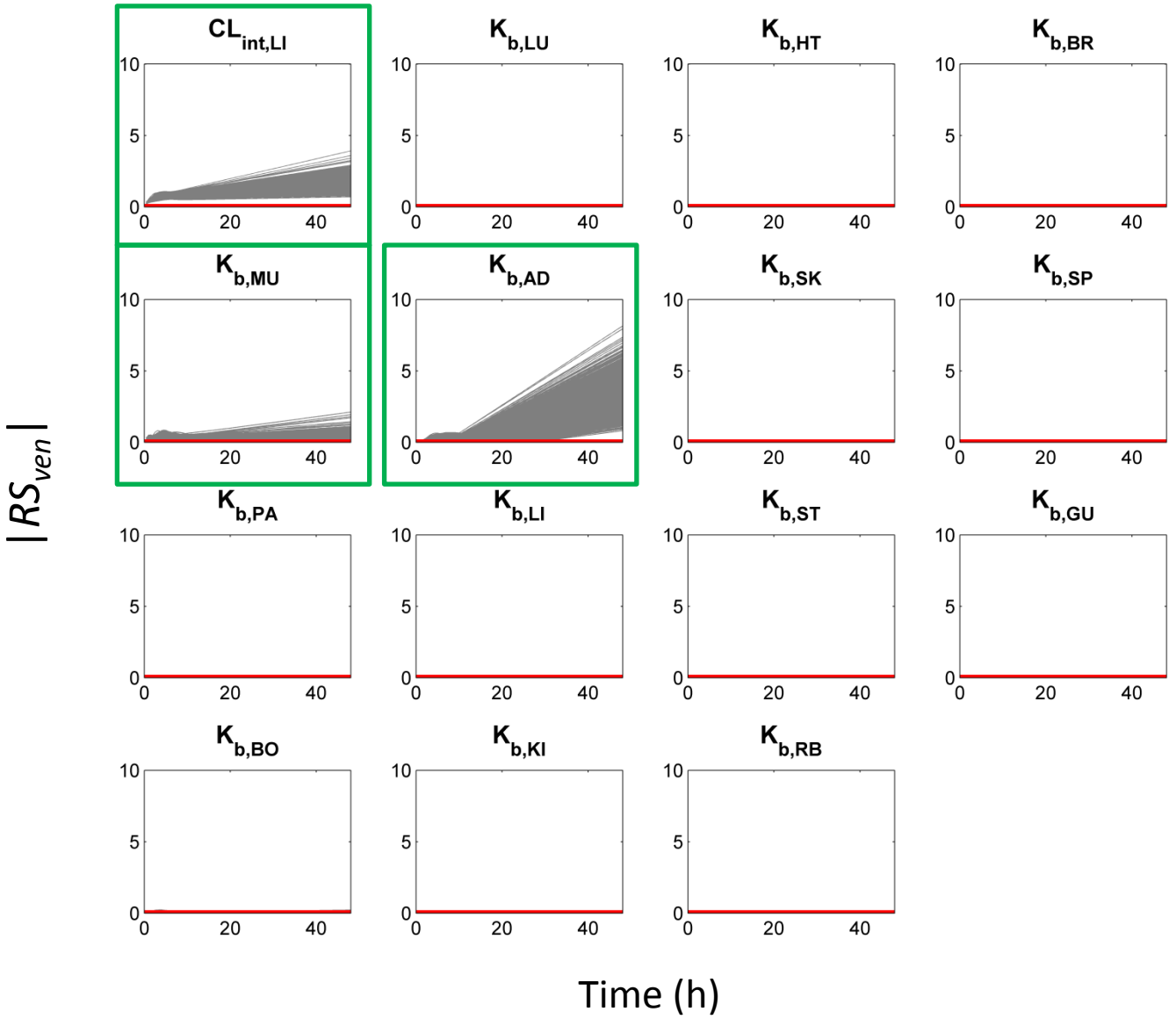
Jacobian matrix

- $|RS_{pj}|$=0.1 means 1% variation in the p^{th} parameter yields 0.1% variation in the j^{th} observations.

$|RS_{pj}|>0.1$ → significant influence

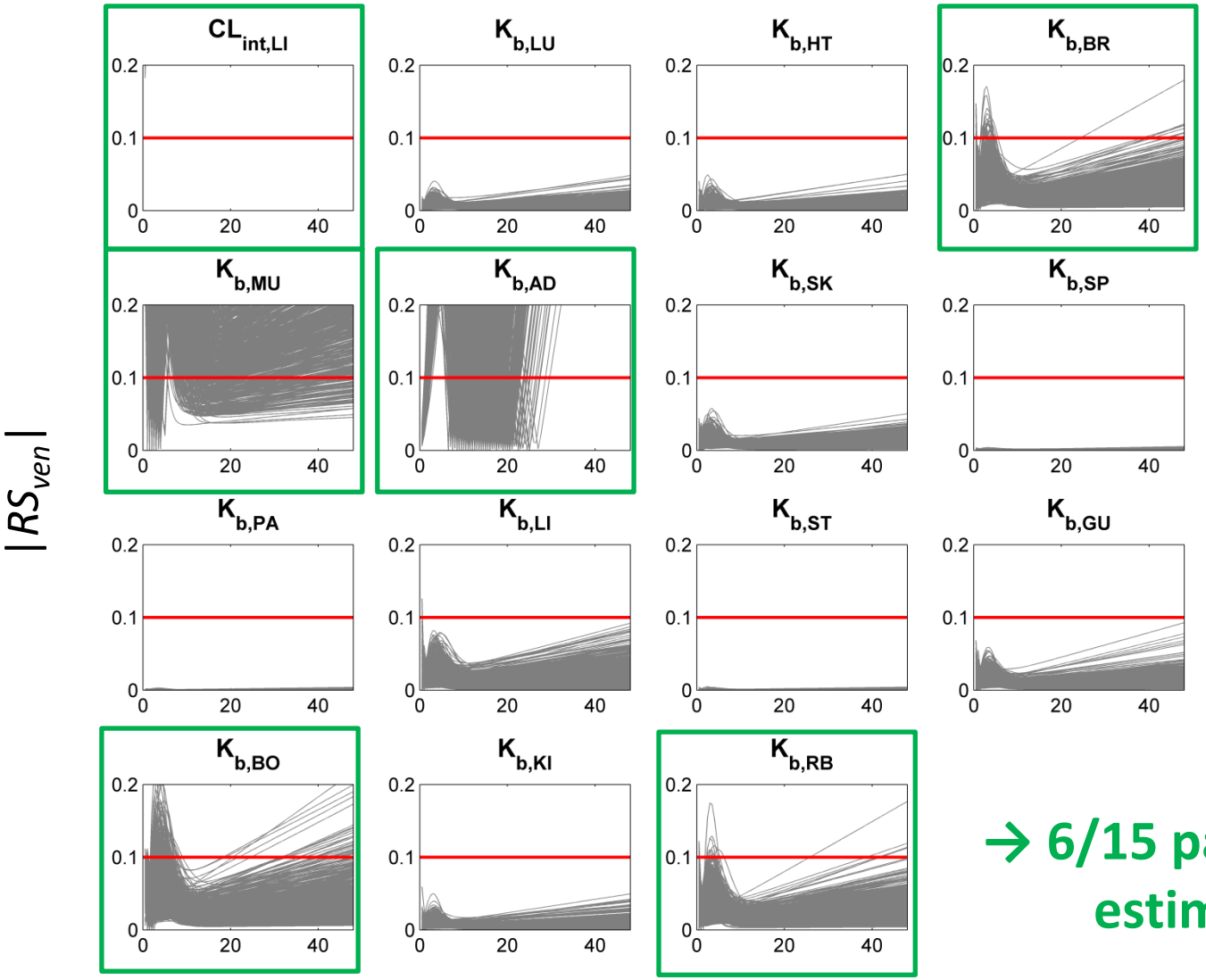
Sensitivity analysis of the model

Results



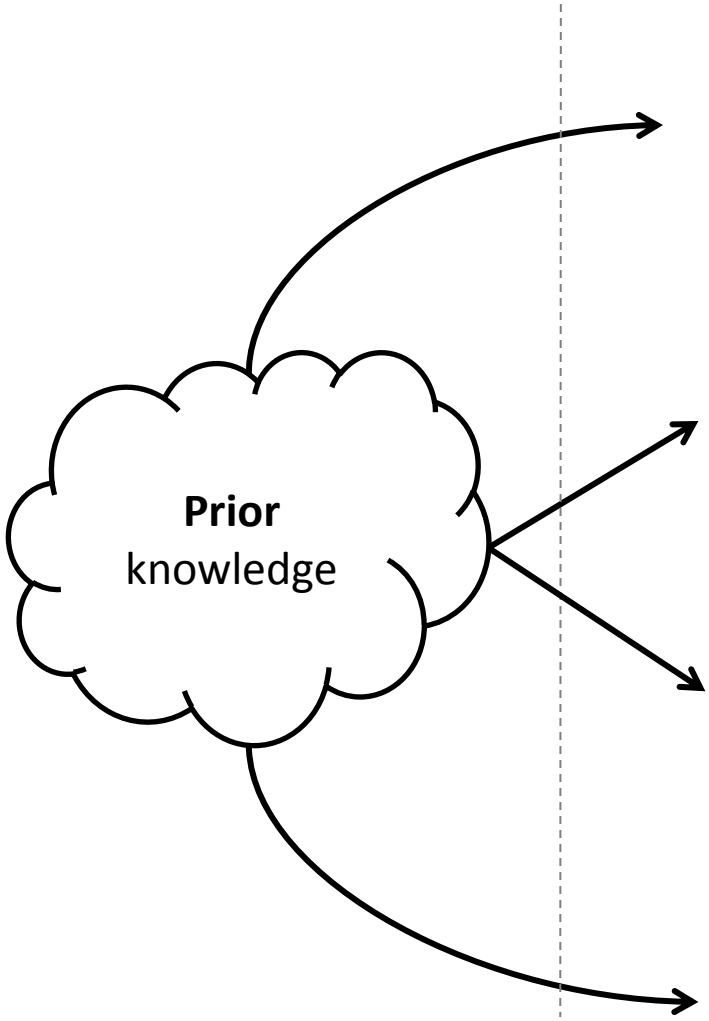
Sensitivity analysis of the model

Results



→ 6/15 parameters estimated

Modelling and simulation workflow



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Statistical model

Three-stage hierarchical model:

1. **Likelihood:** $p\left(\log(y_{ij}) \mid \theta_i, \sigma^2\right) \propto N\left(\log\left(f(D_i; t_{ij}; \theta_i)\right), \sigma^2\right)$

2. **Inter-individual variability:** $p\left(\theta_i \mid \mu, \Omega\right) = MVLN_p(\mu, \Omega)$

3. **Priors:**
   - population parameters $p\left(\mu\right) = MVLN_p\left(\bar{\mu}, \Sigma\right)$ **Pre-clinical data**
   - variance-covariance matrix $p(\Omega) = IW(\Psi, \upsilon)$ **Uninformative**

Variability:

- **Physiologic**: **BW** as **covariate** for **blood flows** and **organ volumes**
- **Random effect** only on $\mathbf{CL_{int,LI}}$

Bayesian computation

likelihood

$$p(\theta \mid y) \propto p(y \mid \theta) \cdot p(\theta)$$

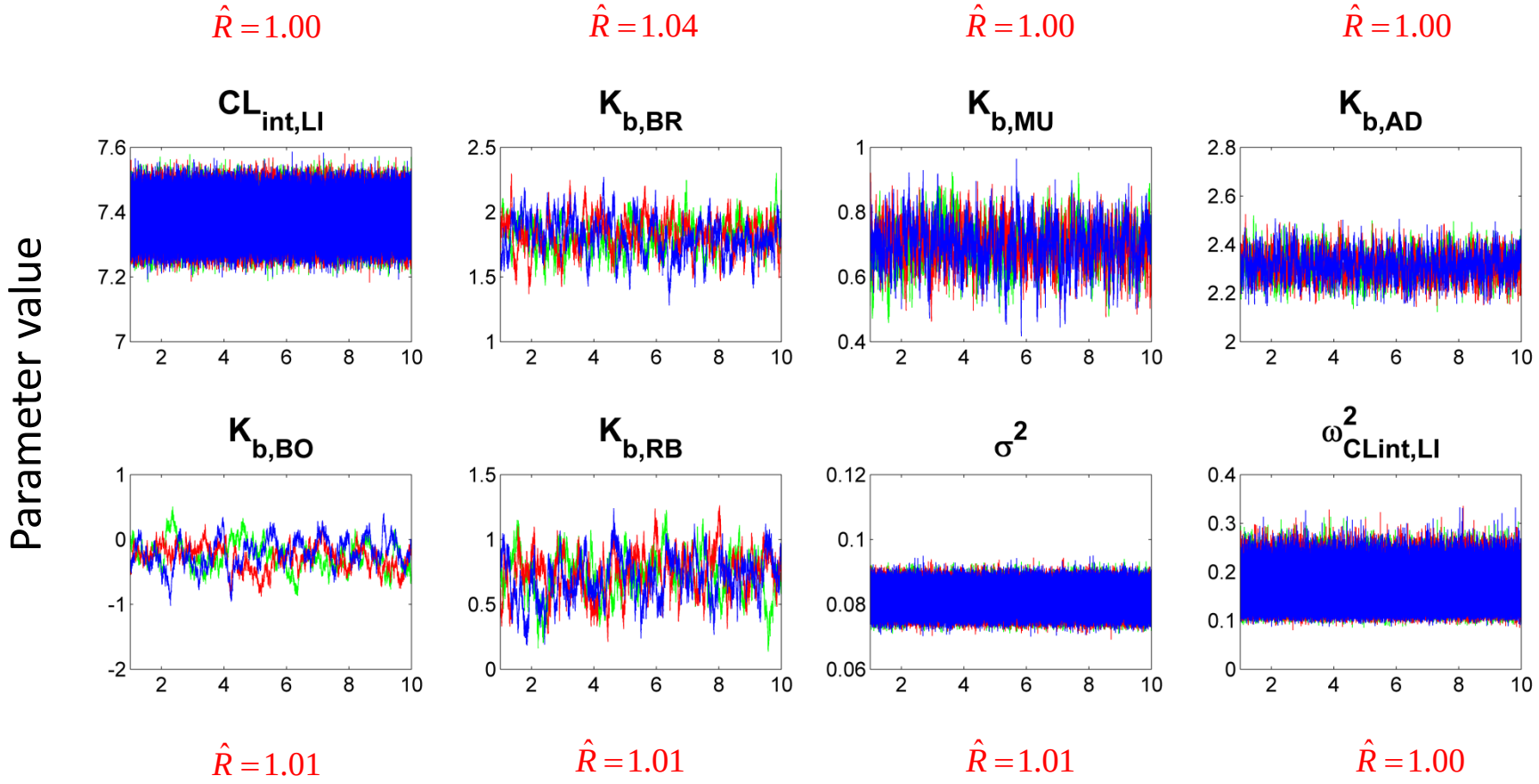
posterior prior

- **Posterior distributions** were **approximated** by random draws using **Markov Chain Monte Carlo** (MCMC) **simulations** implemented in NONMEM 7.3.0.
- The **ODE system** was solved using the **LSODA solver** (ADVAN13 subroutine in NONMEM).
- **3 independent Markov chains** were initialized at different diffuse parameter values and run for **10^6 iterations**.
- **Convergence** to the **equilibrium distribution** was monitored using the **potential scale reduction statistic**[5] ($\hat{R}$) and by visual inspection of the chains.

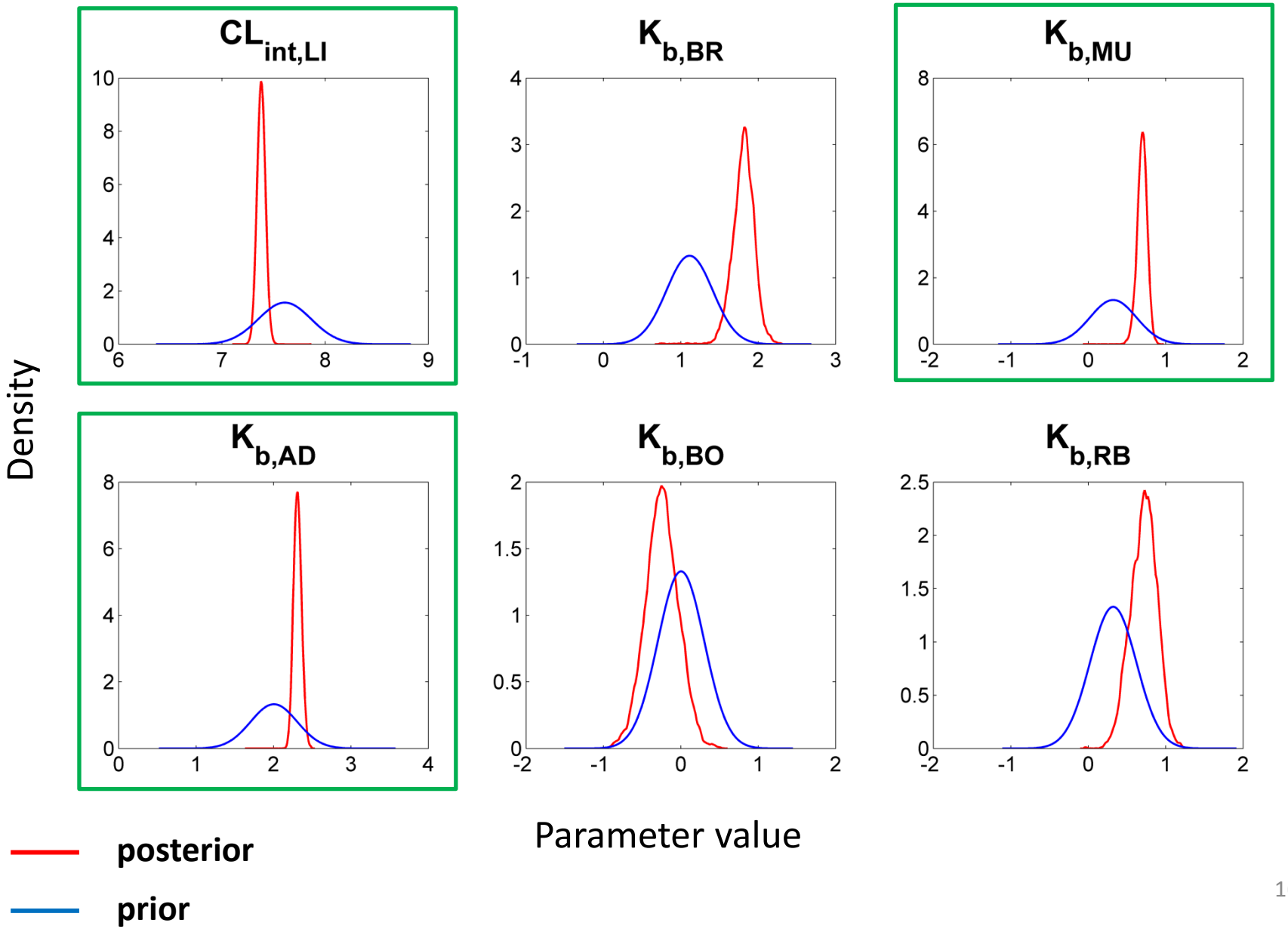
[5] Gelman A and Rubin DB. Stat Science. 1992

Trace-plots of the Markov chains

N = 10^6 iterations

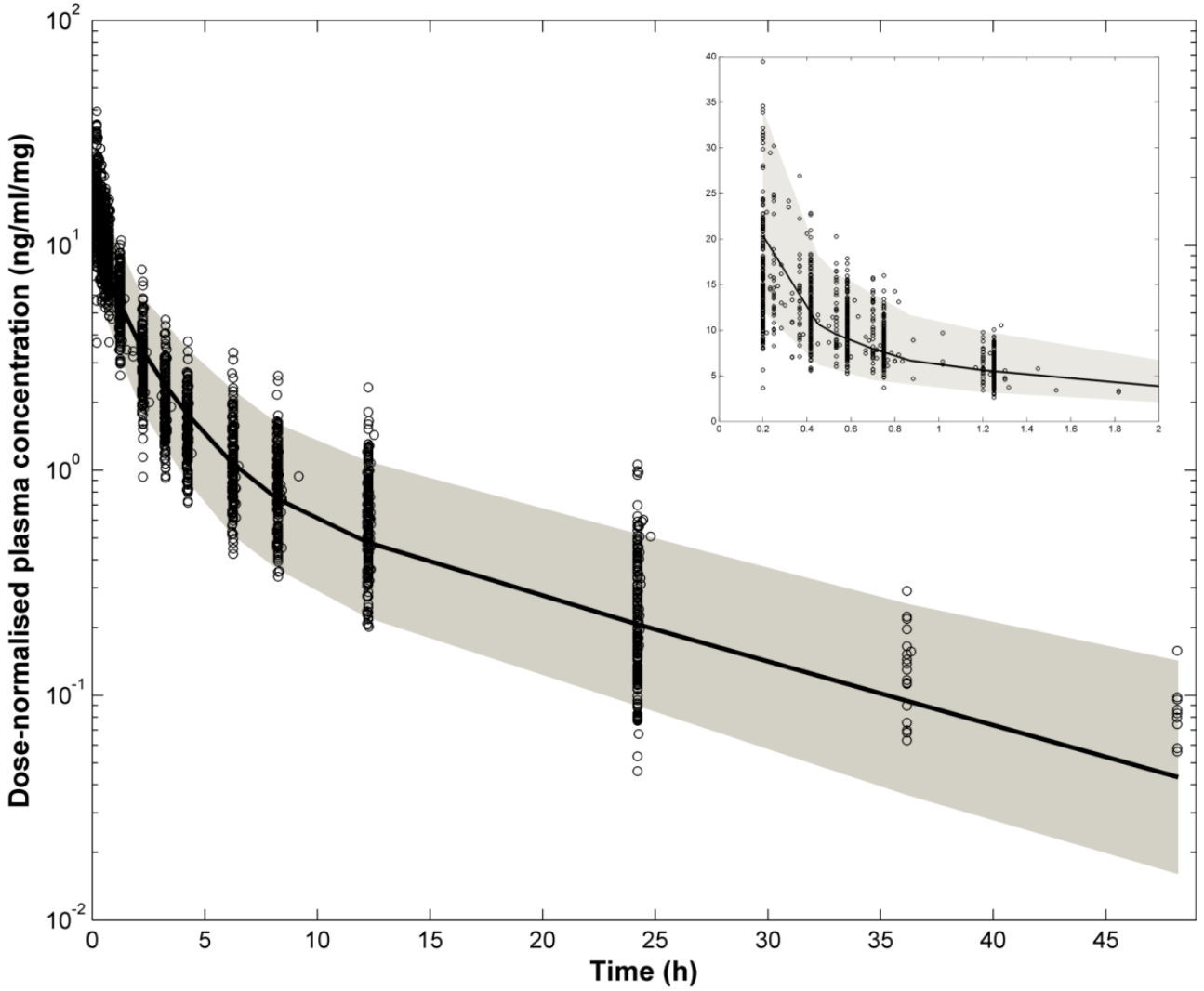


Posterior *versus* prior distributions

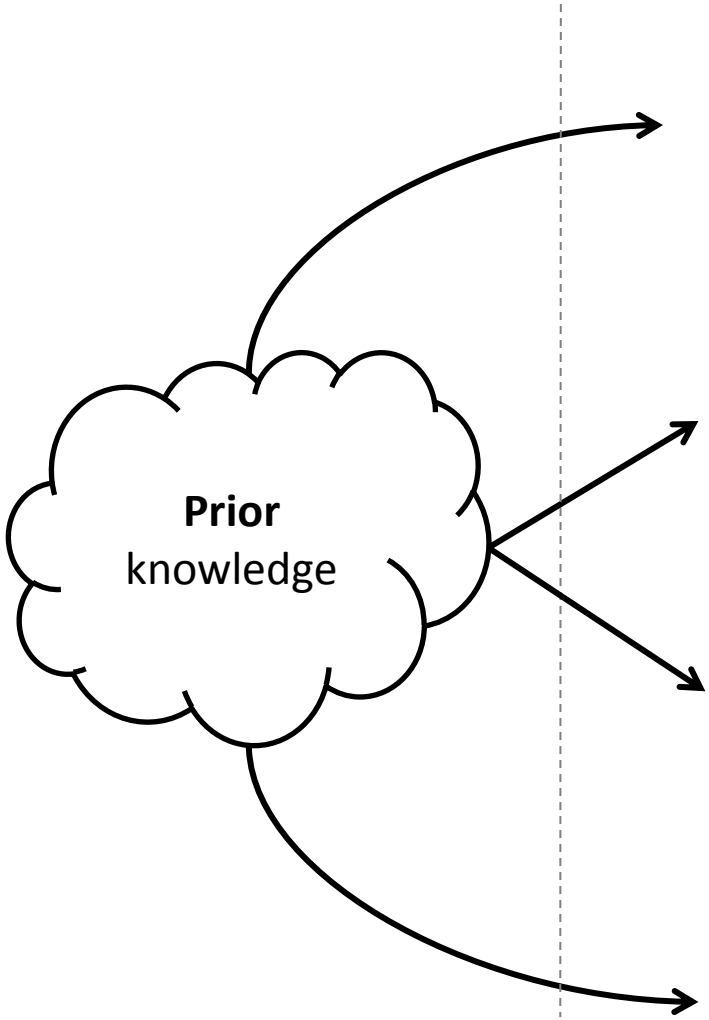


Validation of the population WBPBPK model

IV administration in **adults** (n=120)



Modelling and simulation workflow



Development a WBPBPK structure model

Sensitivity analysis

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Bayesian analysis of clinical data

→ Improve population and individual parameter estimates

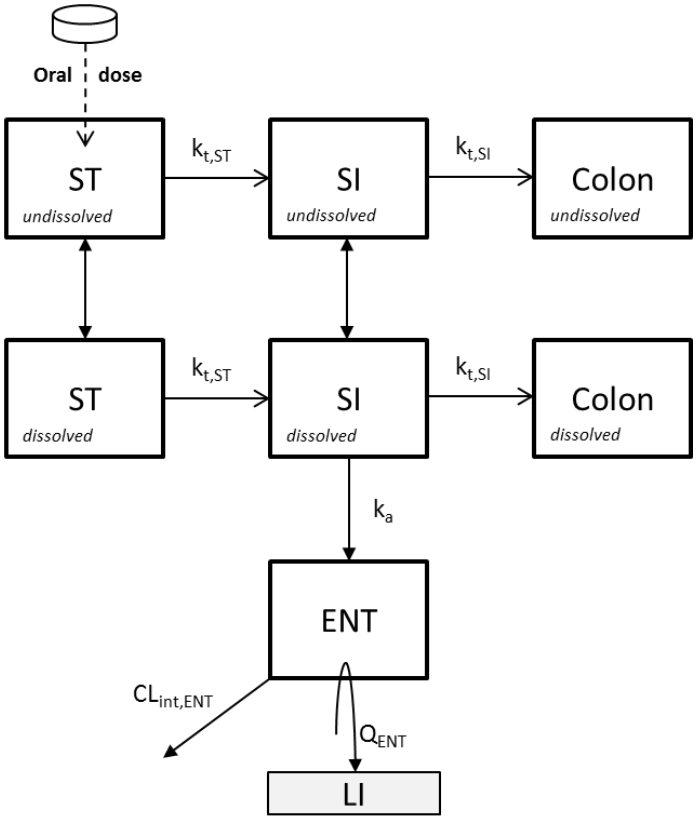
Extrapolations

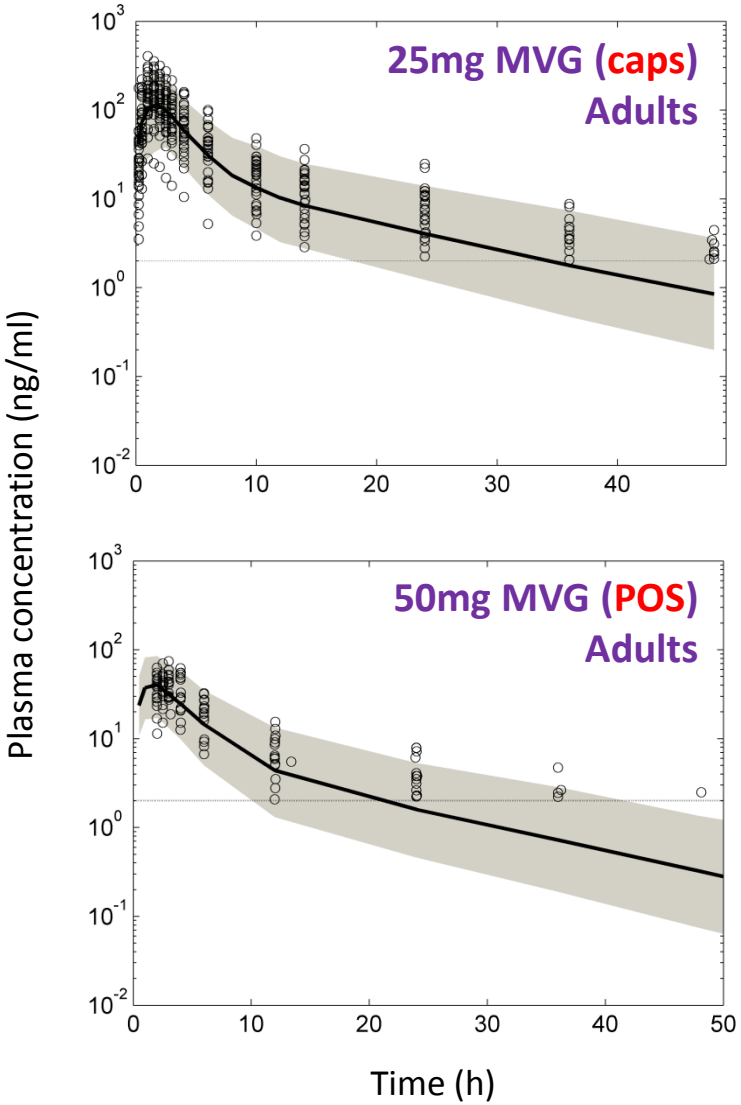
Pre-clinical studies → **Clinical** studies

Extrapolation of MVG PK

From the **IV** to **oral** administration route

Mechanistic absorption model





Extrapolation of MVG PK

Prediction of the **DDI with ketoconazole**

Ketoconazole is a **competitive inhibitor** of **CYP3A4**, **CYP2C8** and **CYP2C9**

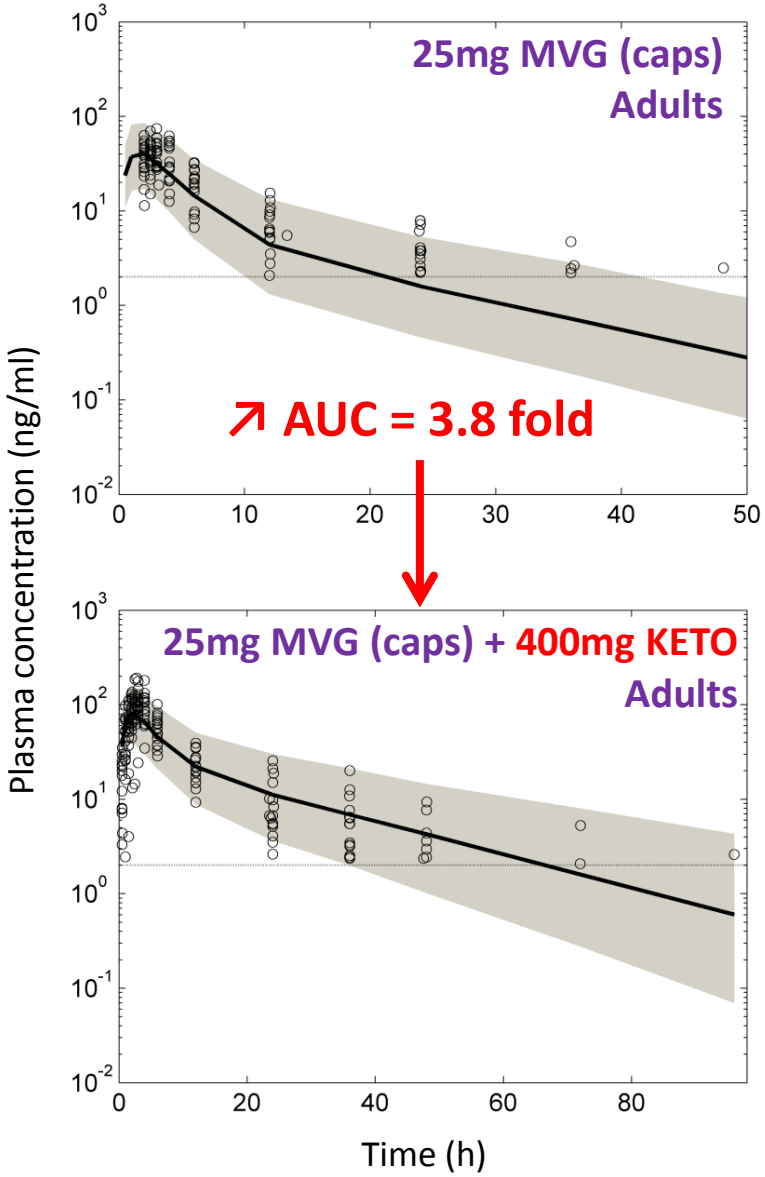
Competitive inhibition:

$$CL_{int,CYP_i}' = \frac{CL_{int,CYP_i}}{\left(1 + \frac{[I]_u}{K_{i,u,CYP_i}}\right)}$$

$$CL_{int,LI}'$$

$$CL_{int,ENT}'$$

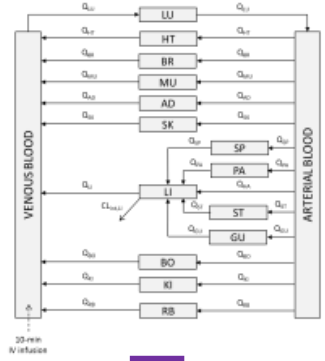
Intrinsic clearances in the presence of inhibitor



Extrapolation of MVG PK

From **adult** to **children** (3 to 11 years)

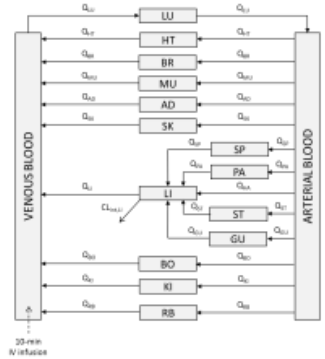
WBPBPK model for **ADULTS**

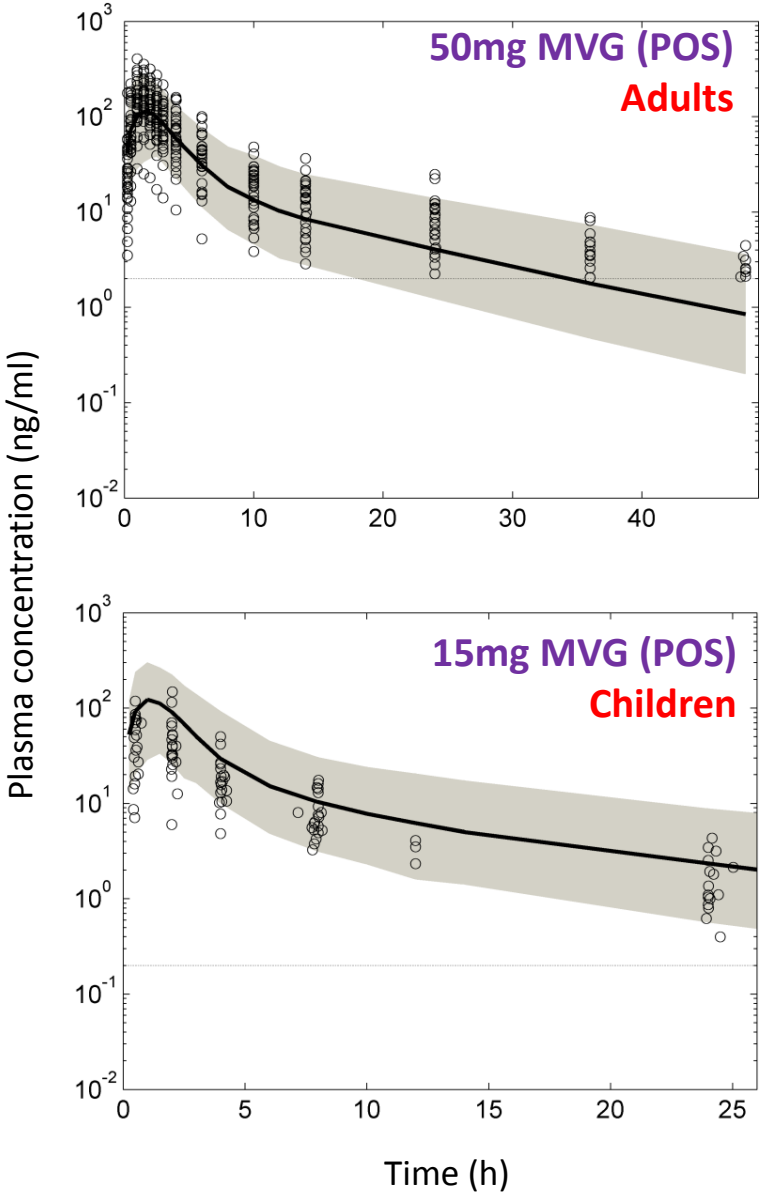


Scaling

Age-related change in the **physiological parameters**

WBPBPK model for **CHILDREN**





Conclusions

- Population PBPK modelling and simulation for MVG provided further insight into its PK, including the **source** and **magnitude** of **population variability**.

- **Bayesian statistics** were applied to **leverage** our **prior preclinical knowledge** of the parameters while maintaining **biological/physiological constraints**.

- The **Bayesian population approach** could be applied to new clinical data to progressively update our current knowledge of MVG population PK.

- The model could be used to predict:
  - **Brain** (target site) concentrations → better PK surrogate than plasma concentrations
  - PK following oral administration of other **immediate-release formulations**
  - The impact of other types of **DDI** → identify drug combination at risk
  - PK in **children** of various ages

Acknowledgements

Supervisors:

Leon Aarons

Kayode Ogungbenro

Colleagues:

Eleanor Howgate

Alison Margolskee

Adam Darwich

Hitesh Mistry

Andres Olivares-Morales

Nikolaos Tsamandouras

Supervisors:

Dumitras Swati

Etienne Pigeolet

Back-up

A priori parameter distributions

System-specific parameters**:**

- Extracted from the **physiology literature**
- **No uncertainty** considered

Drug-specific parameters**:**

- **BP** and **fu_p** were estimated from an ***in vitro*** **binding experiment** (no uncertainty assumed)
- **$CL_{int,LI}$** :
  - The **geometric mean** was calculated by **IVIVE** of isoenzyme-specific intrinsic clearances obtained in **recombinant human CYP enzymes**
  - **Uncertainties** in the **enzyme kinetic parameters** (K_m and V_{max}) were **propagated** (26% CV)
- **$K_{p,T}$** :
  - **Geometric means** estimated from a **distribution experiment** in **rat** (AUC ratio method) then scaled to human assuming equal unbound K_p values between rat and human
  - **No measure of uncertainty** with the AUC ratio method → 30% CV assumed

Methods in Ecology and Evolution

British Ecological Society

Methods in Ecology and Evolution 2012, **3**, 112–115 doi: 10.1111/j.2041-210X.2011.00131.x

FORUM

On thinning of chains in MCMC

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Summary

1. Markov chain Monte Carlo (MCMC) is a simulation technique that has revolutionised the analysis of ecological data, allowing the fitting of complex models in a Bayesian framework. Since 2001, there have been nearly 200 papers using MCMC in publications of the Ecological Society of America and the British Ecological Society, including more than 75 in the journal *Ecology* and 35 in the *Journal of Applied Ecology*.
2. We have noted that many authors routinely 'thin' their simulations, discarding all but every *k*th sampled value; of the studies we surveyed with details on MCMC implementation, 40% reported thinning.
3. Thinning is often unnecessary and always inefficient, reducing the precision with which features of the Markov chain are summarised. The inefficiency of thinning MCMC output has been known since the early 1990's, long before MCMC appeared in ecological publications.
4. We discuss the background and prevalence of thinning, illustrate its consequences, discuss circumstances when it might be regarded as a reasonable option and recommend against routine thinning of chains unless necessitated by computer memory limitations.

Key words: Markov chain Monte Carlo, thinning, WinBUGS

Autocorrelation

Effective sample size N_{eff}

- Discarding **260,000 warm-up iterations** (based on monitoring of $\hat{R}$)
- Discarding all but **every 740th sampled value** of the remaining iterations
- Pooling the three Markov chains yields a sample of **N = 3000** for each parameter

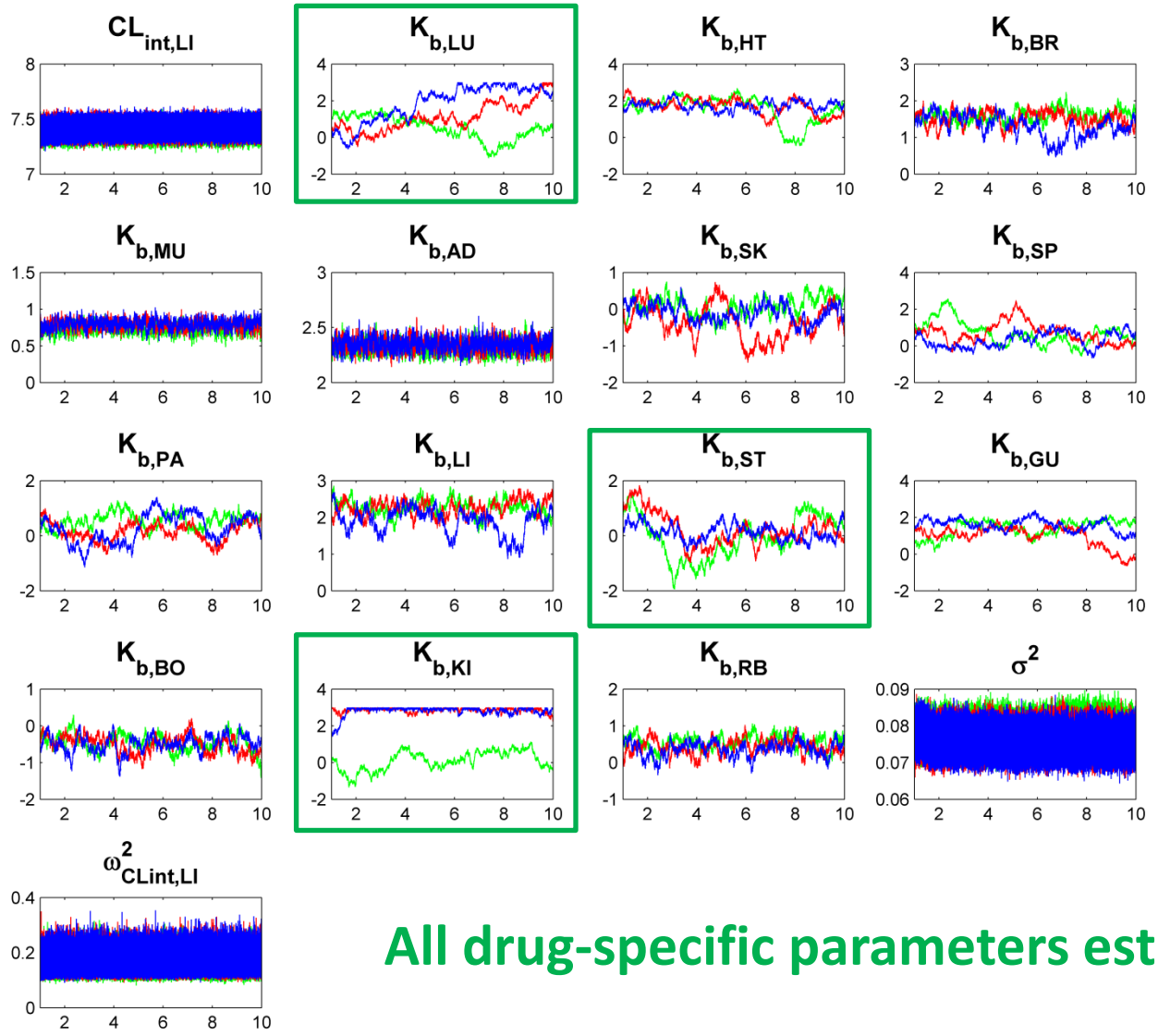
Parameter	$\hat{R}$	N_{eff}
$CL_{int,LI}$	1.00	2964
$K_{b,BR}$	1.03	182
$K_{b,MU}$	1.01	570
$K_{b,AD}$	1.00	883
$K_{b,BO}$	1.07	72
$K_{b,RB}$	1.00	122
$\omega^2_{CLint,LI}$	1.00	3000
σ^2	1.00	2969

$N_{eff} = N$

No autocorrelation

Trace-plots of the Markov chains

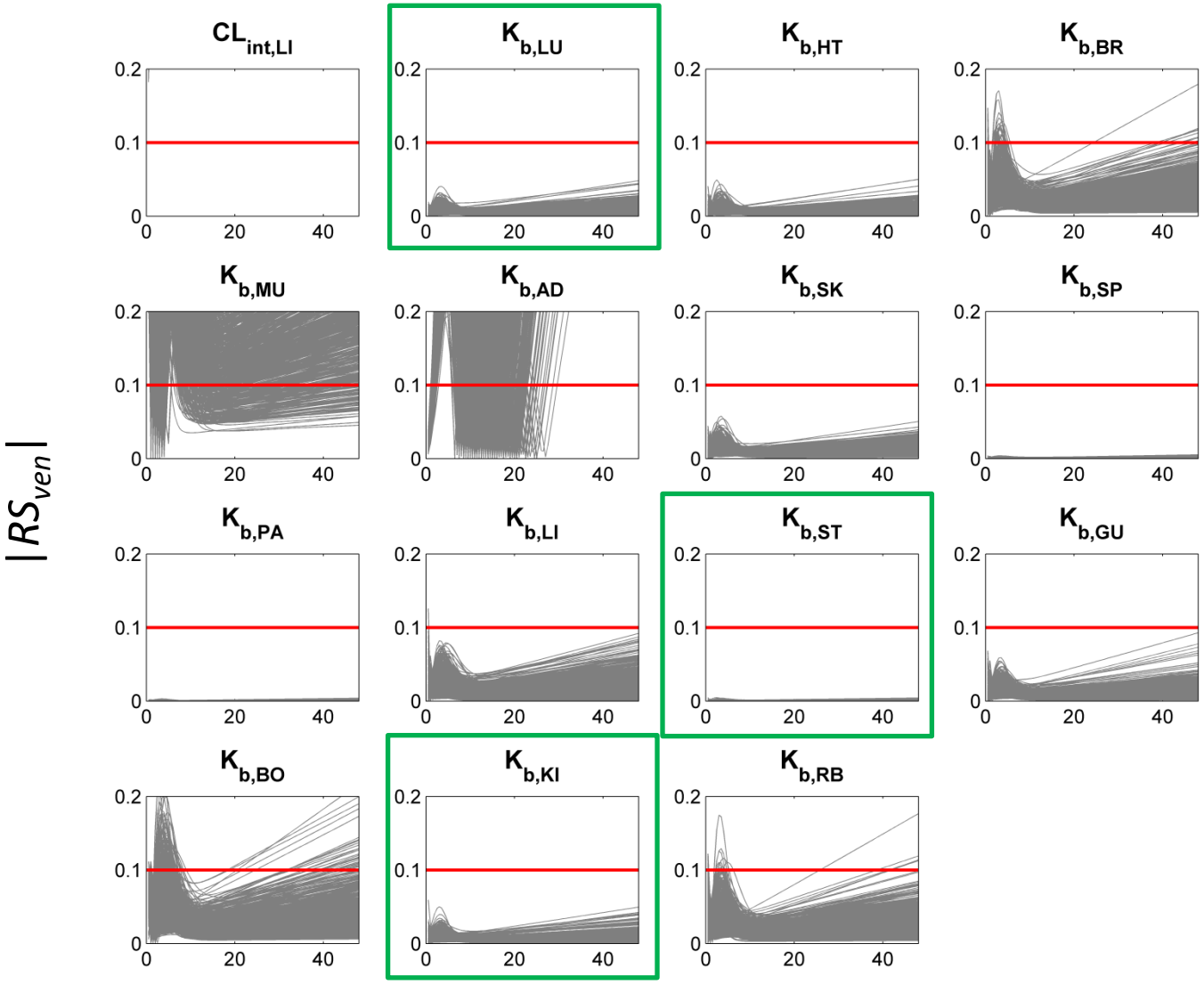
N = 10^6 iterations



All drug-specific parameters estimated

Sensitivity analysis of the model

Results



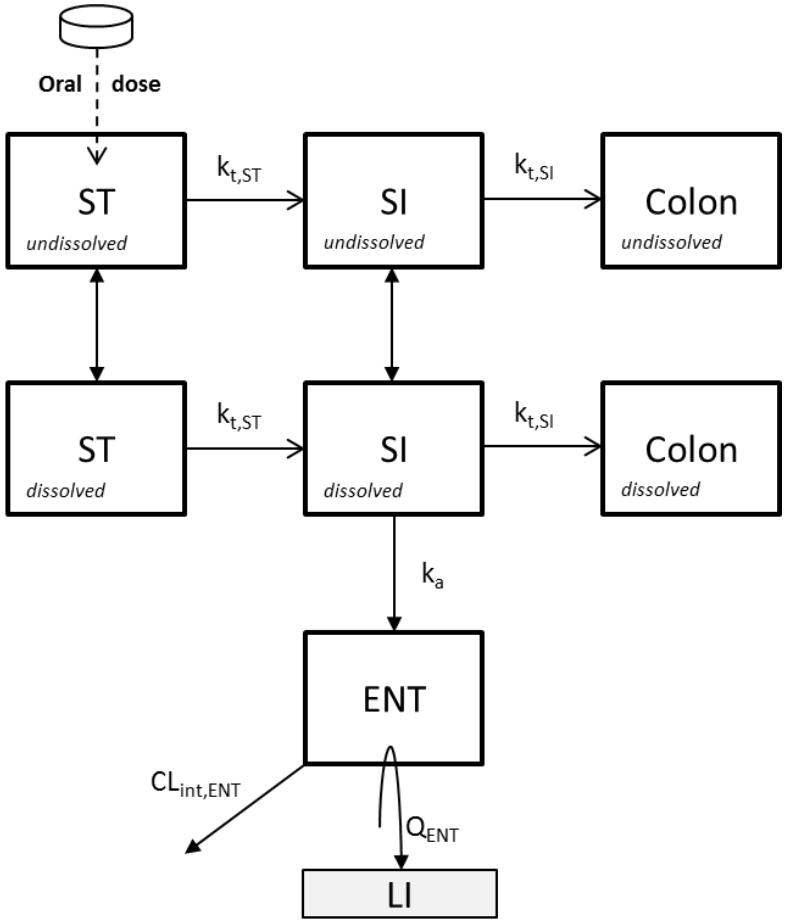
WBPBPK model parametrisation

Well-stirred tissue compartments

$$\frac{dA_T}{dt} = \frac{Q_T}{V_{blood}} \cdot A_{blood} - \boxed{\frac{Q_T}{K_{b,T} \cdot V_T}} \cdot A_T$$

= transfer rate constant

Mechanistic absorption model



Elimination in the small intestine enterocytes (ENT).

Physiological parameters:

- Transit rates ($k_{t,ST/SI}$)
- Radius of the SI
- Blood flow to the ENT (Q_{ENT})
- *etc.*

Drug-specific parameters :

- Dissolution constant (estimated from *in vitro* dissolution profiles)
- P_{eff} (estimated based on a Caco-2 experiment)
- $CL_{int,ENT}$ (derived from $CL_{int,LI}$)

Random Variability:

- Transit rates
- Volume of fluid in the GI lumen

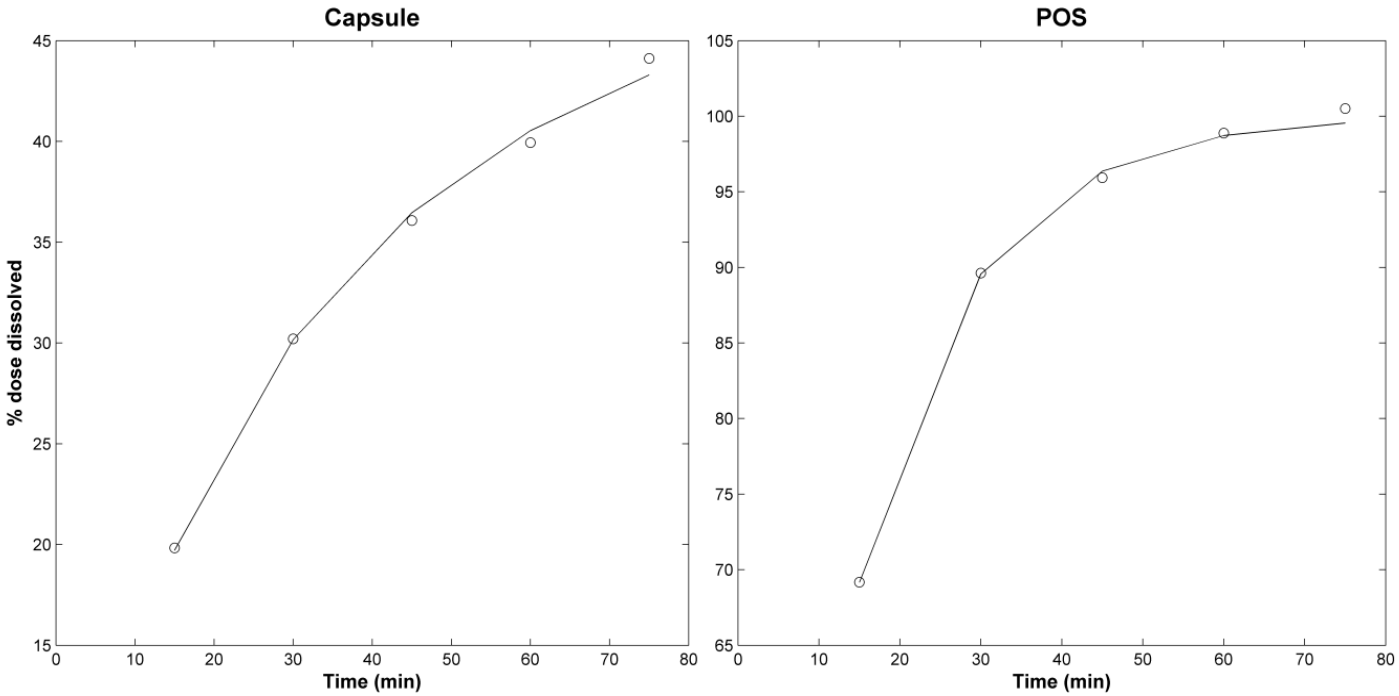
Dissolution model

$$\frac{dA_{und}}{dt} = z \cdot \left(S - \frac{A_{dis}}{V} \right) \cdot A_{und}$$

S: drug solubility in the media (known)

V: volume of the media (known)

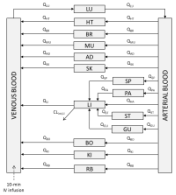
z: dissolution constant (formulation-specific)



Hintz RJ and Johnson KC. Int J Pharm. 1989
Nicolaides E *et al*. Pharm Res. 2001
Takano R *et al*. Pharm Res. 2006

Prediction of MVG oral PK in children

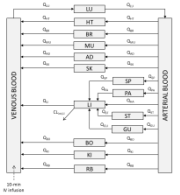
PBPK model for **ADULTS**



Scaling

Age-related change in the **physiological parameters**

PBPK model for **CHILDREN**



- **Blood flows** and **organ volumes** were gathered from the literature for **age groups of 1, 5, 10 and 15 years**[6,7] and were then interpolated between age groups.
- **$CL_{int,LI}$** was scaled from adult to children using **age-specific liver weight** and assuming **complete maturation of the CYP enzymes** in children from 3 to 11 years[7].
- **fu_p** was also scaled from adults to children[8].
- **Variability** was incorporated in :
  - **Blow flows** defined as function of **age** and **BSA**[8]
  - **Organ volumes** defined as function of **BW**[6]
  - **Volume of fluid in the SI lumen** defined as function of **BSA**[6,8]

[6] Valetin J. Annals of the ICRP. 2002
[7] Edginton AN et al. Clin Pharmacokinetics. 2006
[8] Johnson TN et al. Clin Pharmacokinetics. 2006