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Overview of absorption models and modelling issues

Mats O. Karlsson and Rada Savic

Division of Pharmacokinetics and Drug Therapy
Department of Pharmaceutical Biosciences
Uppsala University

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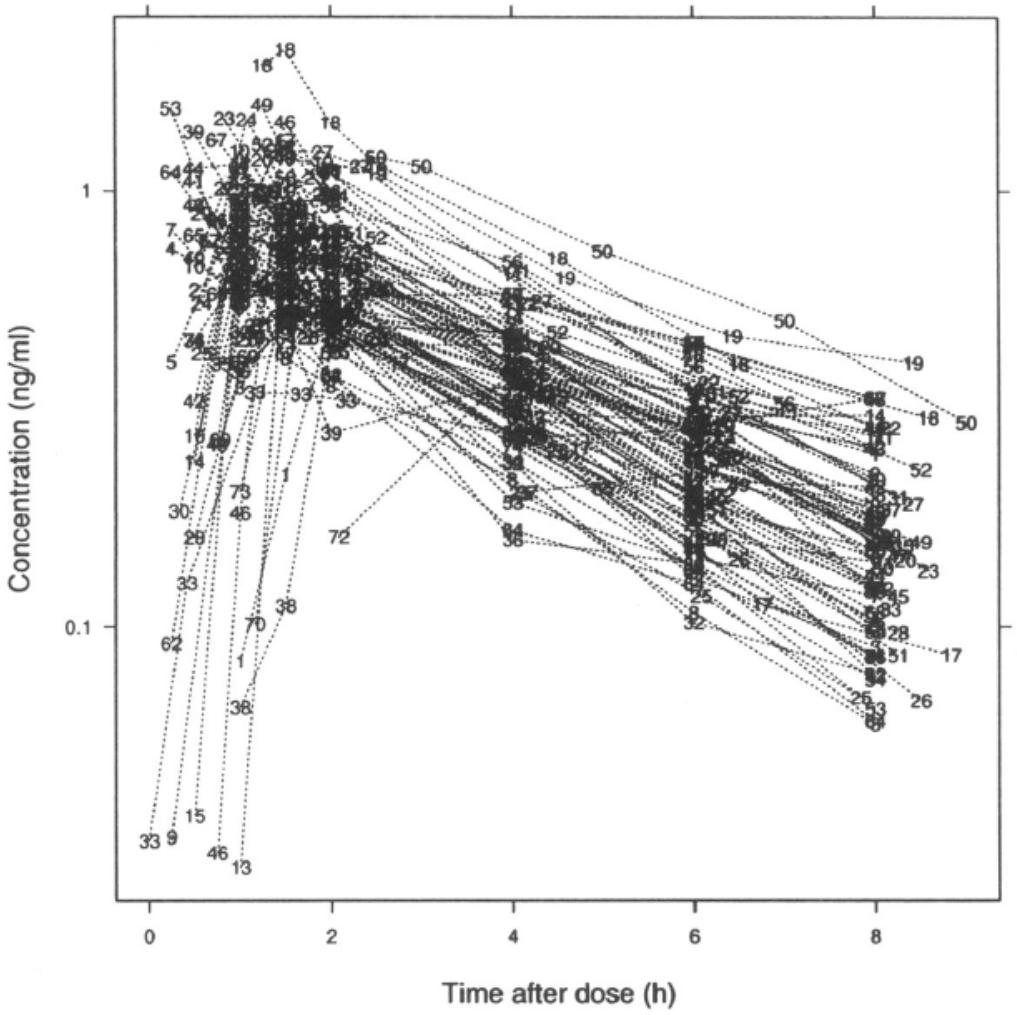
Modelling oral absorption

”Representative” pop PK data set Representative absorption modelling



”Exposure” main interest ⇒ Sparse absorption data

Sparse data ⇒ Simple model

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Outline

- Extent of absorption
- Absorption delay
- Rate of absorption

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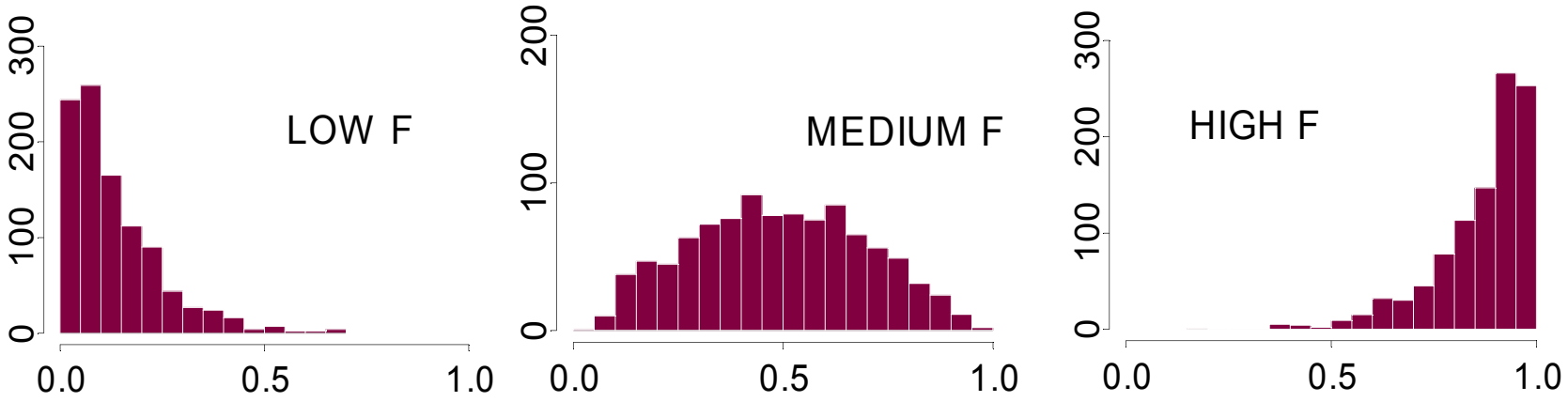
Extent (F) – with iv reference dose

$$0 \le F \le 1$$

$$F = \frac{e^{\theta+\eta}}{1+e^{\theta+\eta}}$$

$$F = \frac{e^{\ln(\theta/(1-\theta))+\eta}}{1+e^{\ln(\theta/(1-\theta))+\eta}}$$



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Extent (F) – with iv reference dose

What if (apparently) F>1?

Nonlinear disposition	→ Model it!
IOV in CL	→ Model it![1]
Variability in content amount	→ Model it?*
Study conduct errors	→ Investigate it!

* $F = \frac{e^{\theta+\eta}}{1+e^{\theta+\eta}} + \eta_{FORM}$ With η_{FORM} fixed to known variability

[1]Karlsson & Sheiner. CPT 1994, 55:623-37

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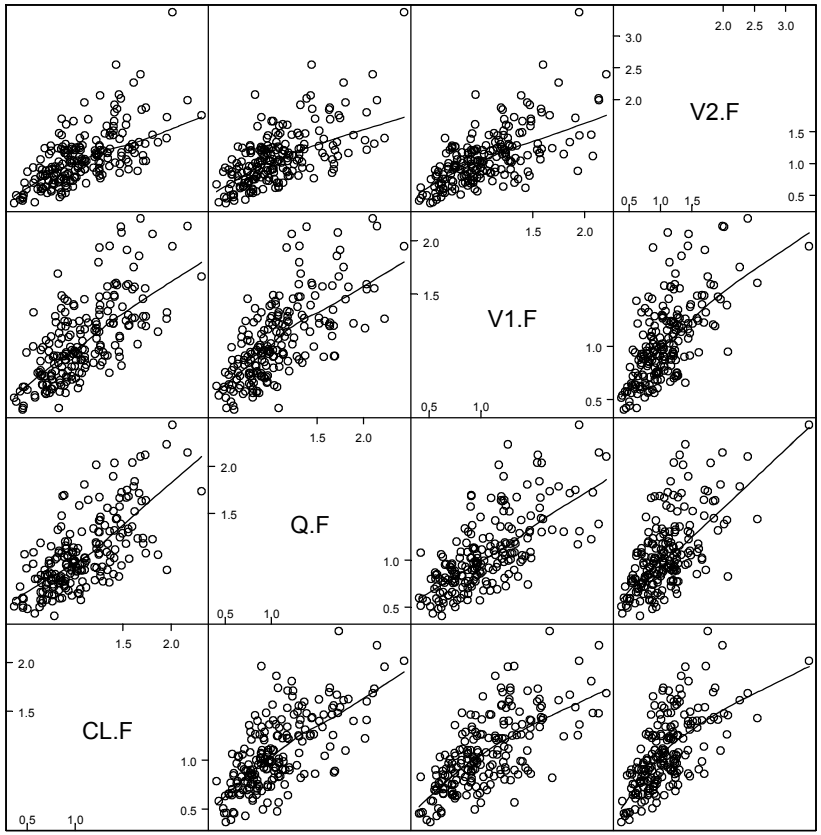
Extent (F) – no reference dose



Lack of reference dose ⇒ Parametrisation CL/F, Q/F, V1/F,...

Variability in F ⇒ Parameter correlation

Parameter correlation ⇒ Estimate all (6) covariances

Parameter correlation ⇒ Estimate variability in "F"

$$F = e^{\eta_F}$$

– 1 instead of 6 parameters (maybe)
– η_F for diagnostic purposes
– Caution in interpretation: η_F may reflect other sources of positive parameter correlation (free fraction, body size,…)

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First-pass effect –

Variability in E_H will influence both CL_H and F_H

Solution 1

Model fixed effects as influencing CL and F separately

Use a (negative) correlation between CL and F

Unnecessarily many parameters!

Solution 2

Create a semiphysiological model where covariate influences and variability can be associated with the single appropriate process

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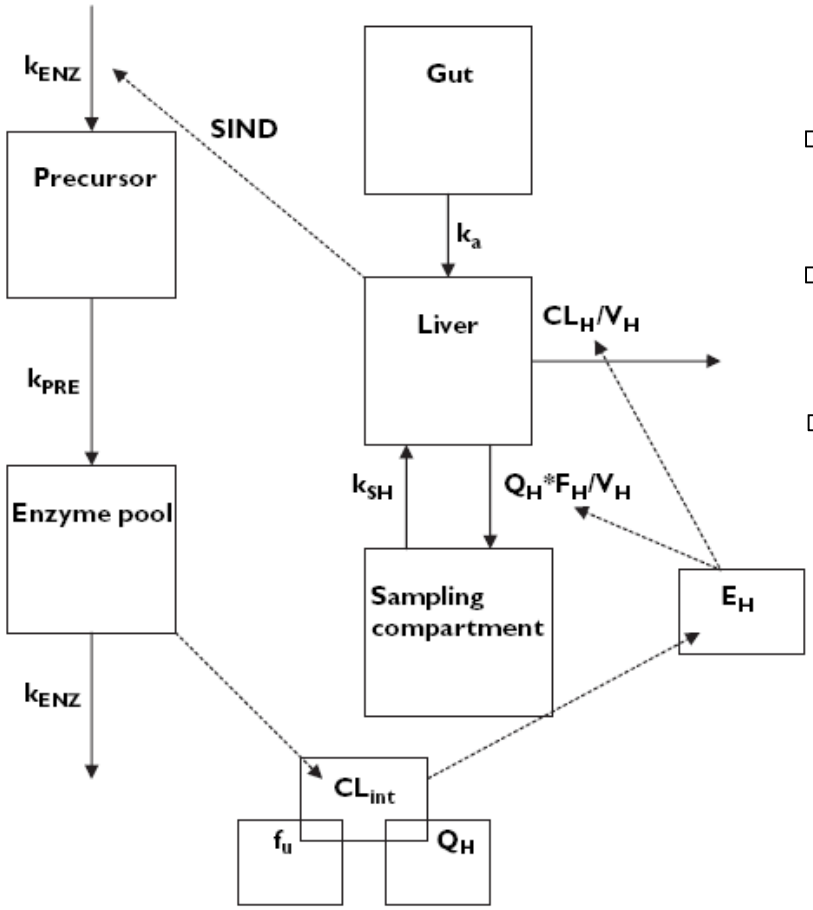
”Mechanistic” modelling of CL_H & F_H



⇒ Covariate effect in 1 place only

⇒ Variability in CL_{int} affects both CL_H & F_H

⇒ Drug in absorption phase contributes to event in liver

Gordi et al. Br J Clin Pharmacol. 2005;59:189-98

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Absorption delay modelling

1. Lag time
2. Erlang-type absorption
   (hard-coded transit compartments)
3. Transit compartment model
   (flexible number of transit compartments)

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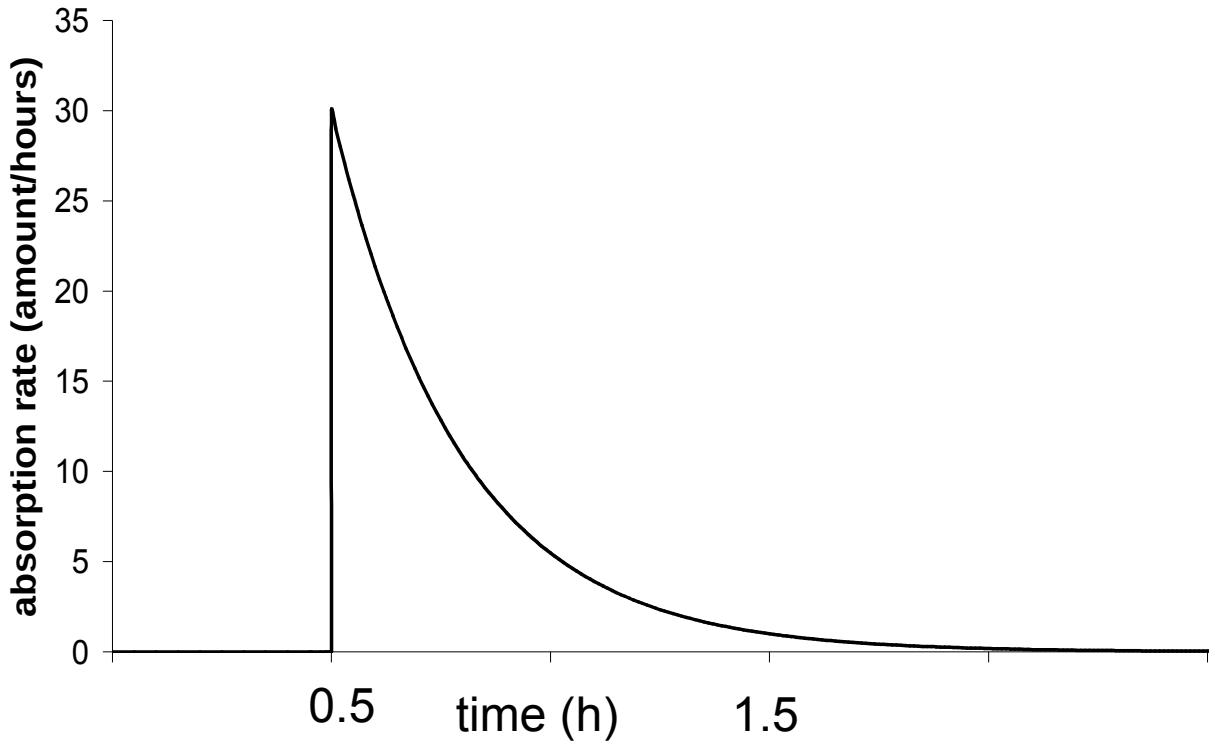
Lag time model

Often used

It improves the model fit

Unphysiological

Change-point model *(numerical difficulties esp. with FOCE)*



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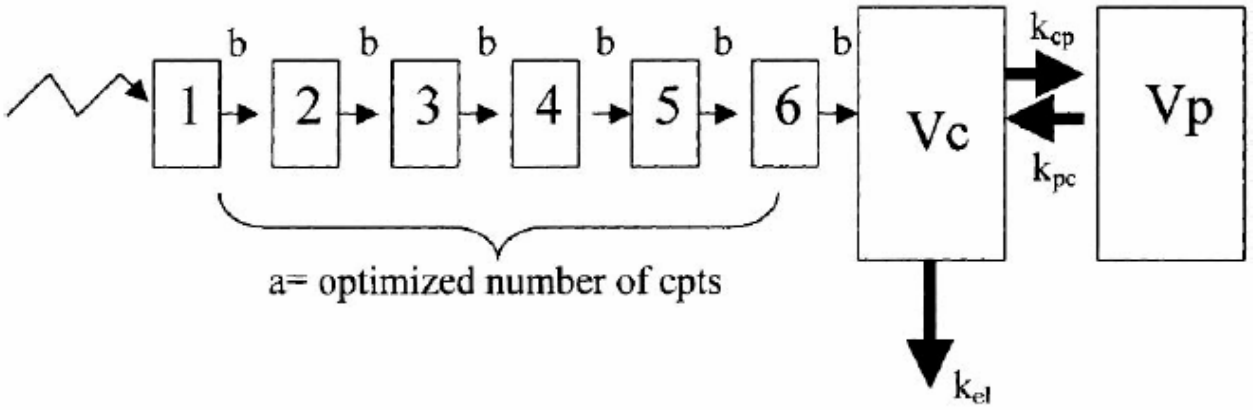
Erlang type absorption

- ✓Characterises the skewed and delayed absorption profiles
- ✓Not a change point model
- ✓No of transit compartments has to be optimised manually
- ✓Does not have an absorption compartment



Rousseau et al. TDM 2004, 26:23-30

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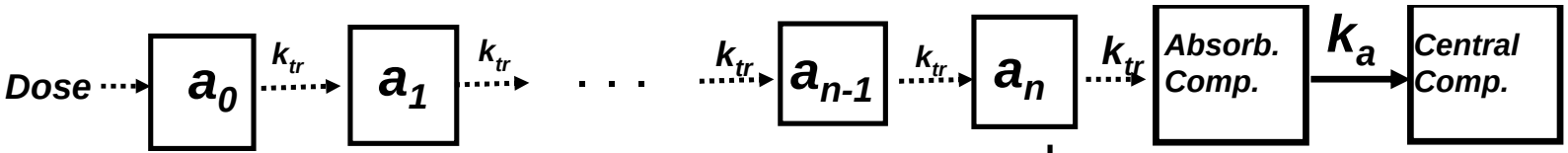
Transit compartment model

- ✓No of transit compartments (along with variability) is estimated
- ✓Equivalent to a gamma distribution function
- ✓Not a change-point model
- ✓General model (previous two models special cases of this model)



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

Savic et al. PAGE 2004

Code for this model will be presented in web-version

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Complexity of the absorption process

- Delayed or incomplete gastric emptying
- Changes along the GI tract
  - Absorptive area, motility/mixing, pH, gut wall properties (metabolic enzymes, transporters), content properties, ...
- Competing processes for drug disappearance
- Nonlinearities
  - High local concentrations may lead to incomplete solubilisation, saturation of enzymes and transporters
  - Nonlinearities usually modelled as dose-dependent, rather than dependent on local concentration
- ”Discrete” events
  - Gastric emptying, disintegration, food, bile release, absorption windows, motility
- Drug-drug interactions
- Formulation

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Rate of absorption

Typical absorption models

- ✓First order model
- ✓Zero order model

Why successful?

⇒ Lack of data

⇒ Lack of impetus

⇒ Lack of models

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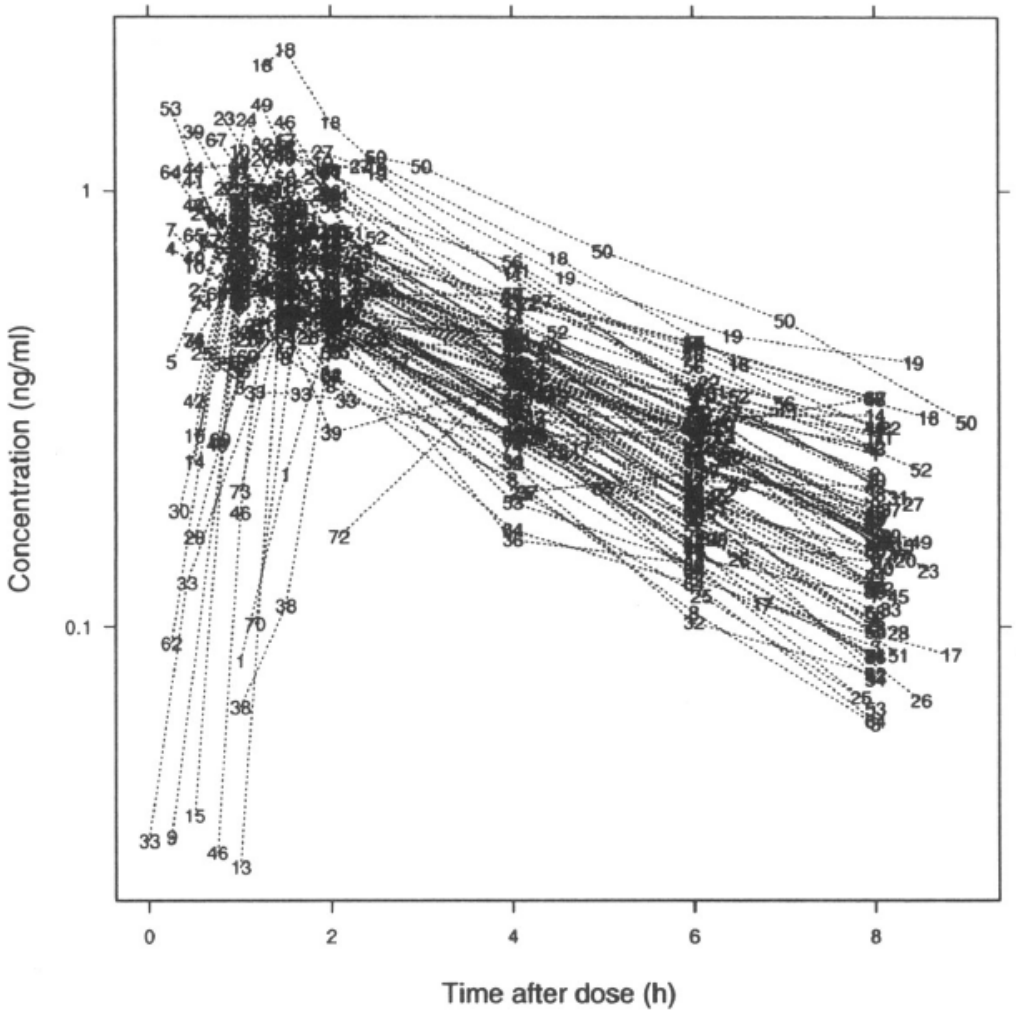
Modelling oral absorption

Representative pop PK data set



Representative absorption modelling

"Exposure" main interest ⇒ Sparse absorption data

Sparse data ⇒ Simple model

Simple model + Complex system ⇒ Model misspecification

Absorption model misspecification ⇒ Fixed effects bias + Inflated IIV + Inflated overall RV

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Ignoring absorption model misspecification

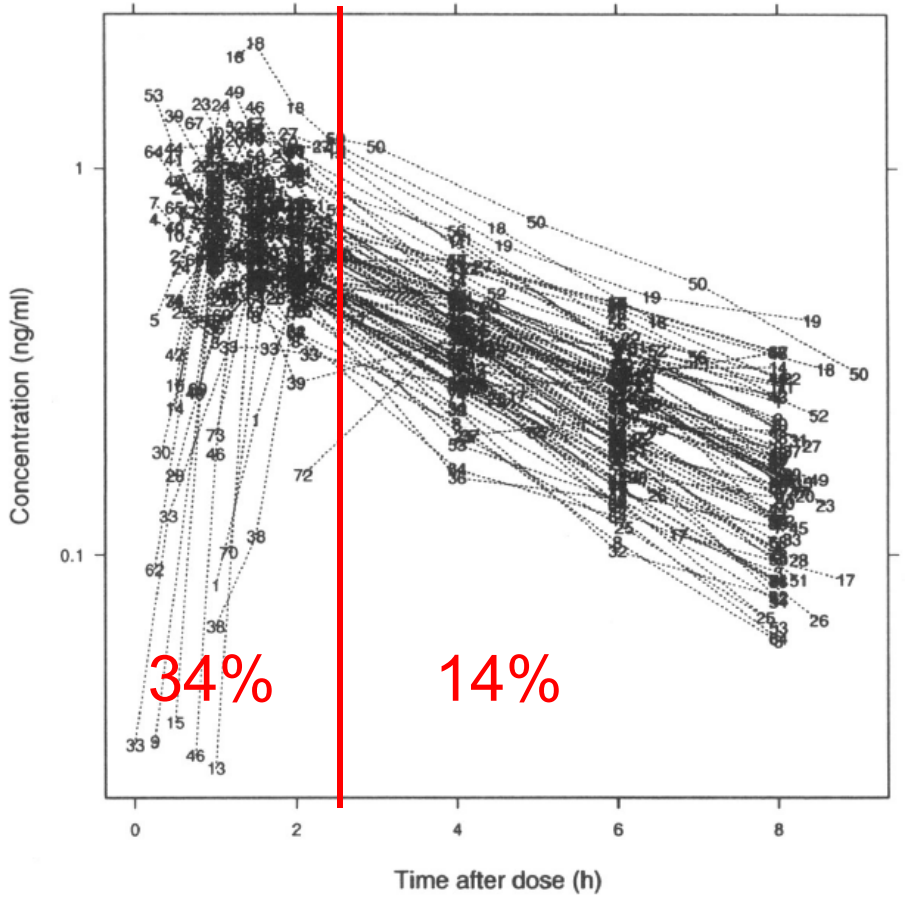

Fig. 1. Observed concentrations after the first dose vs. time after dose plotted on a semilogarithmic scale. Data points are labeled by the ID number and each individuals data points are connected.

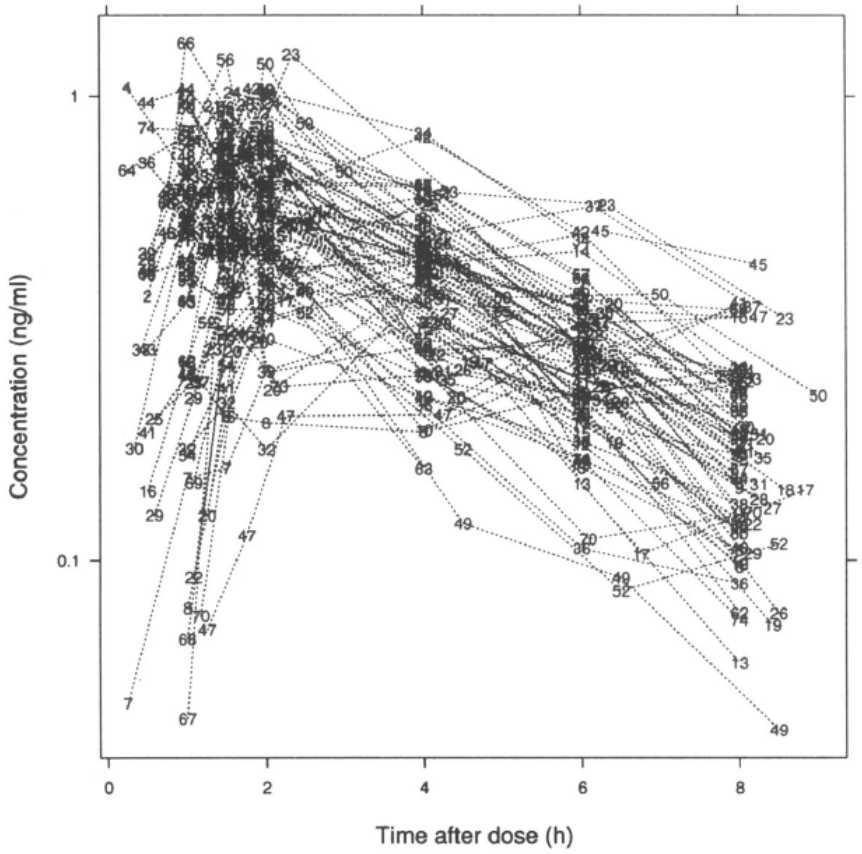

Fig. 13. The logarithm of the "observed" simulated concentrations vs. time after dose for one of the simulated data sets. Individual concentrations are connected by broken lines and labeled by ID numbers.

Karlsson et al. JPKPD 1995, 23:651-72

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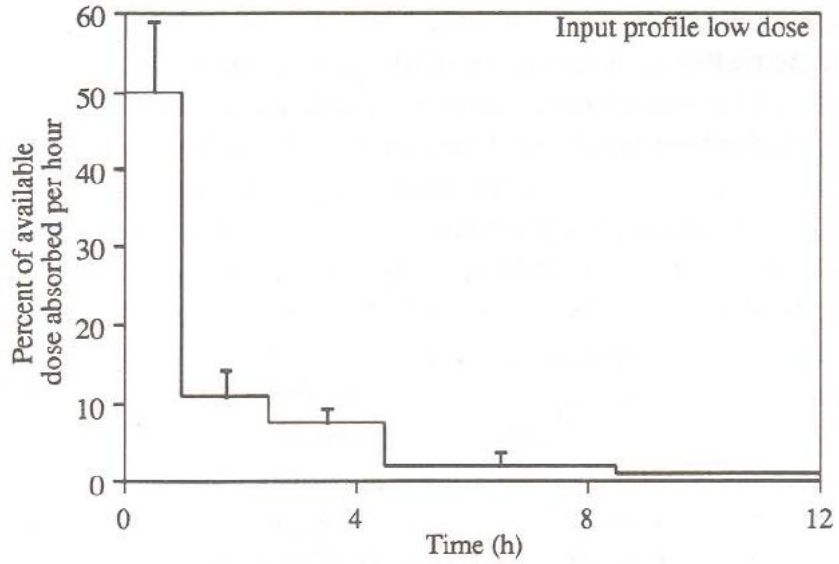
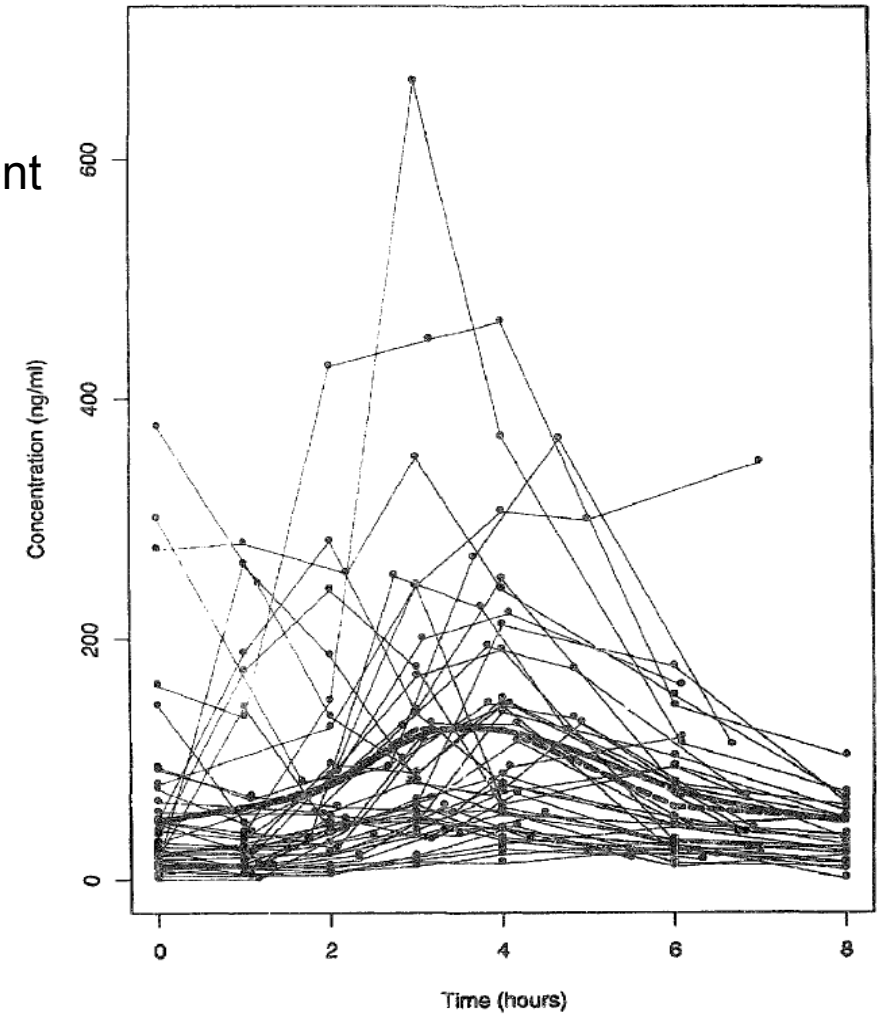
Flexible absorption models

No estimated change-points
Easily adapted to information content
Empirical



NONMEM code in web-version of presentation

Lindberg-Freijs et al. Biopharm Drug Disp 1994, 15:75-86



Park et al. JPB 1997, 25:615-48

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Rate of absorption – other models

✓Parallel first order absorption

✓Mixed zero order and first order (simultaneous or sequential) ⟹ Used as mechanistic & empirical

✓Weibull type absorption (1 or 2 Weibull functions) ⟹ Often overparametrised

✓Saturable absorption (Michaelis-Menten absorption) ⟹ Often change-point models

✓Inverse Gaussian density absorption

✓Time-dependent absorption models

Ref in web-version for Holford et al; Higaki et al; Reigner et al., Williams et al.; Zhou; Valenzuela et al.;etc

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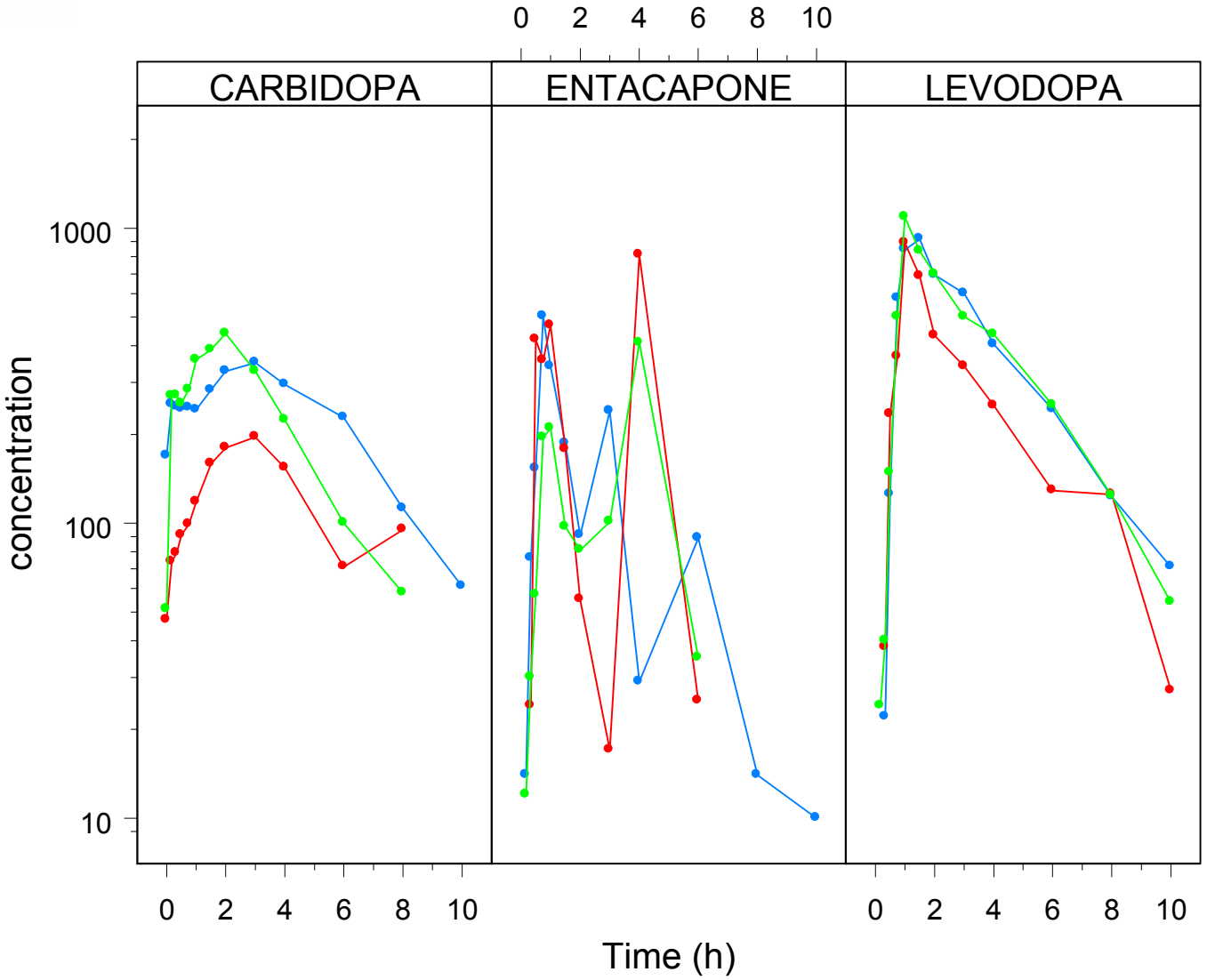
Simultaneous dosing of 3 drugs



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How to model absorption?

Present modelling approach

Model based on (sparse) data only

Prior information (essentially) ignored

Model misspecification (partially) ignored

Present simulation approach

Prior information (partially) included

Data information used in ”ad hoc” procedure

Ideal approach

Posterior model obtained as weighted balance between prior info and data

Study designs adapted to information sought

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Extra slides

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Flexible Input Model

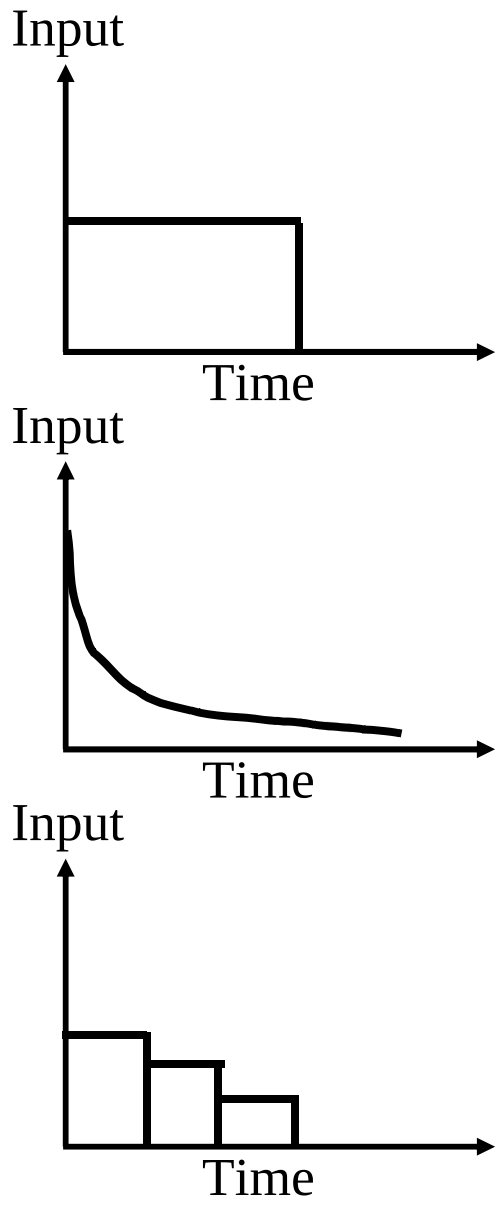
Mats Karlsson, Janet R Wade and Stuart Beal

Division of Pharmacokinetics and Drug Therapy
Department of Pharmaceutical Biosciences
Uppsala University

With a zero-order input, the input rate is constant over time for a finite period.

With a first-order input, the input rate is exponentially decreasing over time.

With the flexible input model, the input rate is an arbitrary step function over a period of time.



Limitations

The idea applies to a single dose with no other drug on board, for example, a single dose cross-over type study. It can be adapted for some multiple dose situations.

The number of steps needed is fixed and determined by trial and error, using the minimum objective function as a guide. However, this number is limited by the number of observations available during the absorption phase.

The duration of the D_i of the ith step is finite and fixed, and is determined by trial and error, shorter durations being tried during the initial part of the absorption phase, when the input rate should be changing most rapidly.

The height H_i of the ith step is estimated. It can be expressed as a fraction of the bioavailable dose absorbed over the ith step per unit time.

Constraints

One might constrain the heights to be monotonically decreasing, and often they are estimated to be decreasing. However, they may not be decreasing and attention should be paid to this.

The H_i can be modeled using a number of different η's. A less flexible model for random interindividual variability can be considered.

In the example IV data are present. If such data are not available bioavailability should be constrained to 1 (and then Vd is volume relative to true bioavailability).

Implementation - Data

A *single* dose of 1000 units given at 0 hours.

```
#ID    TIME        DV      AMT    RATE    EVID    PO
#ORAL DOSE
  1      0          .      1000     -1       1      1
  1     0.5        59         .      .       0      1
  1     1.0        99         .      .       0      1
  1     2.0        90         .      .       0      1
  1     3.0        80         .      .       0      1
  1     4.0        73         .      .       0      1
  1     6.0        55         .      .       0      1
  1     8.0        43         .      .       0      1
  1     10.        23         .      .       0      1
 #IV DOSE
  1      0          .      1000     .       4      0
  1     0.5       399         .      .       0      0
  1     1.0       191         .      .       0      0
  1     2.0       120         .      .       0      0
  1     3.0        90         .      .       0      0
  1     4.0        69         .      .       0      0
  1     6.0        51         .      .       0      0
  1     8.0        46         .      .       0      0
  1     10.        28         .      .       0      0
```

Implementation – Control Stream

```
$INPUT  ID  TIME  DV  AMT  RATE  EVID  PO
$DATA   DATA1  IGNORE #
$SUBROUTINE ADVAN1 TRANS2
$PK
;THETA(1)= CLEARANCE
;THETA(2)= VOLUME
;THETA(3)= BIOAVAILABILITY

IF (TIME.EQ.0) DOSE = AMT

;DISPOSITION AND SCALE MODELS
CL = THETA(1) * EXP(ETA(1))
V  = THETA(2) * EXP(ETA(2))
S1 = V

;BIOAVAILABILITY MODEL
F1 = PO*THETA(3)*EXP(ETA(3))+(1-PO)

;ABSORPTION MODEL
; variables indicating the active step
Q1 = 0
Q2 = 0
Q3 = 0
IF(TIME.LE.1)                Q1 = PO
IF(TIME.GT.1.AND.TIME.LE.3) Q2 = PO
IF(TIME.GT.3.AND.TIME.LE.6) Q3 = PO
```

```
; fraction of bioavailable dose
;    absorbed over step, per unit time
DEN   = 1+THETA(4)*EXP(ETA(4))+ THETA(5)*EXP(ETA(5))
ABR1  = 1/DEN
ABR2  = THETA(4)*EXP(ETA(4))/DEN/2
ABR3  = THETA(5)*EXP(ETA(5))/DEN/3

R1 = F1*DOSE*(Q1*ARB1+Q2*ARB2+Q3*ARB3)

;          CL        V        F        θ4        θ5
$THETA  (0,10)  (0,100)  (0,1)  (0,0.4)  (0,0.3)

;       CL    V    F
$OMEGA  .1   .1   .1

$OMEGA  BLOCK(2)  .2 .1 .2
```

Reference

A Lindberg-Freijs & MO Karlsson.
Dose dependent absorption and linear disposition of cyclosporin A in rat.
Biopharmaceutics & Drug Disposition
Vol 15, 75-85 (1994).

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Transit compartment model

Radojka Savic, Daniel Jonker, Thomas Kerbusch and Mats Karlsson

Division of Pharmacokinetics and Drug Therapy
Department of Pharmaceutical Biosciences
Uppsala University

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Implementation – Control Stream

```
$PROB TRANSIT COMPARTMENT MODEL
$INPUT ID AMT TIME DV CMT EVID
$DATA data1.dta IGNORE=#
$SUBROUTINES ADVAN6 TOL5
$MODEL COMP=(ABS)
       COMP=(CENT)

$PK
IF(AMT.GT.0.AND.CMT.EQ.1)PODO=AMT; oral dosing
IF(AMT.GT.0.AND.CMT.EQ.2)PODO=0  ; intravenous dosing

;DISPOSItiON MODEL

CL    =THETA(1)*EXP(ETA(1))      ; Clearance
V2    =THETA(2)*EXP(ETA(2))      ; Volume of distribution

; BIOAVAILABILITY MODEL

F1   =0
; The amount is explicitly used in differential equation describing
   the absorption process
F2   =1
BIO  =THETA(2)*EXP(ETA(2))      ; Bioavailability
```

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```
; Absorption model

KA   =THETA(4)*EXP(ETA(4))   ; Absorption rate constant
MTT  =THETA(5)*EXP(ETA(5))   ; Mean transit time
N    =THETA(6)*EXP(ETA(6))   ; Number of transit compartments
KTR  =(NN+1)/MTT             ; transit rate constant

;NFAC =SQRT(2*3.1415)*NN**(NN+0.5)*EXP(-NN)
; Stirling approximation to n! function

LNFAC=LOG(2.5066)+(NN+0.5)*LOG(NN)-NN
; Logarithm of Stirling approximation

$DES
;DADT(1)=BIO*PODO*KTR*(KTR*T)**NN*EXP(-KTR*T)/NFAC-KA*A(1)
; Original equation, might cause some nummerical difficulties,
   therefore the log-transformation of original equation is needed

DADT(1)=EXP(LOG(BIO*PODO+.00001)+LOG(KTR)+NN*LOG(KTR*T+.00001)-
   KTR*T-LNFAC)-KA*A(1)
; Log-transformed equation, small number (0.00001) is added to
   avoid Log(0)

DADT(2)=KA*A(1)-K*A(2)
```

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Reference

Radojka M. Savic, Daniël M. Jonker, Thomas Kerbusch & Mats O Karlsson

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

PAGE 13 (2004) Abstr 513 [www.page-meeting.org/?abstract=513]