

Slide  
1

# Absorption Models Using NM-TRAN

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Slide  
2

## Absorption

- Extent of Absorption
- Rate of Absorption

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Slide  
3

## Extent (F)

- Fraction Absorbed (f)
  - into portal vein from gut
  - mainly physicochemistry
    - theophylline (100%) (small, unionized)
    - gentamicin (< 5%) (large, ionized)
    - digoxin (65%) (transporter, bacterial food?)

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Slide  
4

## Extent (F)

- First Pass Extraction (ER)
  - drug removed while passing through liver
  - organ clearance and blood flow
    - morphine (60%)
    - ethanol (10-70%)

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Slide  
5

## Extent (F)

$$F = f \cdot (1 - ER)$$

e.g. morphine

$$F = 1 \cdot (1 - 0.6) = 0.4$$

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Slide  
6

## Input Processes

- Bolus
  - e.g. Intra-venous injection
- Zero-Order
  - e.g. Constant rate IV infusion
- First-Order
  - e.g. Intra-muscular injection

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Slide  
7

## Rate

- Zero-Order
  - Stomach emptying (Tmax)
    - physiological control
  - Slow Release Formulation (Tk0)
    - pharmaceutical control

$$C(t) = \frac{Rate}{CL} \cdot \left( 1 - e^{-\frac{CL}{Vd} \cdot t} \right)$$

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Slide  
8

## Rate

- First Order
  - Intestinal Absorption (KA)
    - Diffusion limited
    - Absorption Thalf = 0.7/KA
    - Complete after 4 x absorption Thalf

$$C(t) = \frac{Dose \cdot Ka}{V \cdot \left( Ka - \frac{CL}{Vd} \right)} \cdot \left( e^{-\frac{CL}{Vd} \cdot t} - e^{-Ka \cdot t} \right)$$

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Slide  
9

## Extent of Absorption Dose or Rate Dependence?

- Empirical Models use Dose
- Mechanistic Models use Rate

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|  |   |  |  |  |
|--|---|--|--|--|
| <p>Slide 10</p>  | <h2 style="text-align: center; color: red;">Finding the Dose</h2> <pre style="text-align: center;"> \$PK  ;Make sure dose is 0 for each subject IF (NEWIND.LE.1) DOSE=0  ;Remember dose using AMT IF (AMT.GT.0) DOSE=AMT </pre> <p style="font-size: small; text-align: left;">©NHG Holland, 2010, all rights reserved.</p>   | <p>NONMEM data files require that the amount of each dose is recorded in the AMT data item only at the time the dose is administered. It is often useful to know the value of the last DOSE. This code shows how to save the DOSE by looking at the AMT data item.</p> |  |  |
| <p>Slide 11</p>  | <h2 style="text-align: center; color: red;">Finding the Time After Dose</h2> <pre style="text-align: center;"> \$PK ;Make sure values are 0 for each subject IF (NEWIND.LE.1) THEN   DOSE=0   TDOS=0 ENDIF ;Remember dose and time of dose IF (AMT.GT.0) THEN   DOSE=AMT   TDOS=TIME ENDIF ;Time after dose for every record TAD=TIME-TDOS  See also <a href="http://www.globomax.com/nonmem_tip3.htm">http://www.globomax.com/nonmem_tip3.htm</a> <a href="http://www.globomax.com/nonmem_tip4.htm">http://www.globomax.com/nonmem_tip4.htm</a> </pre> <p style="font-size: small; text-align: left;">©NHG Holland, 2010, all rights reserved.</p> |  |  |  |
| <p>Slide 12</p>  | <h2 style="text-align: center; color: red;">Empirical Dose and Extent Models</h2> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> <pre> \$THETA -.01 ; KFDOSE \$PK FDOSE=EXP (KFDOSE*DOSE) F1=FDOSE </pre> </td> <td style="width: 50%; vertical-align: top;"> <pre> \$THETA (-1,-.5,0) ; DMAX \$THETA (0,100,) ; D50 \$PK FDOSE=1+DMAX*DOSE/(D50+DOSE) F1=FDOSE </pre> </td> </tr> </table> <p style="font-size: small; text-align: left;">©NHG Holland, 2010, all rights reserved.</p>  | <pre> \$THETA -.01 ; KFDOSE \$PK FDOSE=EXP (KFDOSE*DOSE) F1=FDOSE </pre>   | <pre> \$THETA (-1,-.5,0) ; DMAX \$THETA (0,100,) ; D50 \$PK FDOSE=1+DMAX*DOSE/(D50+DOSE) F1=FDOSE </pre> | <p>Two empirical models are illustrated showing how dose might be used to predict changes in extent of absorption. The model on the right is approximately linear if the effect on bioavailability is small. The model on the left requires an additional parameter to describe a saturable increase in extent of absorption with dose. The maximum extent is 1 + DMAX with 1+DMAX/2 extent at a dose D50.</p> |
| <pre> \$THETA -.01 ; KFDOSE \$PK FDOSE=EXP (KFDOSE*DOSE) F1=FDOSE </pre> | <pre> \$THETA (-1,-.5,0) ; DMAX \$THETA (0,100,) ; D50 \$PK FDOSE=1+DMAX*DOSE/(D50+DOSE) F1=FDOSE </pre>  |  |  |  |

Slide  
13

## Mechanistic Rate and Extent Well Stirred Model

```

$DES
;Systemic circulation conc
DCP=A(1)/V
;Rate in to Portal vein
RATEIN=KA*A(2)
;Portal vein conc
CPV=DCP+RATEIN/Q
ER =CLI/(Q+CLI)
; mixed order component of CL
CLMO = Q*ER
FHEP = 1-ER
CL = CLMO + CLFO
;Solve quadratic for CLI
AXX =KM
B =Q*(CPV+KM)-VMAX
C =-VMAX*Q
SGNB=1
IF (B.LT.0) SGNB=-1
SQRB =SQRT (B*B-4*AXX*C)
D =-.5*(B+SGNB*SQRB)
ISPLUS=1
IF (C/D.LE.0) ISPLUS=0
CLI =ISPLUS*C/D+(1-ISPLUS)*D/AXX

```

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Hepatic extraction can change with concentration delivered to the liver if intrinsic clearance is mixed order in the range of concentrations achieved in the liver during absorption. Under the well stirred model of liver extraction the time changing extraction ratio (ER) can be predicted from the absorption rate and an assume value for hepatic blood flow. CLFO is a parameter describing a first-order elimination clearance process.

<http://pkpdx.com/holford/docs/rate-dependent-extraction.pdf>

Slide  
14

## Two Part Rate Models Parallel/Sequential KOKA

```

Dose is 100
$THETA
1 ; ka h-1
.25 ; tlag1 h
.1 ; tlag2 h
2 ; tk0 h
.5 ; fk0
$SUBR ADVAN2
$PK
KA=ka
D2=tk0
F1=1-fk0
F2=fk0
ALAG1=tlag1
ALAG2=tlag2 ;+tlag1

```

| #ID | TIME | CMT | AMT | RATE |
|-----|------|-----|-----|------|
| 1   | 0    | 1   | 100 | 0    |
| 1   | 0    | 2   | 100 | -2   |

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Two part models require the data file to have two dosing records at the time of each actual dose. The first record has a CMT of 1 (the default absorption compartment for a first-order process when using ADVAN2 or ADVAN4) and a RATE of 0. The second record has a CMT of 2 (the default central compartment when using ADVAN2 or ADVAN4) and a RATE of -2. The duration of input (TK0) by the zero-order process into compartment 2 is defined in \$PK by assigning TK0 to the special variable D2. The fraction of the dose absorbed by each process is determined by FK0 (the fraction absorbed by the zero-order process). ALAG1 and ALAG2 are used to estimate the lagtime (if any) for each process. If it is assumed that the zero-order process starts only when the first-order process has started (sequential input) then ALAG2 must be set to the sum of ALAG1 and ALAG2.

Slide  
15

## Two Part Rate Models Sequential Linked KOKA

```

When Zero-order becomes First-order
Rate Zero-order = Rate First-order i.e.
K0 = KA*GUT
= KA*(1-FK0)*DOSE
FK0*DOSE/TK0 = KA*(1-FK0)*DOSE
therefore
KA = FK0/(TK0*(1-FK0))
$THETA
.25 ; tlag h
2 ; tk0 h
.5 ; fk0
$SUBR ADVAN2
$PK
KA=fk0/(tk0*(1-fk0))
D2=tk0
F1=1-fk0
F2=fk0
ALAG1=tlag+tk0
ALAG2=tlag

```

| #ID | TIME | CMT | AMT | RATE |
|-----|------|-----|-----|------|
| 1   | 0    | 1   | 100 | 0    |
| 1   | 0    | 2   | 100 | -2   |

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The sequential linked zero-order then first-order model can be interpreted in a mechanistic way if the concentration in the gut is initially at the solubility limit for the drug. As drug is absorbed and the concentration falls below the solubility limit then the process converts from a zero-order input to a first-order input. Note that ALAG1 (lag time of the first order process) must be equal to TK0 (the duration of the zero-order process) plus any lagtime for the zero-order process. This ensures that the first-order process will take over at the end of the zero-order input. See Holford NHG, Ambros R, Stoeckel K. Models for describing absorption rate and estimating extent of bioavailability: Application to cefetemet pivoxil. J Pharmacokin Biopharm. 1992;20:421-42.

Slide 16

# Transit Models



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)

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

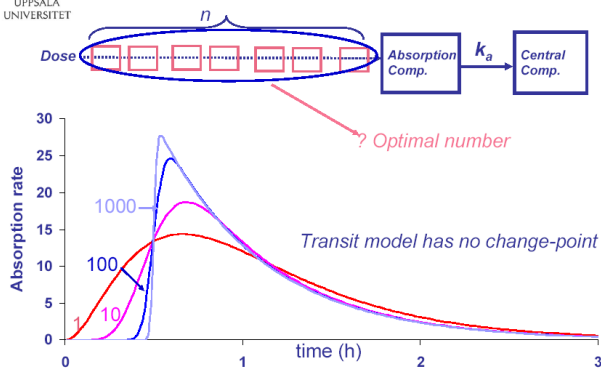
The use of transit compartment models to describe delays in onset of absorption was developed by Radojka Savic at Uppsala. The following set of slides is taken from her work.

Slide 17

# Transit Models



Transit compartment model

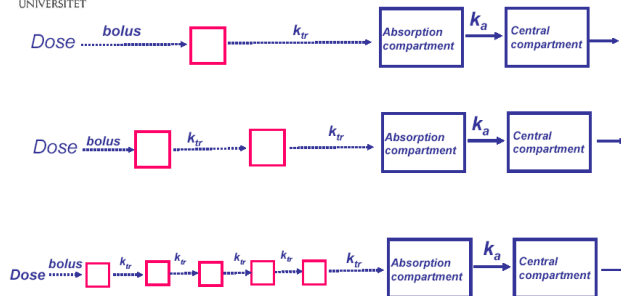


Slide 18

# Transit Models



Step-wise addition

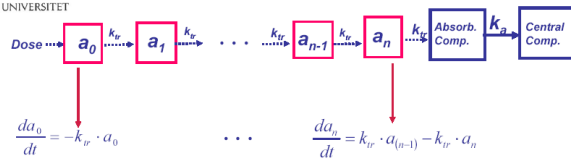


Slide 19

## Transit Models



Estimating the number of transit compartments



Mathematical solution for this system:

$$a_n(t) = Dose \cdot \frac{(k_{tr} \cdot t)^n}{n!} \cdot e^{-k_{tr} \cdot t} ; \text{ amount of drug in the } n^{\text{th}}\text{-compartment at time } t$$

Slide 20

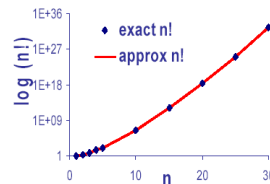
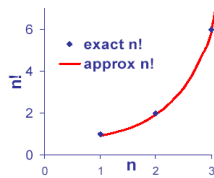
## Transit Models



Stirling approximation

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

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

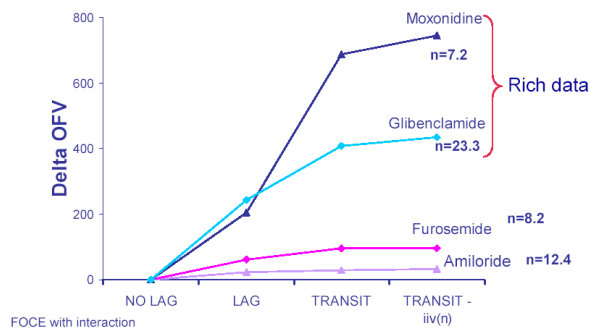


Slide 21

## Transit Models



Improvement in GOF for all compounds



Slide  
22

## Transit Models

### Single Dose

```
$THETA
3 ; pop_cl L/h
10 ; pop_v L
1 ; pop_ka h-1
1 ; pop_mtt h
5 ; pop_nt

$PK
CL=pop_cl
V=pop_v
KA=pop_ka
NT=pop_nt
KTR=(NT+1)/pop_mtt
NFAC= SQRT(2*3.1415)*NT**(NT+0.5)*EXP(-NT)
F1=0 ; Very important!

$SUBR ADVAN6 TOL=3
$MODEL
COMP (GUT)
COMP (CENTRAL)

$DES
DCP=A(2)/V
RATEIN=KA*A(1)
GUT=DOSE*EXP(-KTR*(T-TLAST))
DADT(1)=GUT*KTR*(KTR*(T-TLAST))*NT/NFAC - RATEIN
DADT(2)=RATEIN - CL*DCP
```

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The code for a single dose transit model involves the use of differential equations and closed form solution to transit through NT transit compartments. It is important that the extent of absorption for the dosing compartment 1 is set to 0 because the actual drug input rate from this compartment is modelled explicitly in DADT(1).

Slide  
23

## Transit Models

### Single Dose LOG Version (faster?)

```
$THETA
3 ; pop_cl L/h
10 ; pop_v L
1 ; pop_ka h-1
1 ; pop_mtt h
5 ; pop_nt

$PK
CL=pop_cl
V=pop_v
KA=pop_ka
NT=pop_nt
KTR=(NT+1)/pop_mtt
LNFAC= LOG(2.5066)+(NT+.5)*LOG(NT)-NT
LNDK=LOG(DOSE+.00001)+LOG(KTR)
F1=0 ; Very important!

$SUBR ADVAN6 TOL=3
$MODEL
COMP (GUT)
COMP (CENTRAL)

$DES
DCP=A(2)/V
RATEIN=KA*A(1)
X=KTR*T
DADT(1)=EXP(LNDK+NT*LOG(X+0.00001)-X-LNFAC)-RATEIN
DADT(2)=RATEIN - CL*DCP
```

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Slide  
24

## Transit Models

### Multiple Dose

Absorption must be complete within dosing interval!

```
$THETA
3 ; pop_cl L/h
10 ; pop_v L
1 ; pop_ka h-1
1 ; pop_mtt h
5 ; pop_nt

$PK
CL=pop_cl
V=pop_v
KA=pop_ka
NT=pop_nt
KTR=(NT+1)/pop_mtt
NFAC= SQRT(2*3.1415)*NT**(NT+0.5)*EXP(-NT)
F1=1 ; Very important!
IF (AMT.GT.0) TDOSE=TIME

$SUBR ADVAN9 TOL=3
$MODEL
COMP (GUT)
COMP (TRANSIT)
COMP (CENTRAL)

$DES
DCP=A(3)/V
GUT=A(1)
RATEIN=KA*A(2)
DADT(1)=-KTR*GUT
DADT(2)=GUT*KTR*(KTR*(T-TLAST))*NT/NFAC - RATEIN
DADT(3)=RATEIN - CL*DCP
$ERROR
TLAST=TDOSE
```

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If it can be assumed that absorption is complete within the dosing interval then it is possible to model concentrations arising from multiple doses with a transit time delay after each dose. In this case the first compartment is used to model input from the most recent dose and its extent of bioavailability must be set to 1.