Introduction to PK modeling

Explore and visualize PK models with MLXPlore

Introduction

This is an introductory tutorial for describing and visualizing simple and more complex pharmacokinetic (PK) models.

We will present several PK model examples and visualize the processes of absorption, distribution and elimination that characterize them.

We will suppose in all these examples that a single dose is administered at time t=0.

In each example, the modeling goal is defined. Then, the model and requests for graphical outputs are coded in MLXPlore, a new graphical and interactive software for the exploration and visualization of complex pharmacometric models. MLXPlore uses the easy and intuitive MLXtran model coding language, popularized by the Monolix software.

MLXPlore is used in Section I for computing the predicted amount in the central compartment. We display in Section IV the predicted amount in the depot compartment and the MLXPlore project that was used for computing it.

I Absorption

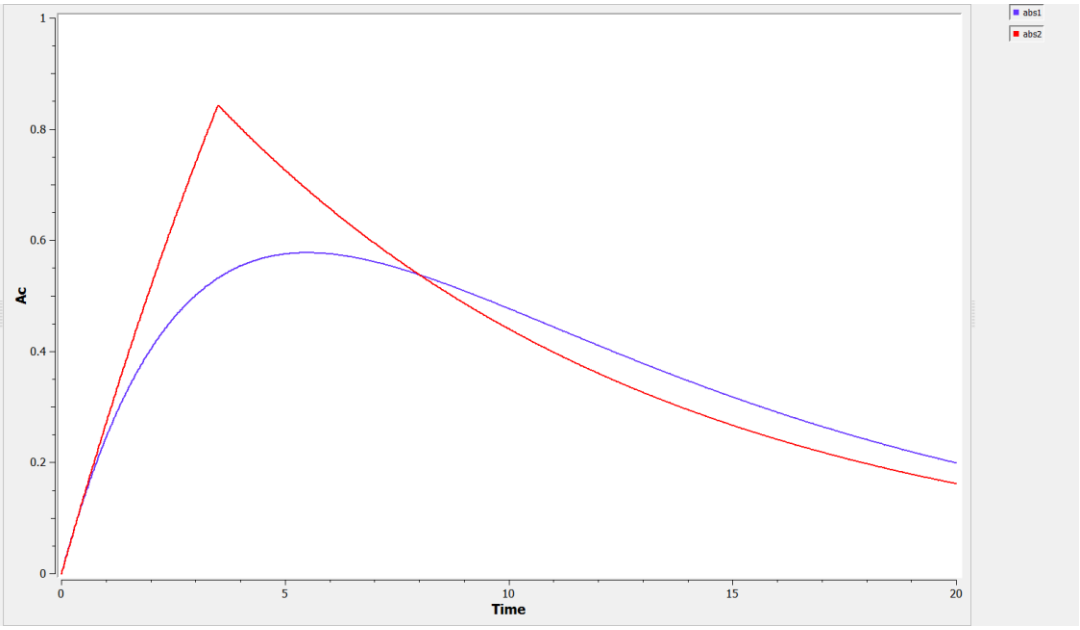
1) First-order and zero-order absorption

absorption1a_script: this computes and displays the amount (Ac) in the central compartment when the drug is absorbed with a first-order or zero-order absorption process. In the right-hand side window, the two (first-order and zero-order) models are described using the MLXtran coding language. In the left-hand side window, the structural model, experimental design, parameters and requested graphical output are defined.

```
<MODEL>
file='model/absorption1a_model.txt'

;----------------------------
<DESIGN>
[ADMINISTRATION]
abs1={time=0, amount=1, type=1}
abs2={time=0, amount=1, type=2}

;----------------------------
<PARAMETER>
ka=0.3
Tk0=3.5
k=0.1

;----------------------------
<OUTPUT>
list=Ac
grid=0:0.02:20
```

```
[PREDICTION]
input={ka,Tk0,k}

PK:
compartment(cmt=1,amount=Ac)
oral(type=1,cmt=1,ka)
oral(type=2,cmt=1,Tk0)
elimination(cmt=1,k)
```

Below is the graphical output of MLXPlore, which was told to output the amount Ac in the central compartment with respect to time for zero-order (red) and first-order (blue) absorption.



2) First-order, zero-order and α–order absorption

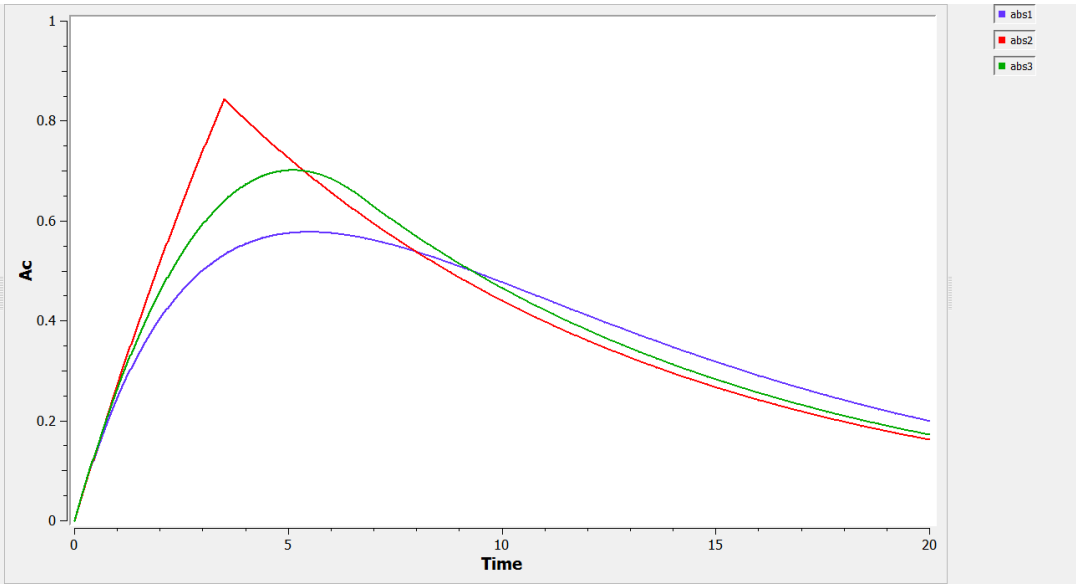
absorption2a_script: we compute and display the amounts in the central and depot compartments when the drug is transferred from the depot to the central compartment with a first-order, zero-order or α–order absorption process.

Note that an α–order absorption process means that $\dot{Ad}(t) = -ka \times Ad^{\alpha}(t)$. Zero-order absorption is obtained with α=0 and first-order absorption with α=1.

```
<MODEL>
file='model/absorption2a_model.txt'

;------------------------------
<DESIGN>
[ADMINISTRATION]
abs1={time=0, amount=1, type=1}
abs2={time=0, amount=1, type=2}
abs3={time=0, amount=1, type=3}

;------------------------------
<PARAMETER>
ka=0.3
alpha=0.5
Tk0=3.5
k=0.1

;------------------------------
<OUTPUT>
list=Ac
grid=0:0.02:20
```

```
[PREDICTION]
input={ka,alpha,Tk0,k}

PK:
compartment(cmt=1,amount=Ac)
oral(type=1,cmt=1,ka)
oral(type=2,cmt=1,Tk0)
depot(type=3,target=Ad3)

EQUATION:
ar3=ka*(max(Ad3,0)^alpha)
er=k*Ac
ddt_Ad3 = -ar3
ddt_Ac = ar3  - er
```

The green curves are with respect to the α–order absorption process.



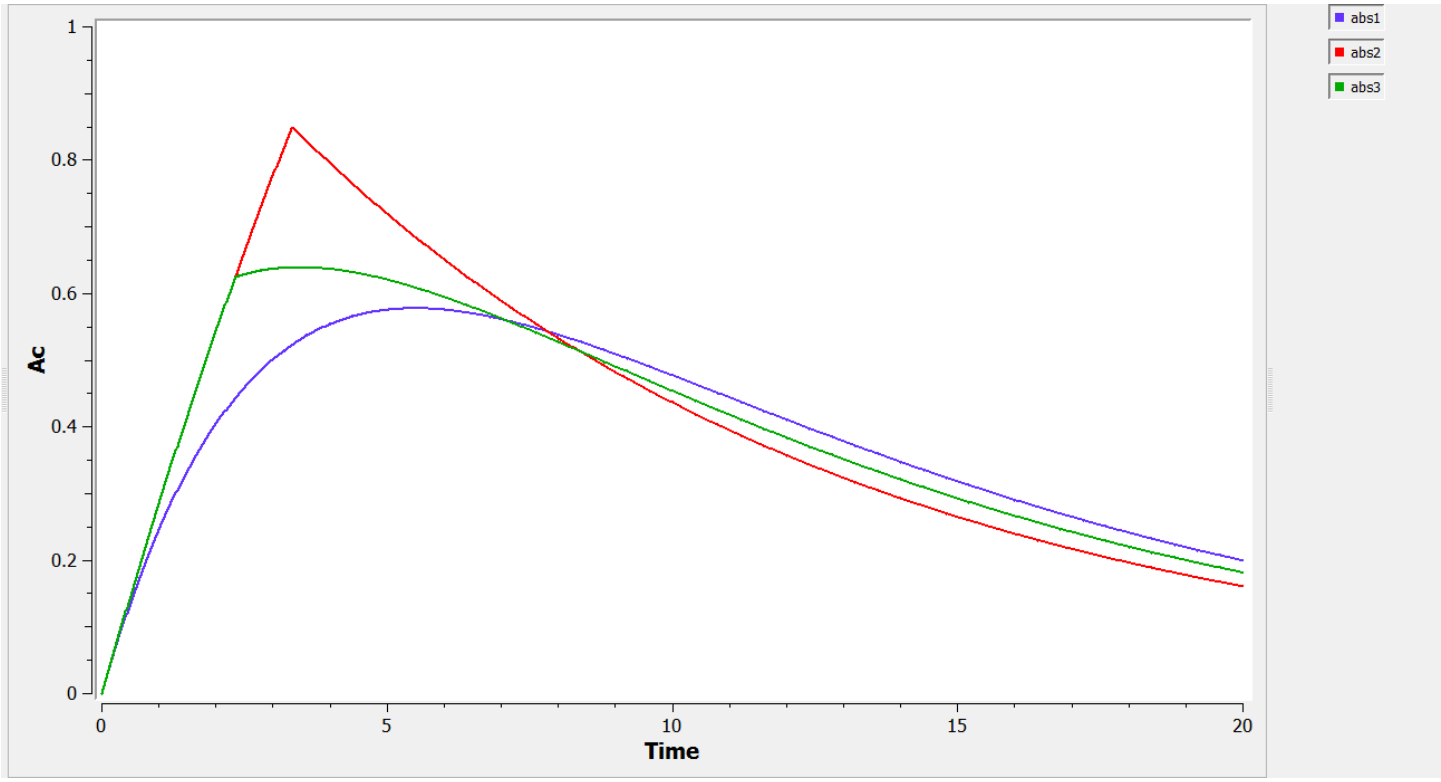
3) First-order, zero-order and sequential zero-order/first-order absorption

absorption3a_script: we compute and display the amount in the central compartment when the drug is transferred from the depot to the central compartment with a first-order, zero-order or sequential zero-order/first-order absorption process. Here, *r0* is the absorption rate for the zero-order process and *F0* the fraction of the dose absorbed in a zero-order process.

```
<MODEL>
file='model/absorption3a_model.txt'

;----------
<DESIGN>
[ADMINISTRATION]
abs1={time=0, amount=1, type=1}
abs2={time=0, amount=1, type=2}
abs3={time=0, amount=1, type=3}

;----------
<PARAMETER>
ka=0.3
alpha=0.5
r0=0.3
F0=0.7
k=0.1

;----------
<OUTPUT>
list=Ac
grid=0:0.02:20
```

```
[PREDICTION]
input={ka,alpha,r0,F0,k}

PK:
tk01=amtDose/r0
tk02=F0*amtDose/r0
compartment(cmt=1,amount=Ac)
oral(type=1,cmt=1,ka)
oral(type=2,cmt=1,Tk0=tk01)
oral(type=3,cmt=1,Tk0=tk02,p=F0)
oral(type=3,cmt=1,ka,p=1-F0,Tlag=tk02)
elimination(cmt=1,k)
```

The green curves refer to the sequential zero-order/first-order absorption process.



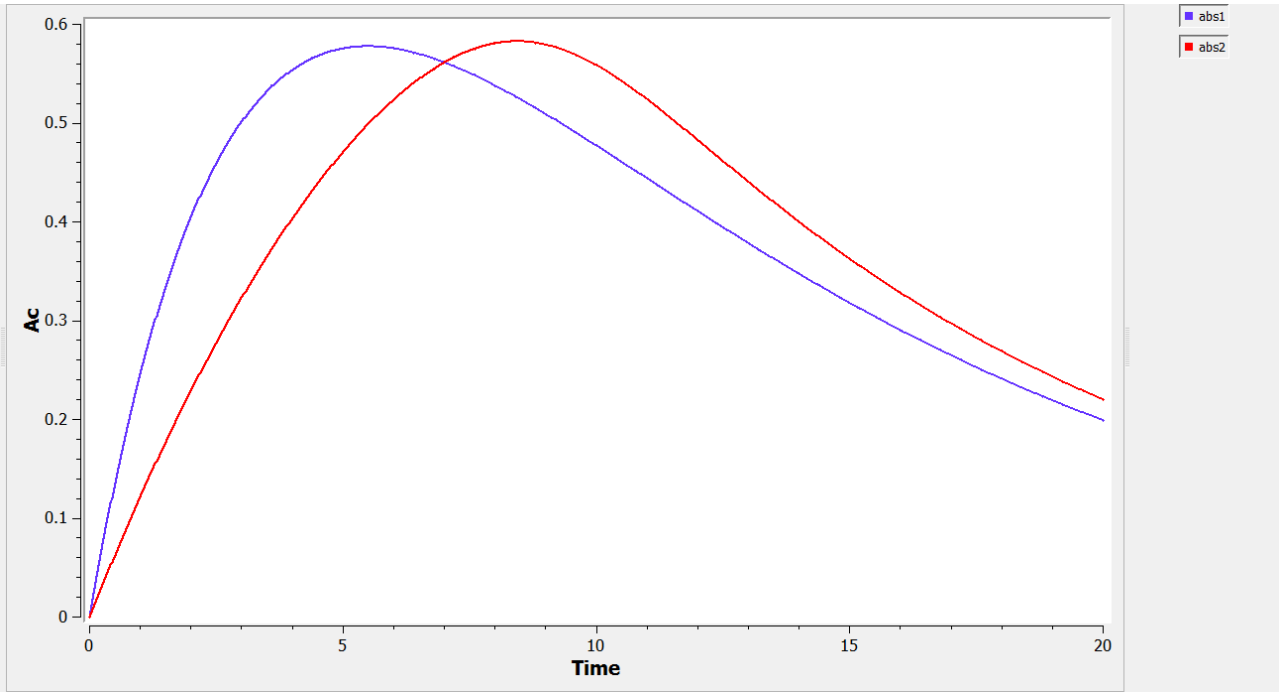
4) First-order and saturated absorption

absorption4_script: we compute and display the amount in the central compartment when the drug is transferred from the depot to the central compartment with a first-order or saturated (Michaelis-Mentens) absorption process.

```
<MODEL>
file='model/absorption4a_model.txt'

;----------------------------
<DESIGN>
[ADMINISTRATION]
abs1={time=0, amount=1, type=1}
abs2={time=0, amount=1, type=2}

;----------------------------
<PARAMETER>
ka=0.3
Vma=0.15
VKma=0.16
k=0.1

;----------------------------
<OUTPUT>
list=Ac
grid=0:0.02:20
```

```
[PREDICTION]
input={ka,Vma,VKma,k}

PK:
depot(type=1,target=Ad1)
depot(type=2,target=Ad2)

EQUATION:
ar1 = ka*Ad1
ddt_Ad1 = -ar1
ar2=Vma*Ad2/(VKma+Ad2)
ddt_Ad2 = -ar2

ar=ar1+ar2
er=k*Ac
ddt_Ac = ar  - er
```

The red curve is now for the saturated absorption process.



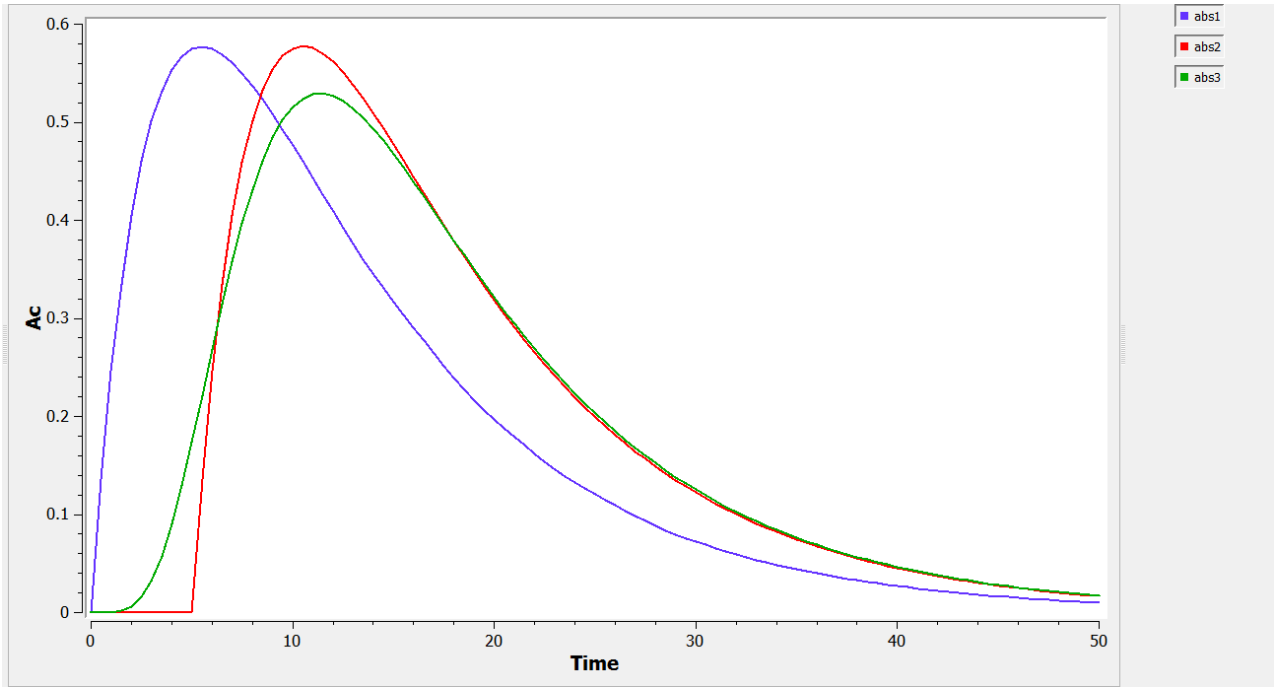
5) Lag-time and transit compartments

absorption5_script: we compute and display the amount in the central compartment when a lag time or a transit compartment model is used.

```
<MODEL>
file='model/absorption5a_model.txt'

;----------------------------
<DESIGN>
[ADMINISTRATION]
abs1={time=0, amount=1, type=1}
abs2={time=0, amount=1, type=2}
abs3={time=0, amount=1, type=3}

;----------------------------
<PARAMETER>
ka=0.3
Tlag=5
Mtt=5
Ktr=1
k=0.1

;----------------------------
<OUTPUT>
list=Ac
grid=0:0.5:50
```

```
[PREDICTION]
input={Tlag,ka,Mtt,Ktr,k}

PK:
compartment(cmt=1,amount=Ac)
oral(type=1,cmt=1,ka)
oral(type=2,cmt=1,ka,Tlag)
oral(type=3,cmt=1,ka,Mtt,Ktr)
elimination(cmt=1,k)
```

Here, the blue curve is for first-order absorption without lag-time, the red curve for the lag-time model and the green one for the transit compartment model. The number of transit compartments is *Ntr=Mtt/Ktr*. When *Mtt=Tlag,* the transit compartment model can be seen as a smooth version of the lag-time model. It converges to the lag-time model when the number of compartments increases (i.e., when the transfer rate constant *Ktr* increases).



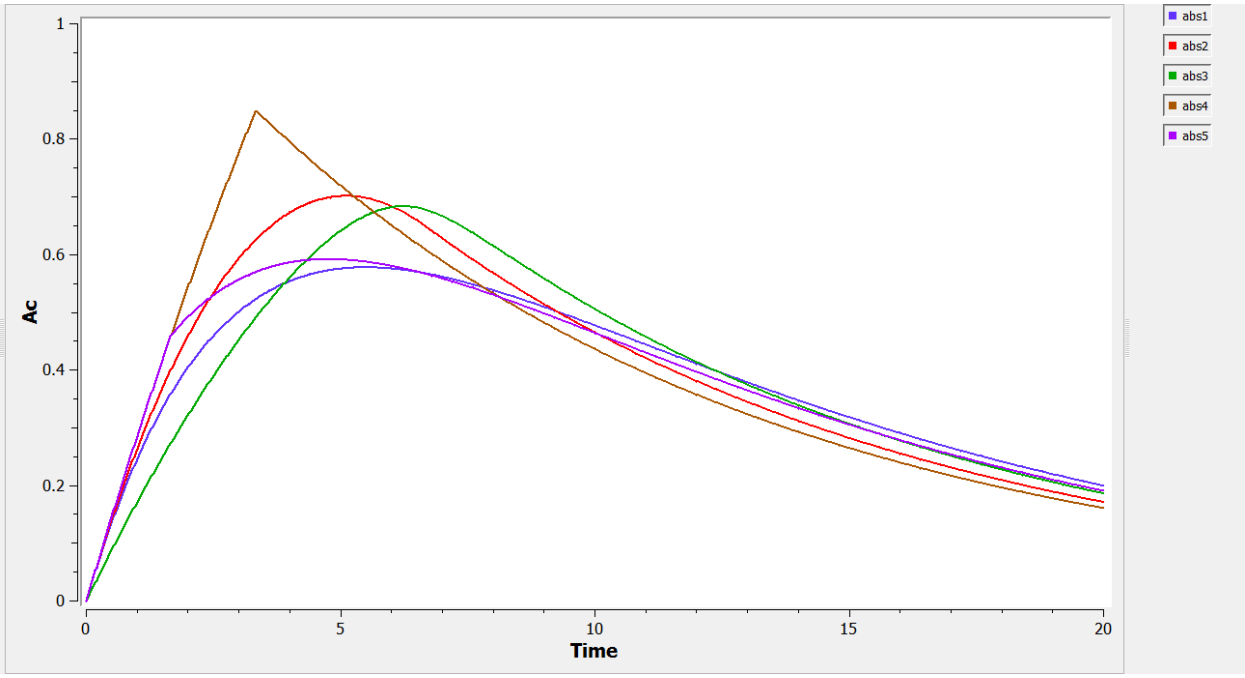
6) Summary

absorption6a_script: we compute and display the amount in the central compartment for all of the different absorption models presented in the previous examples.

```
<MODEL>
file='model/absorption6a_model.txt'

;-------------------------------
<DESIGN>
[ADMINISTRATION]
abs1={time=0, amount=1, type=1}
abs2={time=0, amount=1, type=2}
abs3={time=0, amount=1, type=3}
abs4={time=0, amount=1, type=4}
abs5={time=0, amount=1, type=5}

;-------------------------------
<PARAMETER>
ka=0.3
alpha=0.5
r0=0.3
Vma=0.2
VKma=0.1
F0=0.5
k=0.1

;-------------------------------
<OUTPUT>
list=Ac
grid=0:0.02:20
```

```
[PREDICTION]
input={ka,alpha,Vma,VKma,r0,F0,k}

PK:
tk01=amtDose/r0
tk02=F0*amtDose/r0
compartment(cmt=1,amount=Ac)
depot(type=1,target=Ad1)
depot(type=2,target=Ad2)
depot(type=3,target=Ad3)
oral(type=4,cmt=1,Tk0=tk01)
oral(type=5,cmt=1,Tk0=tk02,p=F0)
oral(type=5,cmt=1,ka,p=1-F0,Tlag=tk02)


EQUATION:
ar1 = ka*Ad1
ar2=ka*(max(Ad2,0)^alpha)
ar3=Vma*Ad3/(VKma+Ad3)
er=k*Ac

ddt_Ad1 = -ar1
ddt_Ad2 = -ar2
ddt_Ad3 = -ar3
ddt_Ac = ar1 + ar2 +ar3 - er
```

In the figure, abs1 is first-order absorption, abs2 is α-order absorption, abs3 is saturated absorption, abs4 is zero-order absorption and abs5 is sequential zero-order/first-order absorption.



II Distribution

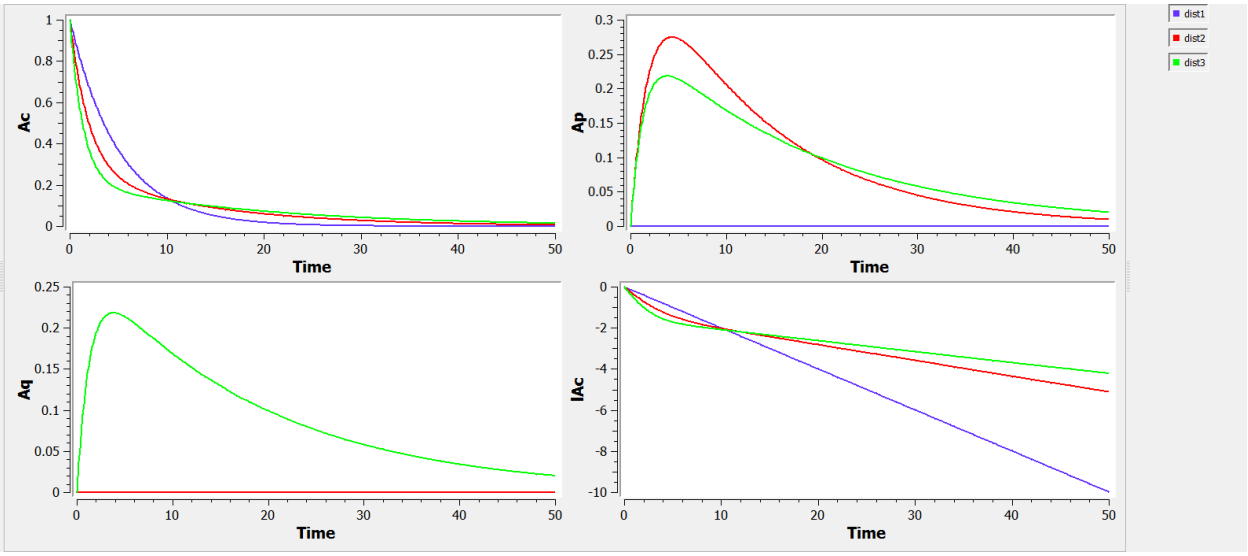
1) One, two and three compartment models

distribution1_script: we compute and display the amount in the central and peripheral compartments when the drug is distributed assuming one, two or three compartment models.

```
<MODEL>
file='model/distribution1_model.txt'

;-------------------------------
<DESIGN>
[ADMINISTRATION]
dist1={time=0, amount=1, type=1}
dist2={time=0, amount=1, type=2}
dist3={time=0, amount=1, type=3}

;-------------------------------
<PARAMETER>
k12=0.2
k21=0.2
k13=0.2
k31=0.2
k=0.2

;-------------------------------
<OUTPUT>
list={Ac,lAc,Ap,Aq}
grid=0:0.1:50
```

```
[PREDICTION]
input={k12,k21,k13,k31,k}

PK:
depot(type=1,target=Ac1)
depot(type=2,target=Ac2)
depot(type=3,target=Ac3)

EQUATION:
ddt_Ac1 = -k*Ac1
ddt_Ac2 =  k21*Ap2 - k12*Ac2 - k*Ac2
ddt_Ap2 = -k21*Ap2 + k12*Ac2
ddt_Ac3 =  k21*Ap3 + k31*Aq3 - k12*Ac3 - k13*Ac3 - k*Ac3
ddt_Ap3 = -k21*Ap3 + k12*Ac3
ddt_Aq3 = -k31*Aq3 + k13*Ac3
Ac=Ac1+Ac2+Ac3
Ap=Ap2+Ap3
Aq=Aq3
lAc=log(Ac)
```

Here, *Ap* and *Aq* are the amounts in the first and second peripheral compartments and *lAc* the log-amount in the central compartment.



III Elimination

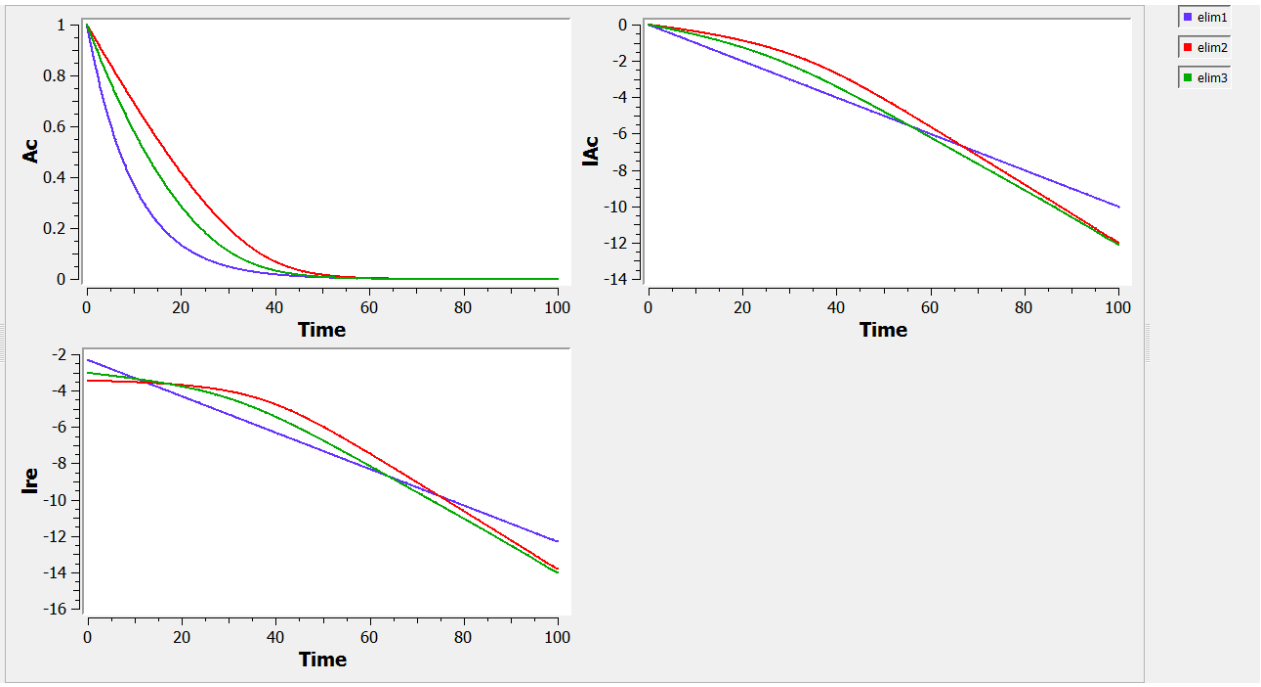
1) Linear, nonlinear and combined elimination

elimination1_script: we compute and display the amount in the central compartment and the rate of elimination when the drug is eliminated with a linear, nonlinear (Michaelis-Mentens) or combined elimination process (linear when α=1 and Michaelis-Mentens when α=1).

```
<MODEL>
file='model/elimination1_model.txt'

;----------------------------
<DESIGN>
[ADMINISTRATION]
elim1={time=0, amount=1, type=1}
elim2={time=0, amount=1, type=2}
elim3={time=0, amount=1, type=3}

;----------------------------
<PARAMETER>
k=0.1
Vm=0.04
V=1
Km=0.25
alpha=0.25

;----------------------------
<OUTPUT>
list={Ac,lAc,lre}
grid=0:0.1:100
```

```
[PREDICTION]
input={k,V,Vm,Km,alpha}

PK:
depot(type=1,target=Ac1)
depot(type=2,target=Ac2)
depot(type=3,target=Ac3)

EQUATION:
re1=k*Ac1
re2=Vm*Ac2/(V*Km+Ac2)
re3= alpha*k*Ac3 + (1-alpha)*Vm*Ac3/(V*Km+Ac3)

ddt_Ac1 = -re1
ddt_Ac2 = -re2
ddt_Ac3 = -re3

re=re1+re2+re3
lre=log(re)
Ac=Ac1+Ac2+Ac3
lAc=log(Ac)
```

Here, *lAc* is the log-amount in the central compartment and l*re* the log-rate of elimination of the drug. By definition, *lre* is a linear function of time for a linear elimination process.



IV Absorption (amounts in the central and depot compartments)

We display here the amounts both in the central and depot compartments for the various PK models presented in Section I. We also show the MLXtran code that was used for computing these two quantities.

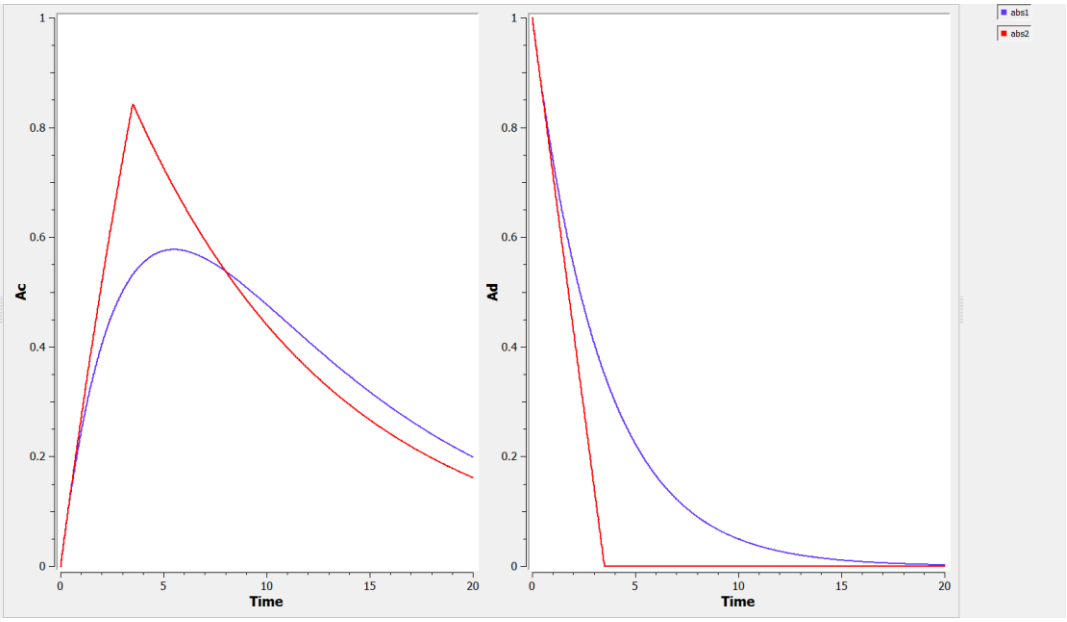
1) First-order and zero-order absorption

absorption1b_script: we compute and display both the amount Ac in the central compartment (as before) and the amount Ad in the depot compartment when a dose is administered at time t=0.

When PK macros are used for absorption, the amount in the depot can be computed by first creating another central compartment (cmt=2) which receives the same dose as the central compartment (cmt=1) with the same absorption processes, but without elimination. The amount in the depot is then the total dose administered minus the amount in the second central compartment.

```
<MODEL>
file='model/absorption1b_model.txt'

;----------------------------------
<DESIGN>
[ADMINISTRATION]
abs1={time=0, amount=1, type=1}
abs2={time=0, amount=1, type=2}

;----------------------------------
<PARAMETER>
ka=0.3
Tk0=3.5
k=0.1

;----------------------------------
<OUTPUT>
list={Ad, Ac}
grid=0:0.02:20
```

```
[PREDICTION]
input={ka,Tk0,k}

PK:
compartment(cmt=1,amount=Ac)
oral(type=1,cmt=1,ka)
oral(type=2,cmt=1,Tk0)
elimination(cmt=1,k)

compartment(cmt=2,amount=Ac0)
oral(type=1,cmt=2,ka)
oral(type=2,cmt=2,Tk0)

EQUATION:
Ad=amtDose-Ac0
```



2) Zero-order, first-order and α–order absorption

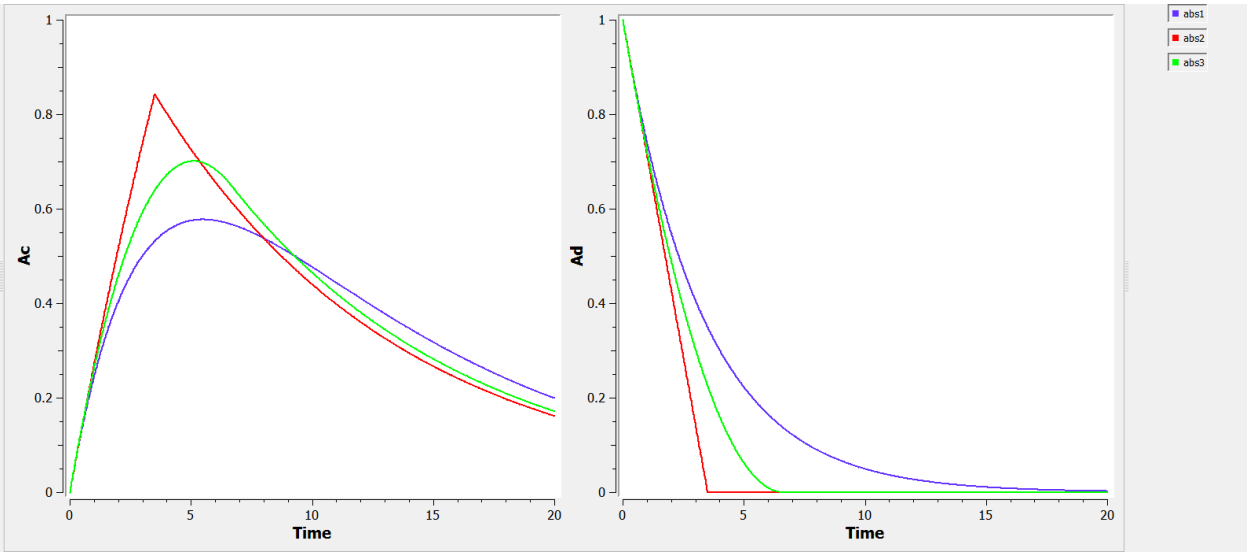
absorption2b_script: we compute and display the amounts in the central and depot compartments when the drug is transferred from the depot to the central compartment with a first-order, zero-order or α–order absorption process.

Note that an α–order absorption process means that $\dot{Ad}(t) = -ka \times Ad^{\alpha}(t)$. Zero-order absorption is obtained with α=0 and first-order absorption with α=1.

```
<MODEL>
file='model/absorption2b_model.txt'

;----------------------------
<DESIGN>
[ADMINISTRATION]
abs1={time=0, amount=1, type=1}
abs2={time=0, amount=1, type=2}
abs3={time=0, amount=1, type=3}

;----------------------------
<PARAMETER>
ka=0.3
alpha=0.5
Tk0=3.5
k=0.1

;----------------------------
<OUTPUT>
list={Ad, Ac}
grid=0:0.02:20
```

```
[PREDICTION]
input={ka,alpha,Tk0,k}

PK:
compartment(cmt=1,amount=Ac)
oral(type=1,cmt=1,ka)
oral(type=2,cmt=1,Tk0)
depot(type=3,target=Ad3)


compartment(cmt=2,amount=Ac0)
oral(type=1,cmt=2,ka)
oral(type=2,cmt=2,Tk0)

EQUATION:
ar=ka*(max(Ad3,0)^alpha)
ddt_Ad3 = -ar

er=k*Ac
ddt_Ac = ar  - er

ddt_Ac0 = ar
Ad=max(amtDose-Ac0, 0)
```

The blue, red and green curves are obtained respectively with first-order, zero-order and α–order absorption processes.



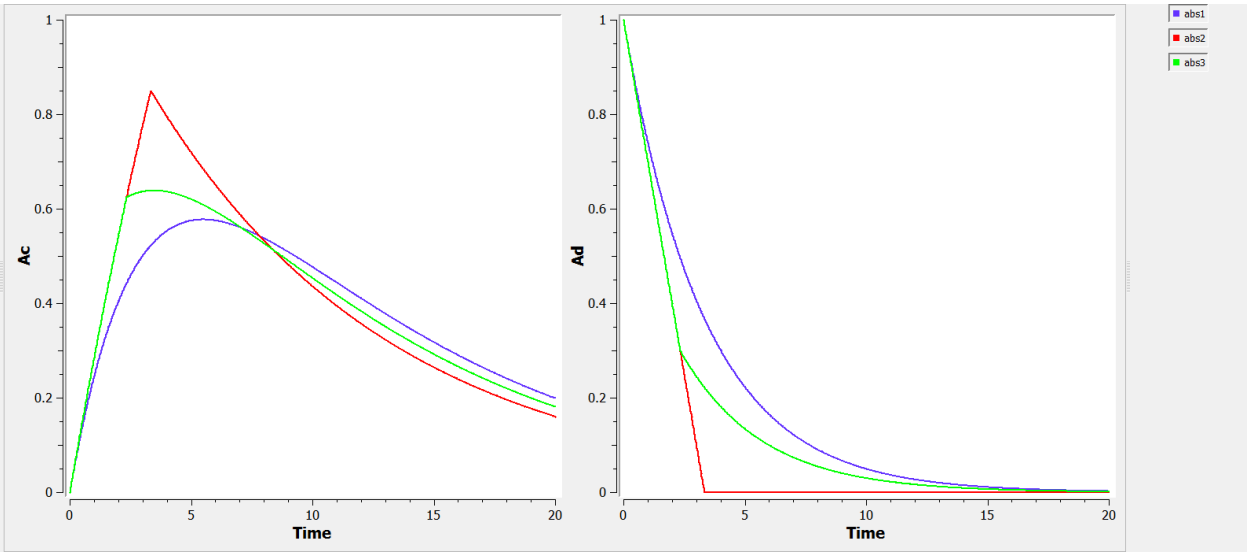
3) First-order, zero-order and sequential zero-order/first-order absorption

absorption3b_script: we compute and display the amounts in the central and depot compartments when the drug is transferred from the depot to the central compartment with a first-order, zero-order or sequential zero-order/first-order absorption process.

```
<MODEL>
file='model/absorption3b_model.txt'

;-------------------------------
<DESIGN>
[ADMINISTRATION]
abs1={time=0, amount=1, type=1}
abs2={time=0, amount=1, type=2}
abs3={time=0, amount=1, type=3}

;-------------------------------
<PARAMETER>
ka=0.3
alpha=0.5
r0=0.3
F0=0.7
k=0.1

;-------------------------------
<OUTPUT>
list={Ad, Ac}
grid=0:0.02:20
```

```
[PREDICTION]
input={ka,alpha,r0,F0,k}

PK:
tk01=amtDose/r0
tk02=F0*amtDose/r0
compartment(cmt=1,amount=Ac)
oral(type=1,cmt=1,ka)
oral(type=2,cmt=1,Tk0=tk01)
oral(type=3,cmt=1,Tk0=tk02,p=F0)
oral(type=3,cmt=1,ka,p=1-F0,Tlag=tk02)
elimination(cmt=1,k)

compartment(cmt=2,amount=Ac0)
oral(type=1,cmt=2,ka)
oral(type=2,cmt=2,Tk0=tk01)
oral(type=3,cmt=2,Tk0=tk02,p=F0)
oral(type=3,cmt=2,ka,p=1-F0,Tlag=tk02)


EQUATION:
Ad=max(amtDose-Ac0,0)
```

The blue, red and green curves are obtained respectively with first-order, zero-order and sequential zero-order/first-order absorption processes.



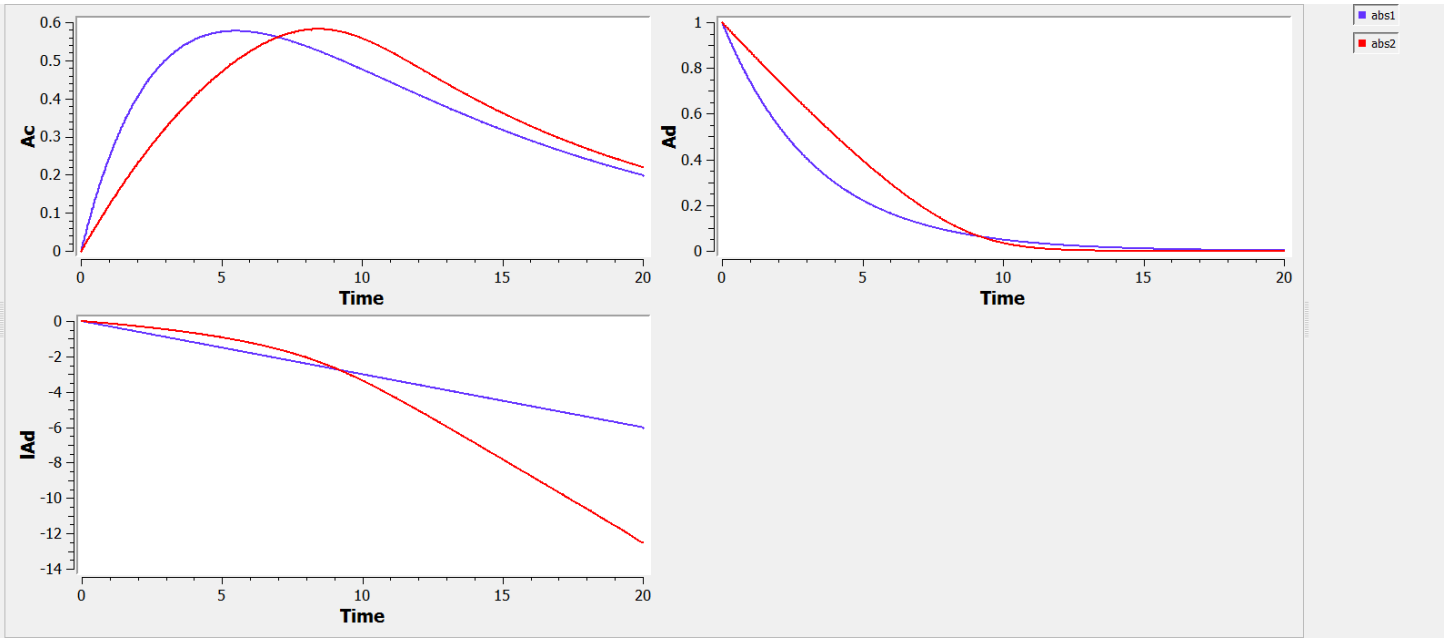
4) First-order and saturated absorption

absorption4b_script: we compute and display the amounts in the central and depot compartments when the drug is transferred from the depot to the central compartment with a first-order or saturated (Michaelis-Mentens) absorption process.

```
<MODEL>
file='model/absorption4b_model.txt'

;--------------------------------
<DESIGN>
[ADMINISTRATION]
abs1={time=0, amount=1, type=1}
abs2={time=0, amount=1, type=2}

;--------------------------------
<PARAMETER>
ka=0.3
Vma=0.15
VKma=0.16
k=0.1

;--------------------------------
<OUTPUT>
list={Ad, Ac,lAd}
grid=0:0.02:20
```

```
[PREDICTION]
input={ka,Vma,VKma,k}

PK:
depot(type=1,target=Ad1)
depot(type=2,target=Ad2)

EQUATION:
ar1 = ka*Ad1
ar2=Vma*Ad2/(VKma+Ad2)
er=k*Ac

ddt_Ad1 = -ar1
ddt_Ad2 = -ar2
ddt_Ac = ar1 + ar2   - er

Ad=Ad1+Ad2
lAd=log(Ad)
```

The red curve is now for the saturated absorption process. The log plot (*lAd vs Time*) shows that the log of the amount in the depot department *lAd* decreases linearly for first-order absorption but not for saturated absorption.



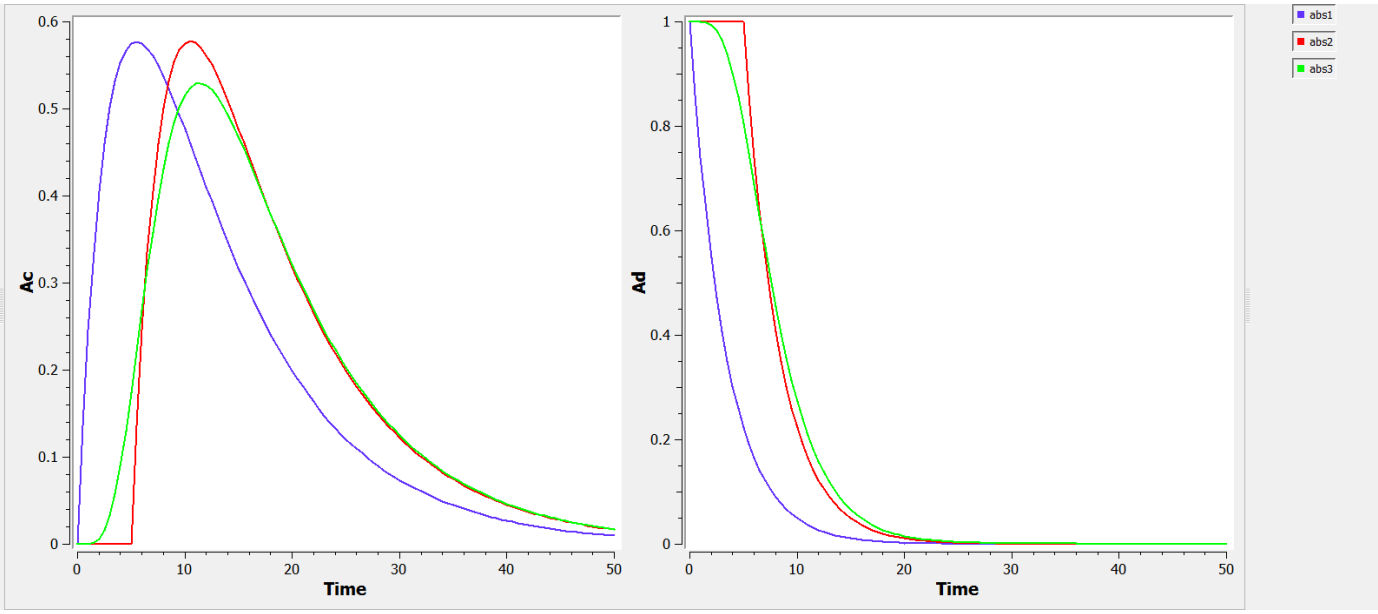
5) Lag-time and transit compartments

absorption5b_script: we compute and display the amounts in the central and depot compartments when a lag time or transit compartment model is used.

```
<MODEL>
file='model/absorption5b_model.txt'

;----------------------------
<DESIGN>
[ADMINISTRATION]
abs1={time=0, amount=1, type=1}
abs2={time=0, amount=1, type=2}
abs3={time=0, amount=1, type=3}

;----------------------------
<PARAMETER>
ka=0.3
Tlag=5
Mtt=5
Ktr=1
k=0.1

;----------------------------
<OUTPUT>
list={Ac,Ad}
grid=0:0.5:50
```

```
[PREDICTION]
input={Tlag,ka,Mtt,Ktr,k}

PK:
compartment(cmt=1,amount=Ac)
oral(type=1,cmt=1,ka)
oral(type=2,cmt=1,ka,Tlag)
oral(type=3,cmt=1,ka,Mtt,Ktr)
elimination(cmt=1,k)

compartment(cmt=2,amount=Ac0)
oral(type=1,cmt=2,ka)
oral(type=2,cmt=2,ka,Tlag)
oral(type=3,cmt=2,ka,Mtt,Ktr)

EQUATION:
Ad=amtDose-Ac0
```

Here, the blue curves are for first-order absorption without lag-time, red curves for the lag-time model and green for the transit compartment model. The number of transit compartments is *Ntr=Mtt/Ktr*. When *Mtt=Tlag*, the transit compartment model compartment can be seen as a smooth version of the lag-time model. It converges to the lag-time model when the number of compartments increases (i.e., when the transfer rate constant *Ktr* increases).



6) Summary

absorption6b_script: we compute and display the amounts in the central and depot compartments for the various absorption models presented in the previous examples.

```
<MODEL>
file='model/absorption6b_model.txt'

;--------------------------------
<DESIGN>
[ADMINISTRATION]
abs1={time=0, amount=1, type=1}
abs2={time=0, amount=1, type=2}
abs3={time=0, amount=1, type=3}
abs4={time=0, amount=1, type=4}
abs5={time=0, amount=1, type=5}

;--------------------------------
<PARAMETER>
ka=0.3
alpha=0.5
r0=0.3
Vma=0.2
VKma=0.1
F0=0.5
k=0.1

;--------------------------------
<OUTPUT>
list={Ad, Ac}
grid=0:0.02:20
```

```
[PREDICTION]
input={ka,alpha,Vma,VKma,r0,F0,k}

PK:
tk01=amtDose/r0
tk02=F0*amtDose/r0
compartment(cmt=1,amount=Ac)
depot(type=1,target=Ad1)
depot(type=2,target=Ad2)
depot(type=3,target=Ad3)
oral(type=4,cmt=1,Tk0=tk01)
oral(type=5,cmt=1,Tk0=tk02,p=F0)
oral(type=5,cmt=1,ka,p=1-F0,Tlag=tk02)

compartment(cmt=2,amount=Ac0)
oral(type=4,cmt=2,Tk0=tk01)
oral(type=5,cmt=2,Tk0=tk02,p=F0)
oral(type=5,cmt=2,ka,p=1-F0,Tlag=tk02)

EQUATION:
ar1 = ka*Ad1
ar2=ka*(max(Ad2,0)^alpha)
ar3=Vma*Ad3/(VKma+Ad3)
er=k*Ac

ddt_Ad1 = -ar1
ddt_Ad2 = -ar2
ddt_Ad3 = -ar3
ddt_Ac = ar1 + ar2 +ar3  - er

ddt_Ac0 = ar1 + ar2 +ar3
Ad=max(amtDose-Ac0,0)
```

In the figure below, abs1 is first-order absorption, abs2 is α-order absorption, abs3 is saturated absorption, abs4 is zero-order absorption and abs5 is sequential zero-order/first-order absorption.