UPPSALA UNIVERSITET

Evaluation of a transit compartment model versus a lag time model for describing drug absorption delay

Radojka Savic(1), Daniël M. Jonker(1), Thomas Kerbusch(2), Mats O. Karlsson(1)

(1) Div. of Pharmacokinetics and Drug Therapy, Dept of Pharmaceutical Biosciences, Faculty of Pharmacy, Uppsala University, Sweden.

(2) Dept. Clinical PK/PD M&S, Pfizer Global R&D, Sandwich, Kent, UK

UPPSALA UNIVERSITET

Absorption delay

A delay in the initial appearance of drug in plasma

Of interest:

- **Facilitate modeling of pharmacokinetic profiles**
- Impact on predicted time-effect profile
- To learn about absorption properties

UPPSALA UNIVERSITET

Absorption delay modelling

Two models were evaluated:

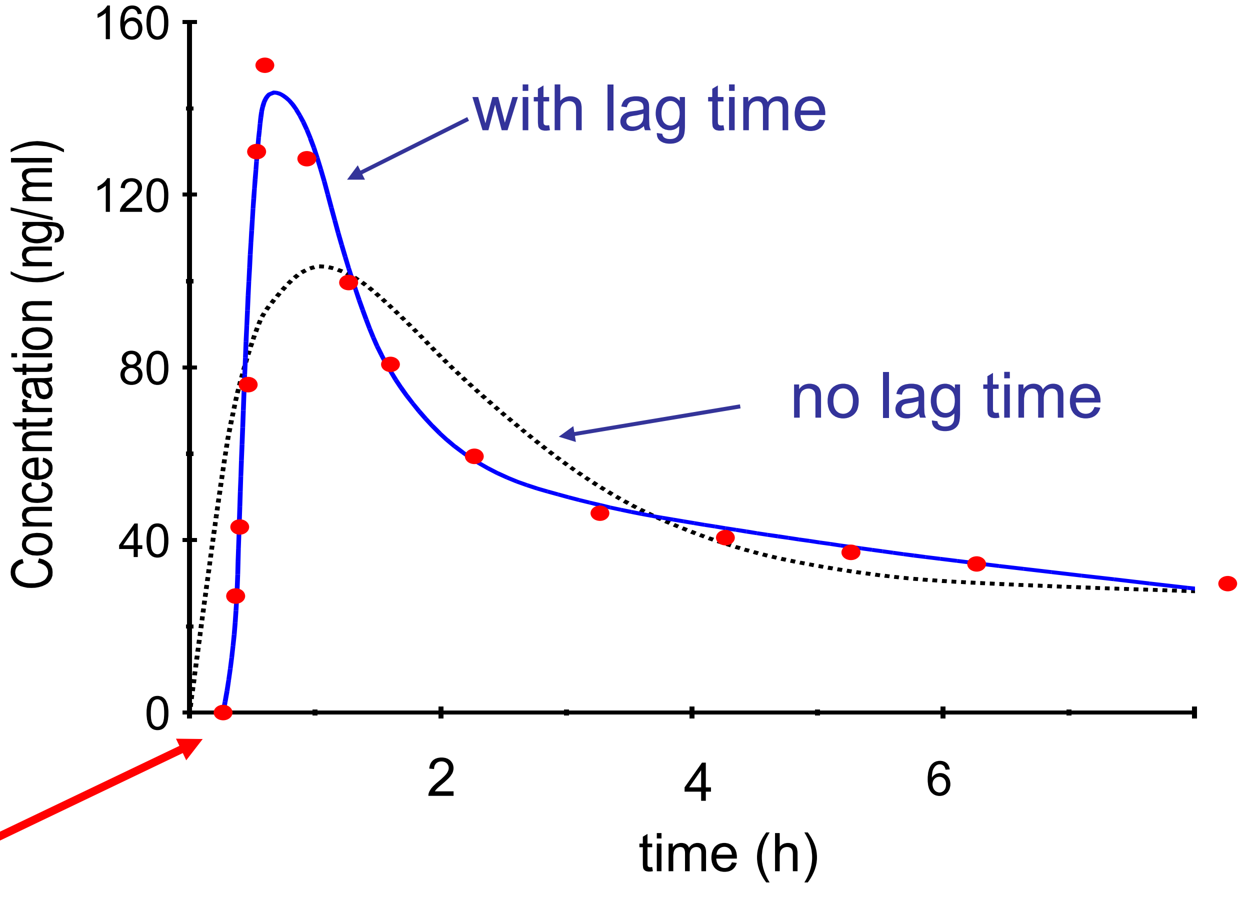
1. **Lag time model**

   Estimation of lag time

2. **Transit compartment model**

   Delay due to passage of drug through a chain of transit compartments

Improvement in the fit with a lag time

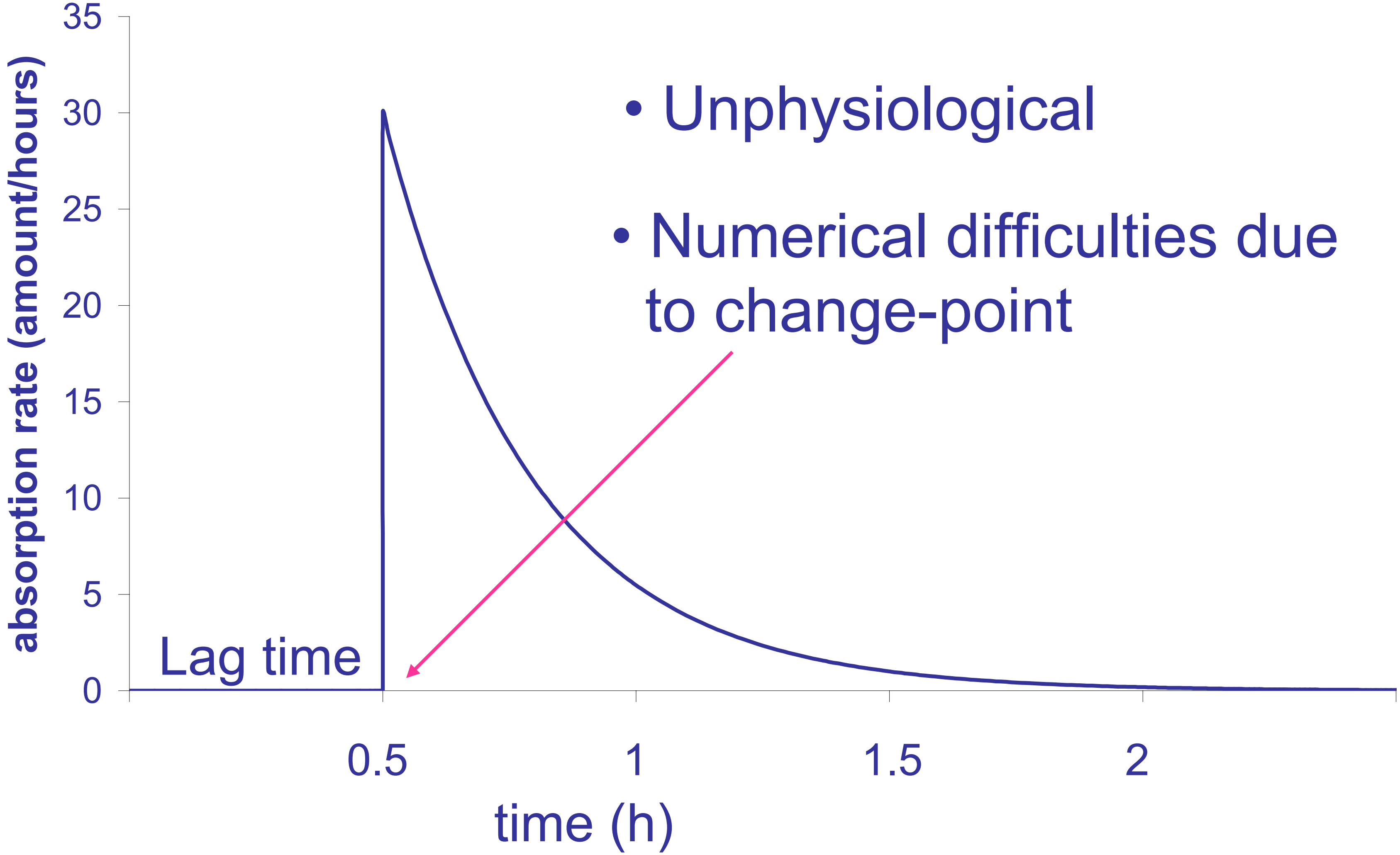


Shift of the dose time

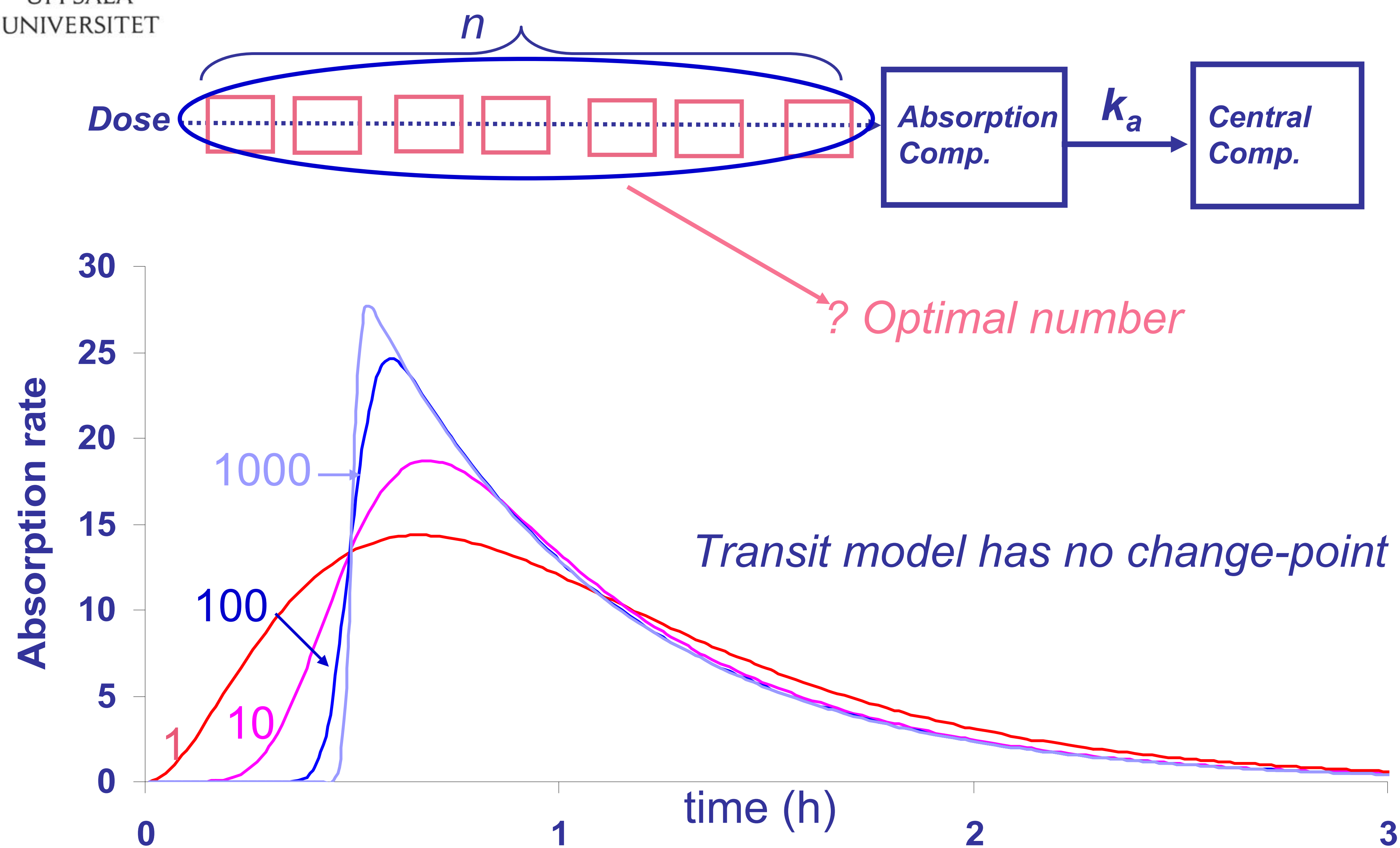
UPPSALA UNIVERSITET

Drawbacks with the Lag time model

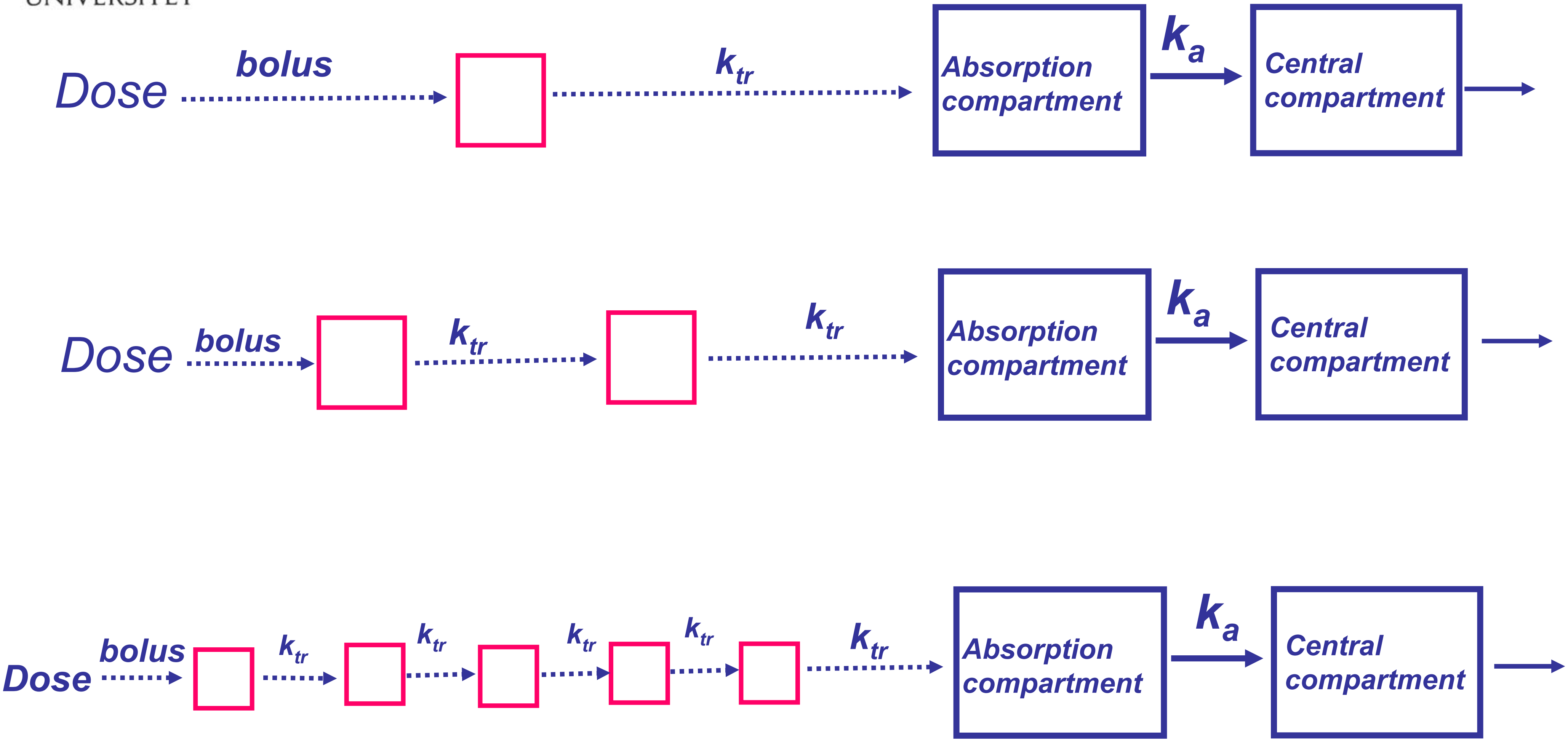
- Unphysiological
- Numerical difficulties due to change-point



Transit compartment model

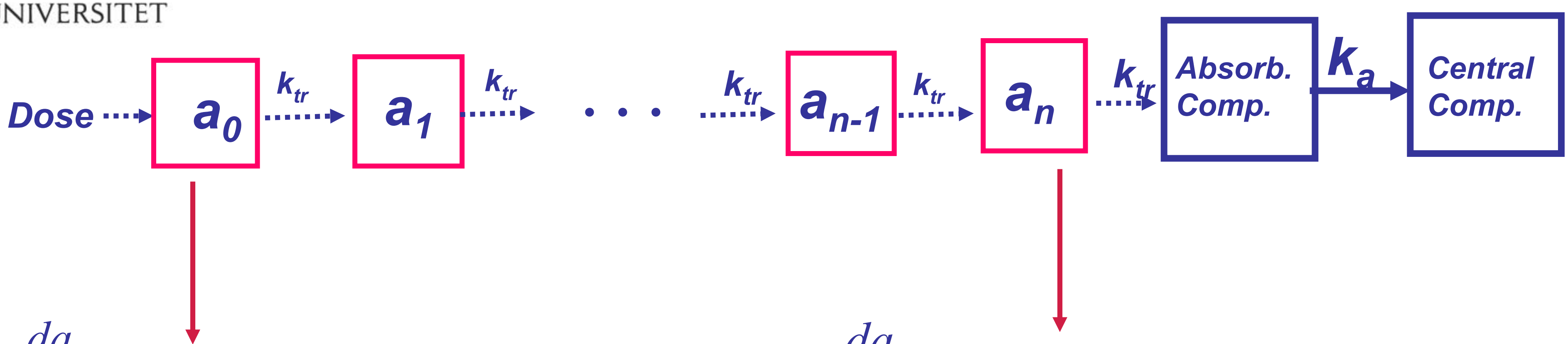


Step-wise addition



UPPSALA
UNIVERSITET

Estimating the number of transit compartments



$$\frac{da_0}{dt} = -k_{tr} \cdot a_0 \qquad \cdots \qquad \frac{da_n}{dt} = k_{tr} \cdot a_{(n-1)} - k_{tr} \cdot a_n$$

Mathematical solution for this system:

$$a_n(t) = Dose \cdot \frac{(k_{tr} \cdot t)^n}{n!} \cdot e^{-ktr \cdot t}$$

; *amount of drug in the n^{th}-compartment at time t*

UPPSALA UNIVERSITET

Implementation in NONMEM

$$\frac{dA(1)}{dt} = Dose \cdot \frac{(k_{tr} \cdot t)^n \cdot e^{-k_{tr} \cdot t}}{n!} \cdot k_{tr} - k_a \cdot A(1)$$

Mean Transit Time to the absorption compartment:

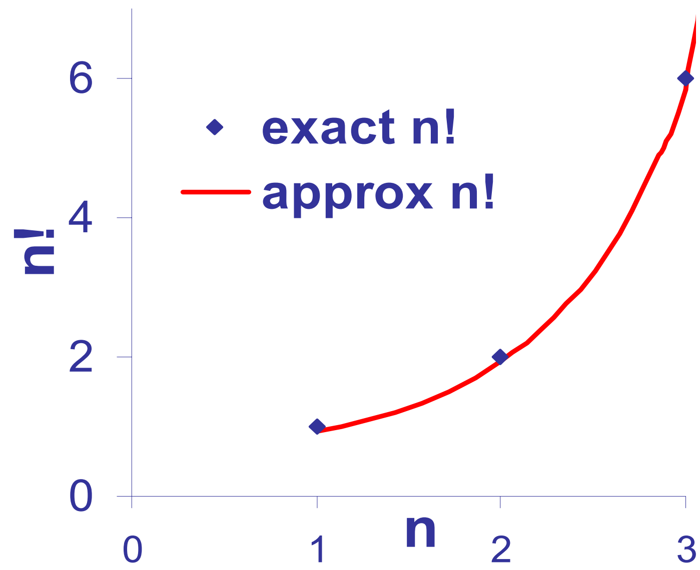
$$MTT = \frac{n+1}{k_{tr}}$$

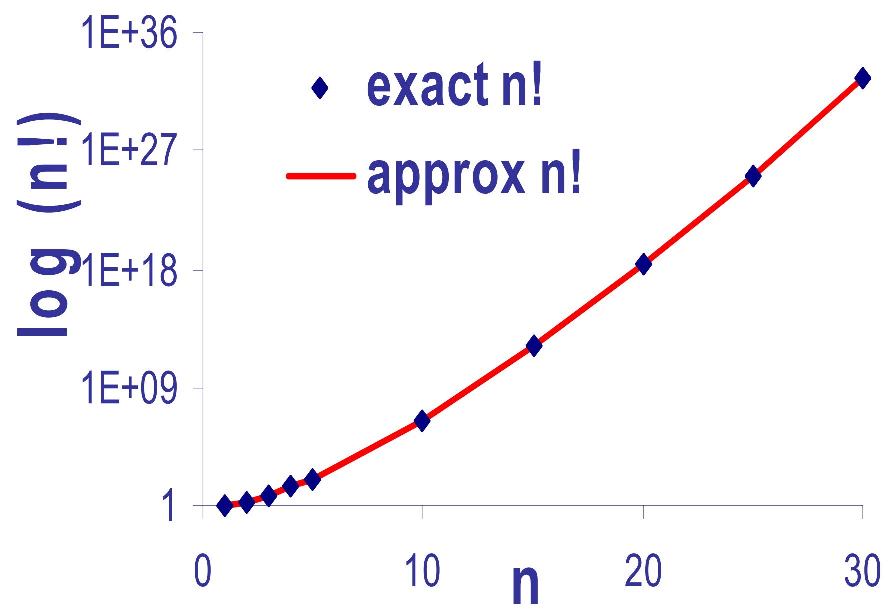
UPPSALA UNIVERSITET

Stirling approximation

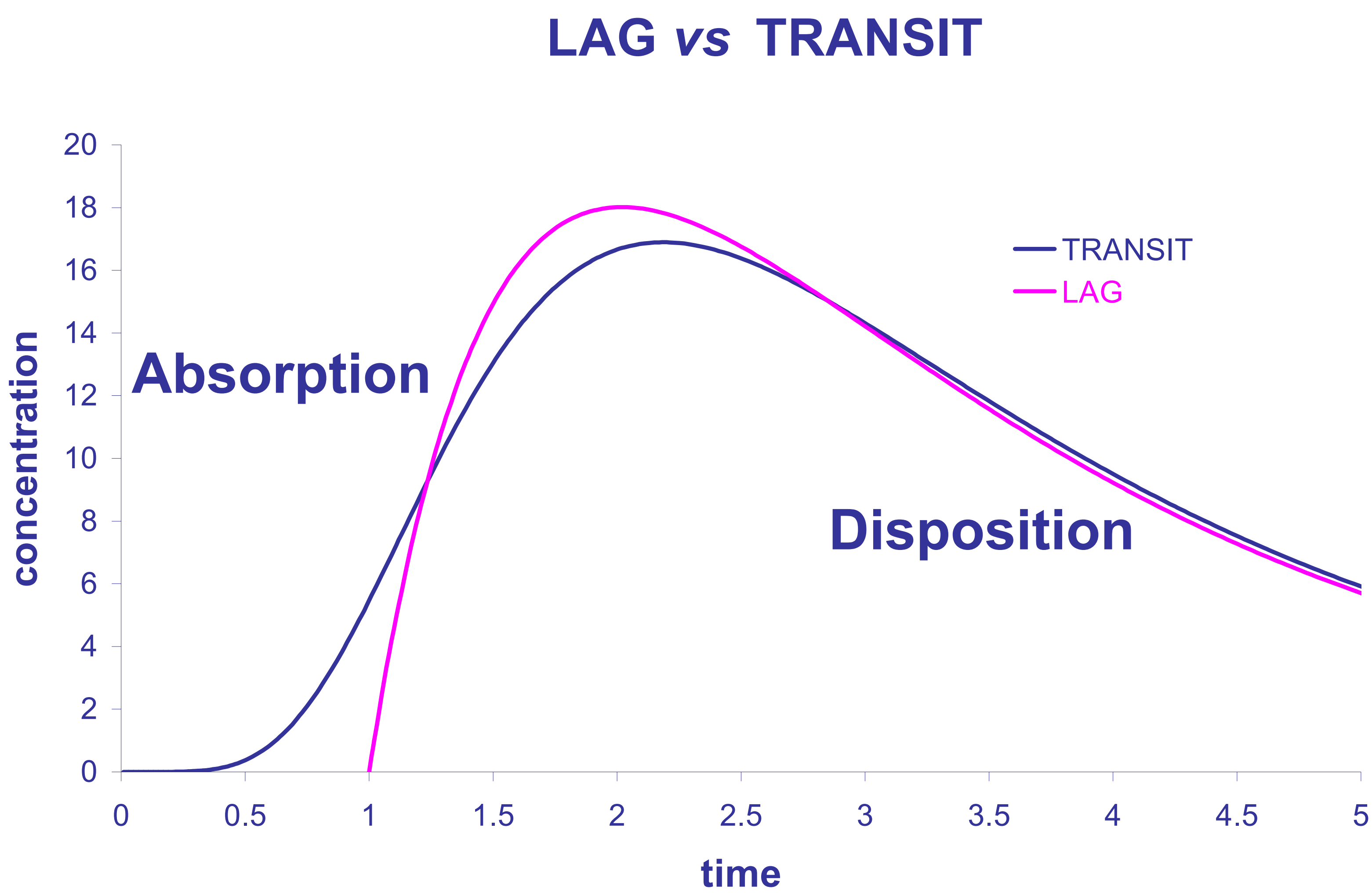
$$\frac{dA(1)}{dt} = Dose \cdot \frac{(k_{tr} \cdot t)^n \cdot e^{-k_{tr} \cdot t}}{n!} \cdot k_{tr} - k_a \cdot A(1)$$

$$n! = \sqrt{2\pi} \cdot n^{n+0.5} \cdot e^{-n}$$



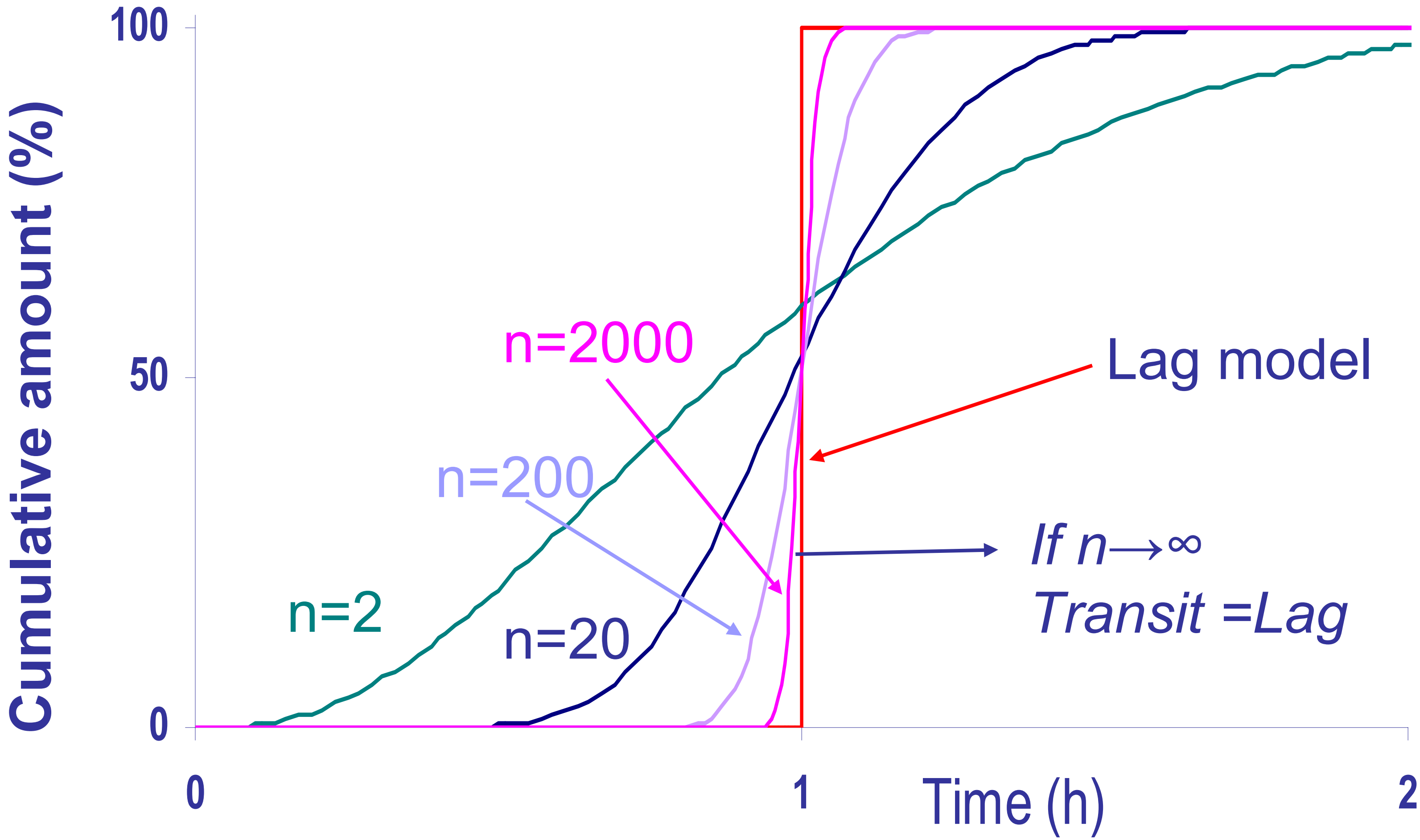


Simulation – concentration-time profile



Simulation – amount in absorption compartment

LAG vs. TRANSIT



UPPSALA UNIVERSITET

Application to data

Objective:

- *to compare the performance of a TRANSIT model with the LAG model*

Data sets:

- *glibenclamide, moxonidine, furosemide, amiloride*

Method: *Population analysis in NONMEM*

Goodness of fit:

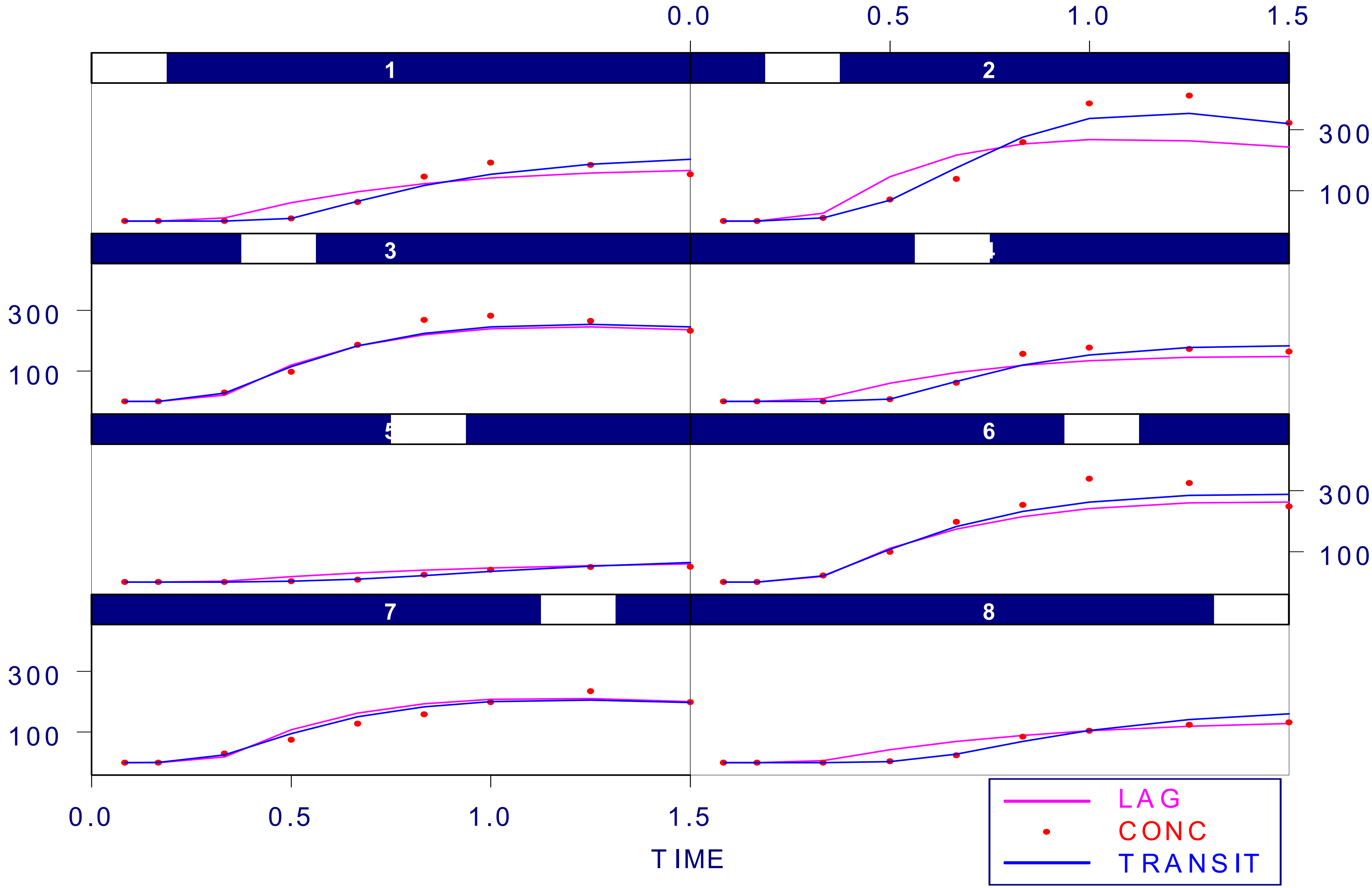
By eye: Diagnostic graphs

Numerical: Objective Function Value (OFV)

Example: *glibenclamide*

Glibenclamide - absorption

LAG vs. TRANSIT



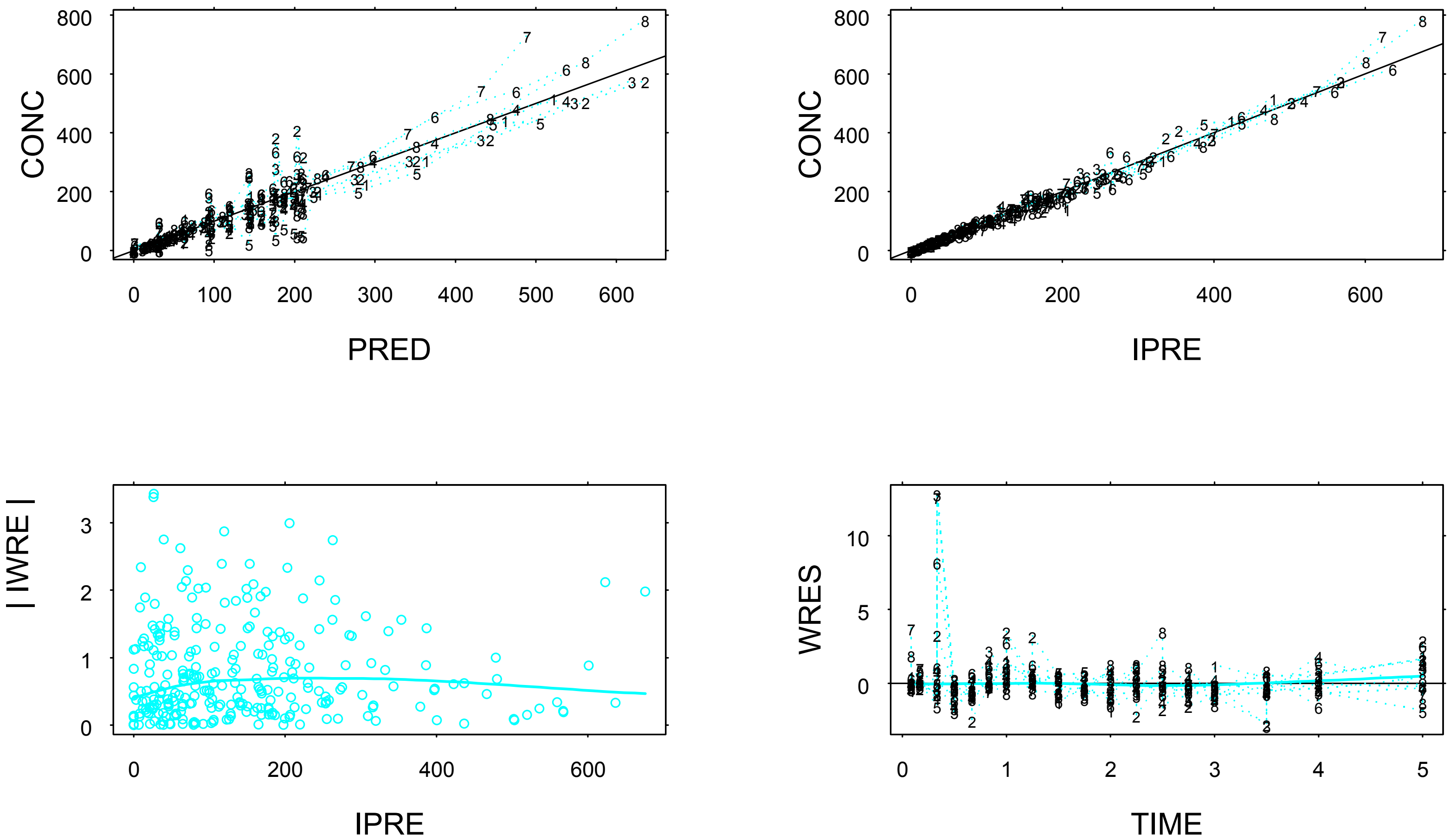
Parameter Estimates

UPPSALA UNIVERSITET

Est. (RSE %)	LAG model		TRANSIT model		TRANSIT model IIV (n)	
OFV	**1840**		**1676**		**1649**	
	Absorption					
ka	0.51	(29)	0.626	(27)	0.652	(31)
t_{lag} / *MTT*	0.306	(2.4)	0.438	(10)	0.458	(12)
F	0.948	(11)	0.96	(9.8)	0.959	(10)
n	-		**23.3**	(45)	**22.9**	(41)
IIV (n)	-		-		**89%**	(57)
IIV(LAG/MTT)	-		29%	(18)	30%	(21)
	Disposition					
k	1.13	(5)	1.14	(4.5)	1.14	(4.3)
V	3.84	(6.5)	3.81	(6.1)	3.79	(6)
k23	0.34	(9.2)	0.356	(8.3)	0.363	(8.3)
K32	0.66	(12)	0.681	(11)	0.691	(12)

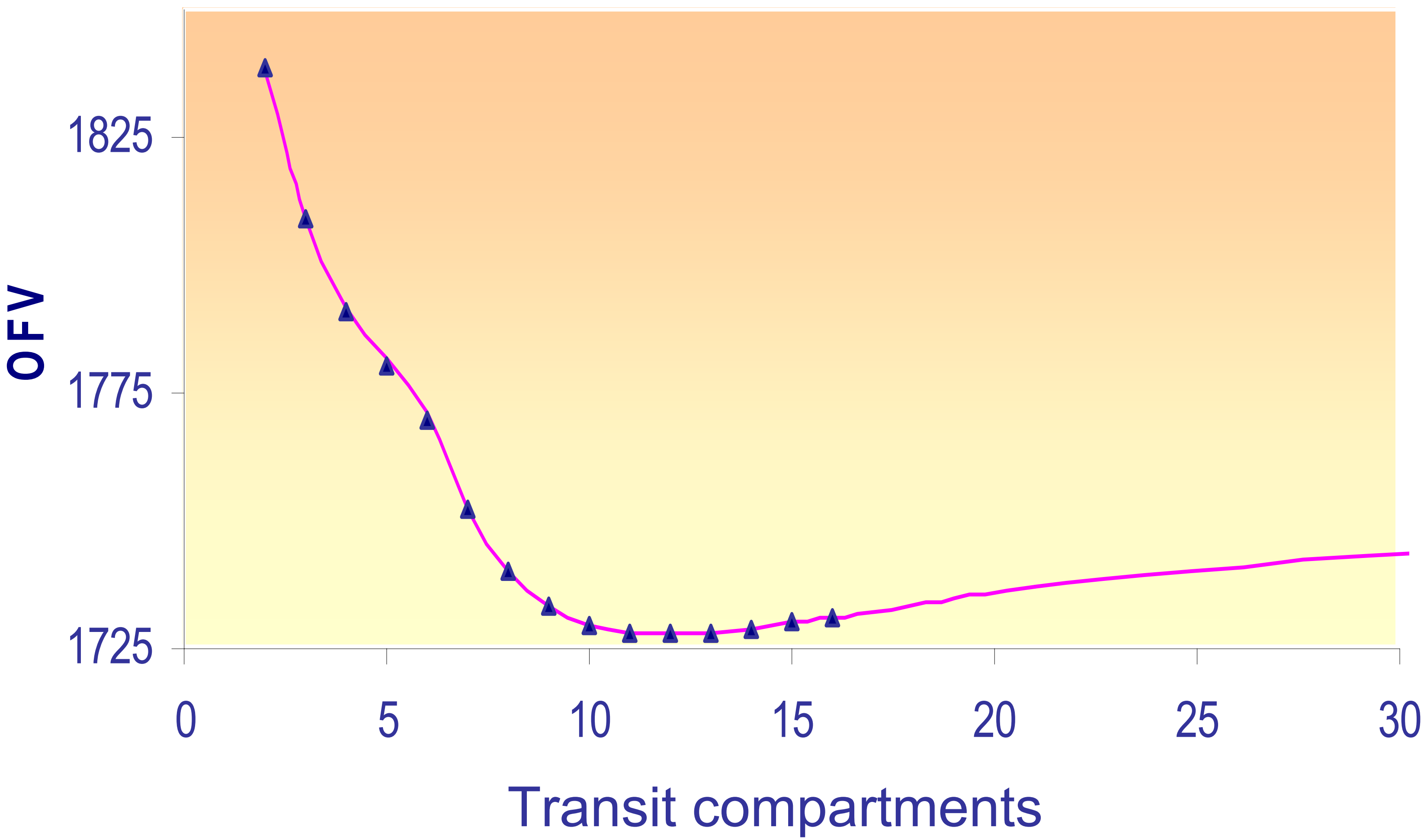
Estimation method: FOCE with interaction

Goodness-of-fit



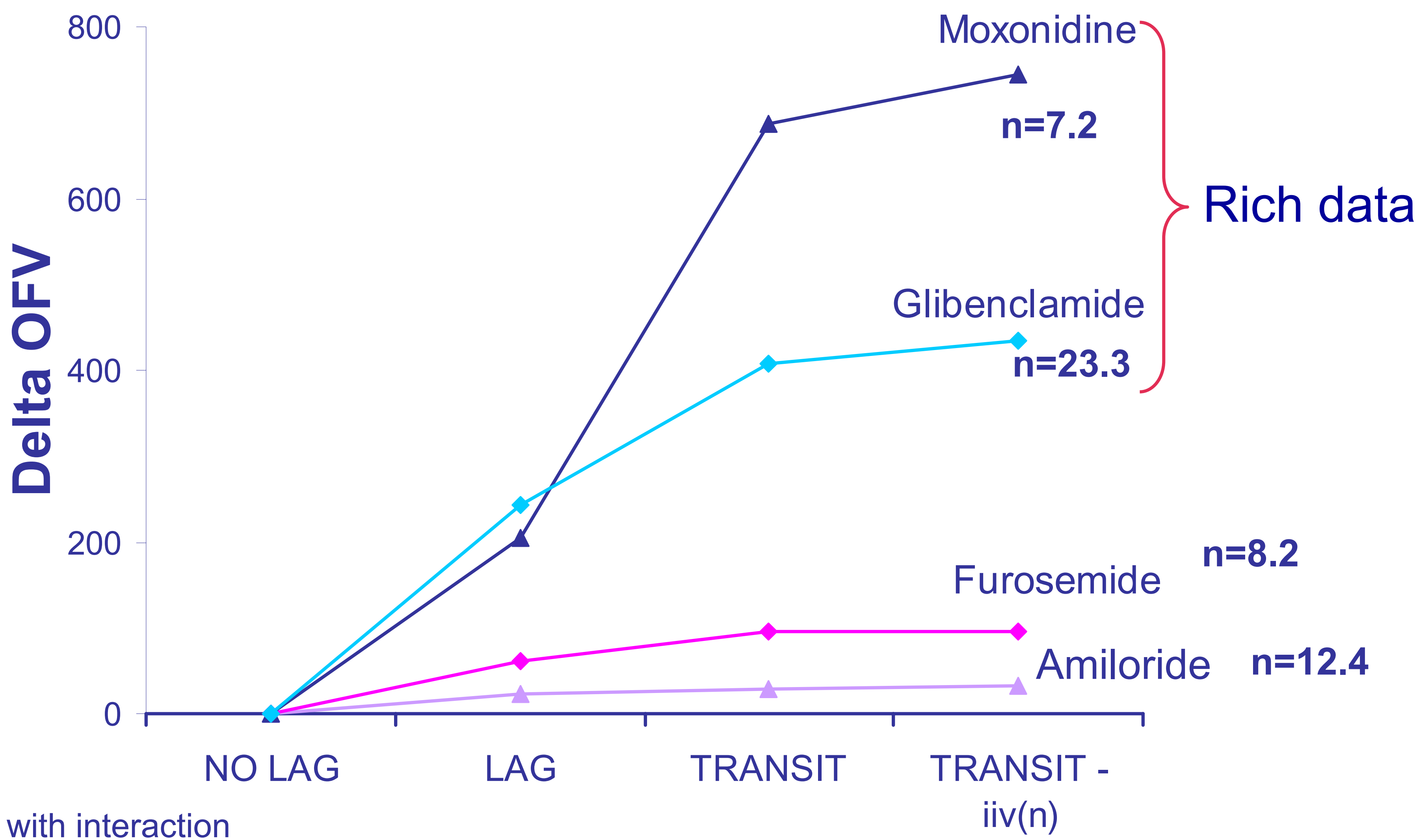
FOCE with interaction

Stepwise addition vs. Estimation



Estimation method: FO

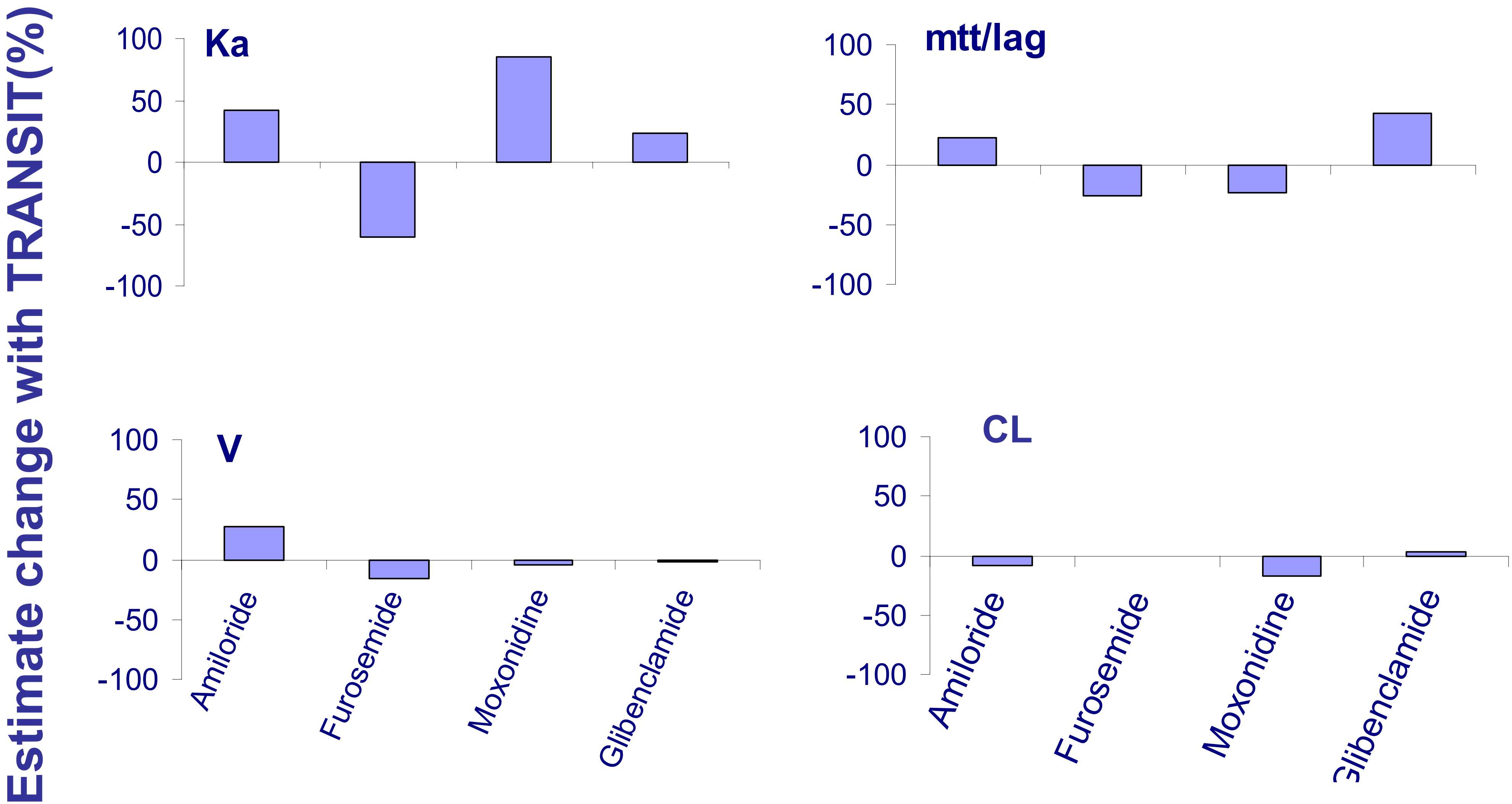
Improvement in GOF for all compounds



FOCE with interaction

Estimates TRANSIT vs. LAG model

UPPSALA
UNIVERSITET



FOCE with interaction

Conclusion

Compared to the LAG model, the TRANSIT model:

1. Provided a significantly better model fit due to a more accurate description of the absorption phase
2. Is not a change-point model and was numerically more stable
3. Non-trivial differences in parameter estimates

UPPSALA UNIVERSITET

Finally...

The implementation of the TRANSIT model in NONMEM can be obtained by contacting me:

rada.savic@farmbio.uu.se