# *MONOLIX 4.3*

## Model description with MLXTRAN

*The following slidedeck provides a tutorial on how to easily describe simple and complex pharmacometric models, including PK, PK-PD and discrete data models, using the MLXTRAN language included in MONOLIX 4.3.*

# *MONOLIX 4.3*

# Model description with MLXTRAN

# MONOLIX 4.3

## MLXTRAN

## 1. Introduction to MLXTRAN

**DESCRIPTION:**
Example of model defined with a system of ODEs

**INPUT:**
parameter = {D, ka, kb}
regressor = {x1, x2}

**EQUATION:**
A_0 = D
t_0 = 0
ddt_A = -ka*A + x1
ddt_B = ka*A - kb*B +x2

**OUTPUT:**
output = {A, B}

**DESCRIPTION:**
Exponential decay model
Analytical solution

$$\text{if } t \leq 0, \quad A = D$$

$$\text{if } t > 0, \quad A = De^{-k \times t}$$

Use the block **DESCRIPTION** to comment the model

**DESCRIPTION:**
Exponential decay model
Analytical solution

**INPUT:**
parameter = {D, k}

$$\text{if } t \le 0, \quad A = D$$

$$\text{if } t > 0, \quad A = De^{-k \times t}$$

Block **INPUT** is used to define

– the list of parameters $\psi$. Here, $\psi = (D, k)$ .

– the list of additional regression variables $x(t)$.
Here, there is no additional regression variables ($t$ is the only regression variable).

LIXOFT

**DESCRIPTION:**
Exponential decay model
Analytical solution

**INPUT:**
parameter = {D, k}

**EQUATION:**

```
if t <= 0
   A = D
else
   A = D*exp(—k*t)
end
```

$$\text{if } t \le 0, \quad A = D$$

$$\text{if } t > 0, \quad A = De^{-k \times t}$$

Block **EQUATION** is used to describe the mathematical model

By default, time **t** is the primary regressor,

**t** is a reserved keyword that can be used in the model.

**DESCRIPTION:**
Exponential decay model
Analytical solution

**INPUT:**
parameter = {D, k}

**EQUATION:**
```
if t <= 0
   A = D
else
   A = D*exp(—k*t)
end
```

**OUTPUT:**
output = A

$$\text{if } t \le 0, \quad A = D$$

$$\text{if } t > 0, \quad A = De^{-k \times t}$$

Block **OUTPUT** is used to define the output of the model.

**DESCRIPTION:**
Exponential decay model
ODE solution

**INPUT:**
parameter = {D, k}

**EQUATION:**
t0 = 0
A_0 = D
ddt_A = -k*A

**OUTPUT:**
output = A

$$\text{if } t \leq 0,$$

$$A = D$$

$$\text{if } t > 0,$$

$$\frac{dA(t)}{dt} = -k \times A(t)$$

Ordinary differential equations (ODEs) can be introduced in the block **EQUATION :**

**ddt_A** is the derivative of **A** with respect to time ***t***.

**A_0** is the initial value of the system, *i.e.* the value of **A** at time **t0** (**A** is constant before **t0**).

If **A_0** is not specified, then **A_0** = 0.

If **t0** is not specified, then **t0** is the first time **A** is computed.

**DESCRIPTION:**

Population growth with delayed impact of resource limitation

**INPUT:**

parameter = {b, r, tau, K}

**EQUATION:**

t0 = 0

A_0 = b

ddt_A = r * A * (1-delay(A, tau)/K)

**OUTPUT:**

output = A

$$\text{if } t \le 0,$$

$$A = b$$

$$\text{if } t \ge 0,$$

$$\frac{dA(t)}{dt} = r \times A(t) \times (1 - A(t-\tau)/K)$$

Delayed differential equations (DDEs) can be defined. The keyword **delay** introduces delays for some components of the system. A specific solver is set for DDEs, so **odeType** is not required.

Here, **A_0** is the value of **A** between **t0-tau** and **t0**. **A_0** can be either a constant or a function of tim

**DESCRIPTION:**
ODEs defined model

**INPUT:**
parameter = {D, ka, kb}

**EQUATION:**
t0 = 0
A_0 = D
ddt_A = -ka*A
ddt_B = ka*A - kb*B
odeType = stiff

**OUTPUT:**
output = B

$$\text{if } t \le 0,$$

$$A = D$$

$$B = 0$$

$$\text{if } t \ge 0,$$

$$\frac{dA(t)}{dt} = -k_a \times A(t)$$

$$\frac{dB(t)}{dt} = k_a \times A(t) - k_b \times B(t)$$

A system of several ODE's can be introduced in the block **EQUATION.**

The solver for the ODE system is set using **odeType.** If **odeType** is not specified, the solver for non-stiff ODE systems is set.

**DESCRIPTION:**
ODEs defined model

**INPUT:**
parameter = {D, ka, kb}
regressor = x

**EQUATION:**
t0 = 0
A_0 = D
ddt_A = -ka*A + x
ddt_B = ka*A - kb*B

**OUTPUT:**
output = B

$$\text{if } t \le 0,$$

$$A = D$$

$$B = 0$$

$$\text{if } t \ge 0,$$

$$\frac{dA(t)}{dt} = -k_a \times A(t) + x(t)$$

$$\frac{dB(t)}{dt} = k_a \times A(t) - k_b \times B(t)$$

Additional regression variables can be defined in the block **INPUT,**

By definition, a regressor ***x=x(t)*** is a time-varying variable.

**DESCRIPTION:**
Example of model defined with a system of ODEs

**INPUT:**
parameter = {D, ka, kb}
regressor = {x1, x2}

**EQUATION:**
t0 = 0
A_0 = D
ddt_A = -ka*A + x1
ddt_B = ka*A - kb*B +x2

**OUTPUT:**
output = {A, B}

if $t \leq 0$,

$$A = D$$

$$B = 0$$

if $t \geq 0$,

$$\frac{dA(t)}{dt} = -k_a \times A(t) + x_1(t)$$

$$\frac{dB(t)}{dt} = k_a \times A(t) - k_b \times B(t) + x_2(t)$$

Several regressors can be defined in the block **INPUT.**

Several outputs can be defined in the block **OUTPUT.**

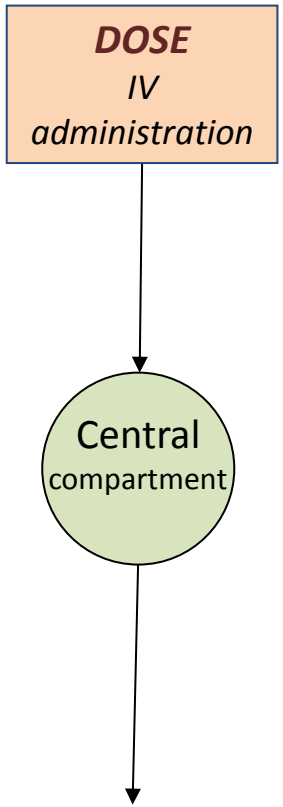
# MONOLIX 4.3

# MLXTRAN

## 2. MLXTRAN for PK models

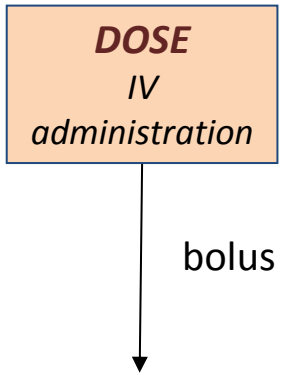
### 2.1 IV administration





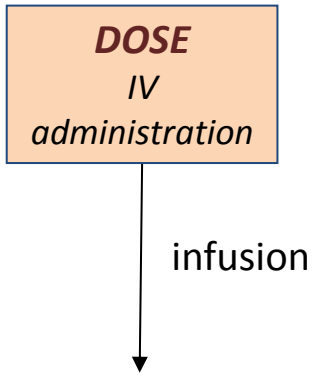
# *The data file*

| ID | TIME | AMT | Y |
|---|---|---|---|
| 1 | 0 | 500 | . |
| 1 | 2 | . | 44.6 |
| 1 | 6 | . | 37 |
| 1 | 12 | . | 16.1 |
| 1 | 18 | . | 14.2 |
| 1 | 24 | . | 6.79 |
| 2 | 0 | 500 | . |
| 2 | 2 | . | 48.6 |
| 2 | 6 | . | 37.6 |
| 2 | 12 | . | 20.2 |
| 2 | 18 | . | 6.09 |
| 2 | 24 | . | 4.34 |
| 3 | 0 | 500 | . |
| 3 | 2 | . | 56.3 |
| 3 | 6 | . | 29.6 |
| 3 | 12 | . | 16.9 |
| 3 | 18 | . | 7.96 |
| 3 | 24 | . | 2.71 |




If there is no RATE (or TINF) column in the data, then administration is assumed to be an IV bolus

| ID | TIME | AMT | RATE | Y |
|---|---|---|---|---|
| 1 | 0 | 500 | 200 | . |
| 1 | 2 | . | . | 34 |
| 1 | 6 | . | . | 38.2 |
| 1 | 12 | . | . | 23.6 |
| 1 | 18 | . | . | 24.9 |
| 1 | 24 | . | . | 13.3 |
| 2 | 0 | 500 | 200 | . |
| 2 | 2 | . | . | 17 |
| 2 | 6 | . | . | 16.9 |
| 2 | 12 | . | . | 5.39 |
| 2 | 18 | . | . | 1.63 |
| 2 | 24 | . | . | 0.35 |
| 3 | 0 | 500 | 200 | . |
| 3 | 2 | . | . | 48.7 |
| 3 | 6 | . | . | 41.2 |
| 3 | 12 | . | . | 14.5 |
| 3 | 18 | . | . | 6.32 |
| 3 | 24 | . | . | 4.42 |



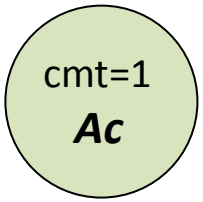

If there is a RATE (or TINF) column in the data, then administration is assumed to be an IV infusion

# *The PK macros*

**DESCRIPTION:**
PK model, IV administration,
linear elimination, parameters (V, k)

**INPUT:**
parameter = {V, k}

**PK:**
compartment(cmt=1, amount=Ac)



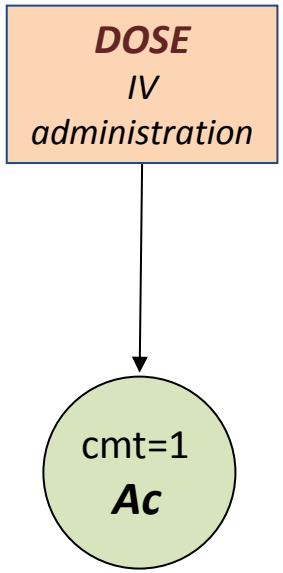

Block **PK** is used to define the PK model, using macros with unordered named arguments

– **compartment(cmt=1, amount=Ac)** creates a compartment 1 which amount is ***Ac***,

**DESCRIPTION:**
PK model, IV administration,
linear elimination, parameters (V, k)

**INPUT:**
parameter = {V, k}

**PK:**
compartment(cmt=1, amount=Ac)
iv(cmt=1)



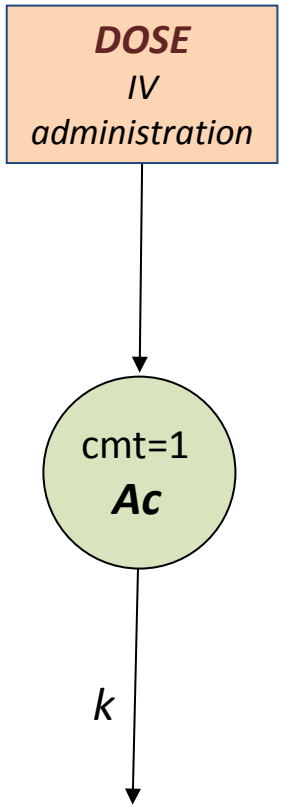

Block **PK** is used to define the PK model, using macros with unordered named arguments

- **compartment(cmt=1, amount=Ac)** creates a compartment 1 which amount is ***Ac***,
- **iv(cmt=1)** means an IV (bolus or infusion, according to the data) administration in compartment 1

**DESCRIPTION:**
PK model, IV administration,
linear elimination, parameters (V, k)

**INPUT:**
parameter = {V, k}

**PK:**
compartment(cmt=1, amount=Ac)
iv(cmt=1)
elimination(cmt=1, k)



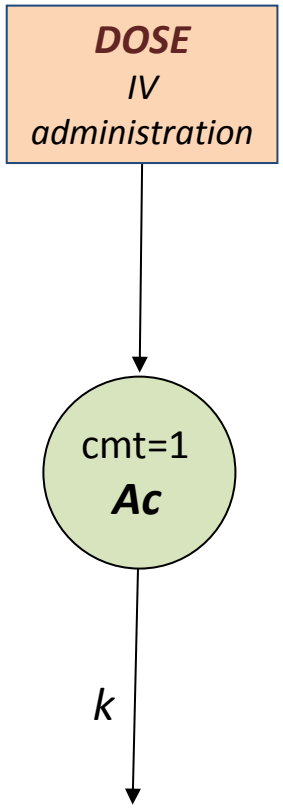

Block **PK** is used to define the PK model, using macros with unordered named arguments

- **compartment(cmt=1, amount=Ac)** creates a compartment 1 which amount is ***Ac***,
- **iv(cmt=1)** means an IV (bolus or infusion, according to the data) administration in compartment 1
- **elimination(cmt=1, k)** defines a linear elimination from compartment 1 with rate constant ***k***

**DESCRIPTION:**
PK model, IV administration,
linear elimination, parameters (V, k)

**INPUT:**
parameter = {V, k}

**PK:**
compartment(cmt=1, amount=Ac)
iv(cmt=1)
elimination(cmt=1, k)
Cc = Ac/V



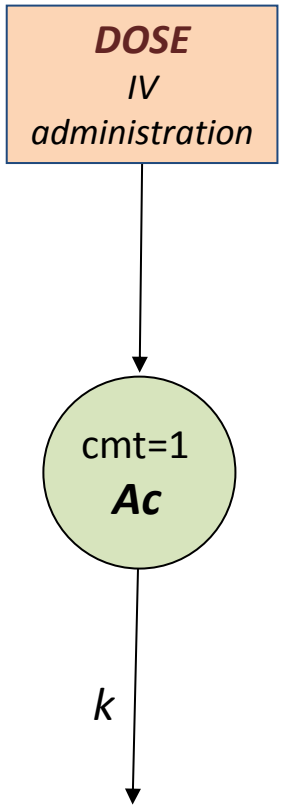

**Cc = Ac/V** computes the concentration **Cc** in compartment 1

**DESCRIPTION:**
PK model, IV administration,
linear elimination, parameters (V, k)

**INPUT:**
parameter = {V, k}

**PK:**
compartment(cmt=1, amount=Ac)
iv(cmt=1)
elimination(cmt=1, k)
Cc = Ac/V

**OUTPUT:**
output = Cc




Block **OUTPUT** is used to define the outputs of the model

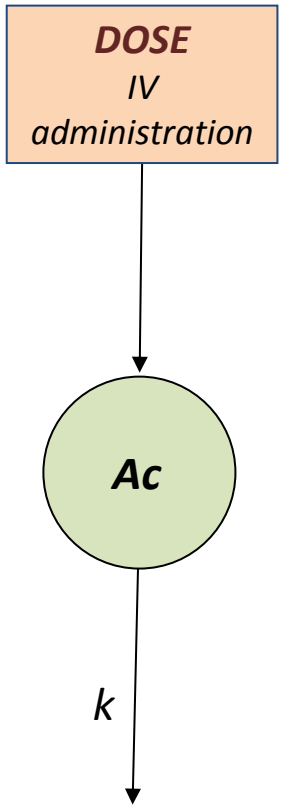
Here, **output = Cc** defines the predicted concentration **Cc** as the only output of the model.

**DESCRIPTION:**
PK model, IV administration,
linear elimination, parameters (V, k)

**INPUT:**
parameter = {V, k}

**PK:**
compartment(amount=Ac)
iv()
elimination(k)
Cc = Ac/V

**OUTPUT:**
output = Cc




When the number of the compartment is not specified, **cmt=1** is assumed by default.

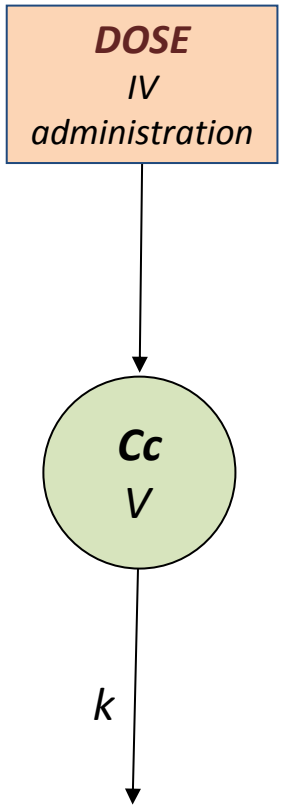
There is only one compartment here. Then, the default can be used and the number of the compartment can be ommited.

**DESCRIPTION:**
PK model, IV administration,
linear elimination, parameters (V, k)

**INPUT:**
parameter = {V, k}

**PK:**
compartment(cmt=1,concentration=Cc, volume=V)
iv(cmt=1)
elimination(cmt=1,k)

**OUTPUT:**
output = Cc




Concentration **Cc** in compartment **1** can be defined in PK macro **compartment** instead of the amount ***Ac***.

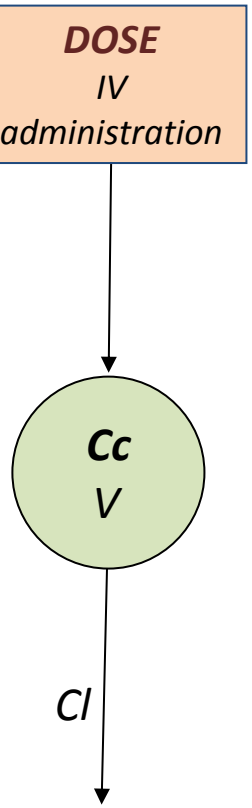
In this case, the volume of the compartment is required.

**DESCRIPTION:**
PK model, IV administration,
linear elimination, parameters (V, Cl)

**INPUT:**
parameter = {V, Cl}

**PK:**
compartment(cmt=1,concentration=Cc, volume=V)
iv(cmt=1)
elimination(cmt=1, Cl)

**OUTPUT:**
output = Cc




Several parametrizations can be used.

Here, clearance ***Cl*** is used instead of the elimination rate constant ***k***,

PK macro **elimination** accepts the parametrization with ***Cl*** instead of ***k***.

# *Combining PK macros & equations*

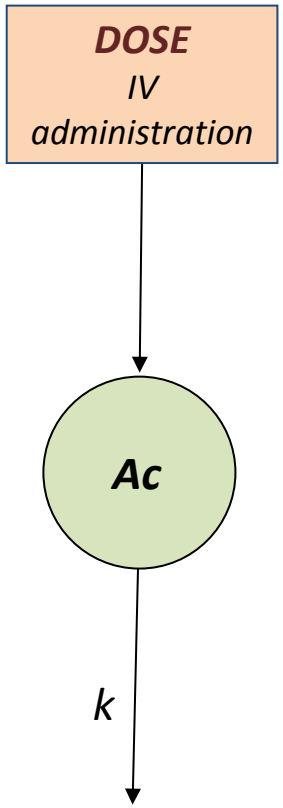
**DESCRIPTION:**
PK model, IV administration,
linear elimination, parameters (V, k)

**INPUT:**
parameter = {V, k}

**PK:**
compartment(cmt=1,amount=Ac)
iv(cmt=1)

**EQUATION:**
ddt_Ac = -k*Ac
Cc = Ac/V

**OUTPUT:**
output = Cc




Some components of the PK model can be described using equations in a block **EQUATION**.

Here, ***Ac*** is the solution of an ODE defined by **ddt_Ac = -k*Ac**

It is equivalent to define ODEs in a block **EQUATION** or PK macros in a block **PK**

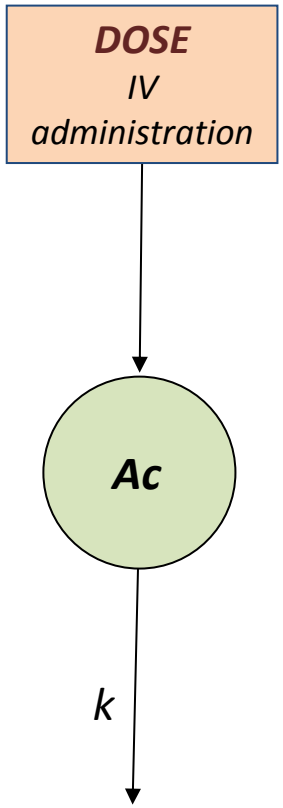
**DESCRIPTION:**
PK model, IV administration,
linear elimination, parameters (V, k)

**INPUT:**
parameter = {V, k}

**PK:**
depot(target=Ac)

**EQUATION:**
ddt_Ac = -k*Ac
Cc = Ac/V

**OUTPUT:**
output = Cc




Instead of using the PK macros **compartment** & **iv**, it is possible to consider the doses as source terms of the autonomous system defined with ODEs.

***depot(target=Ac)*** means that ***Ac*** is the target of the source term :
$Ac(tDose^{+}) = Ac(tDose^{-}) + amtDose$

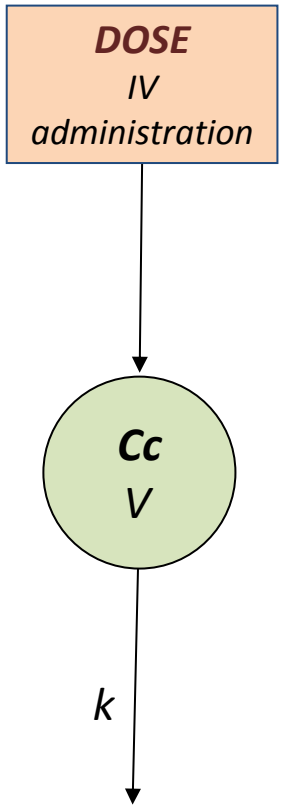
LIXOFT

**DESCRIPTION:**
PK model, IV administration,
linear elimination, parameters (V, k)

**INPUT:**
parameter = {V, k}

**EQUATION:**
deltat = t - tDose
Cc = amtDose/V*exp(-k*deltat)

**OUTPUT:**
output = Cc




The analytical expression of **Cc** for a single dose administration can be used in the block **EQUATION**,

**tDose** and **amtDose** are reserved keywords:

- **tDose** is the time of the last dose (if **tDose**=0 for all subjects, then it can be omitted).
- **amtDose** is the amount of drug administrated at time **tDose**.

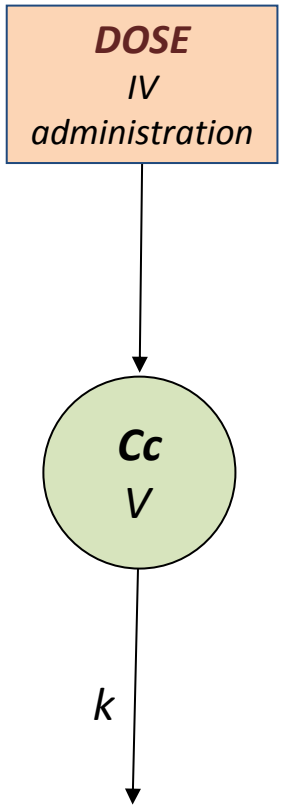
# *The* pkmodel *function*

**DESCRIPTION:**
PK model, IV administration,
linear elimination, parameters (V, k)

**INPUT:**
parameter = {V, k}

**EQUATION:**
Cc = pkmodel(V, k)

**OUTPUT:**
output = Cc




Instead of the PK macros, function **pkmodel** can be used to define most standard PK models.

The PK model is defined according to the unordered named arguments of function **pkmodel**.

Here, **pkmodel(V,k)** assumes a linear elimination with rate constant ***k.***

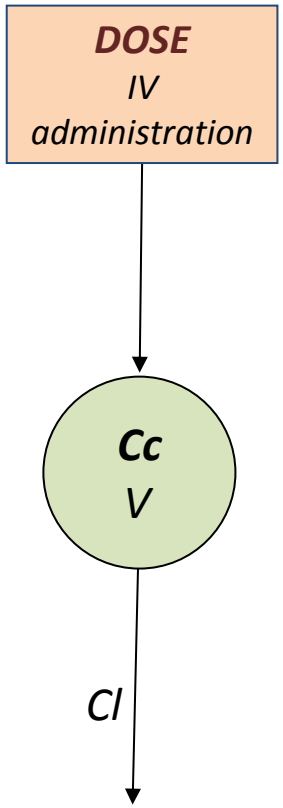
There is no parameters defining the absorption, then, an IV administration is assumed.

**DESCRIPTION:**
PK model, IV administration,
linear elimination, parameters (V, Cl)

**INPUT:**
parameter = {V, Cl}

**EQUATION:**
Cc = pkmodel(V, Cl)

**OUTPUT:**
output = Cc




Function **pkmodel** also accepts the parametrization with ***Cl*** instead of ***k***.

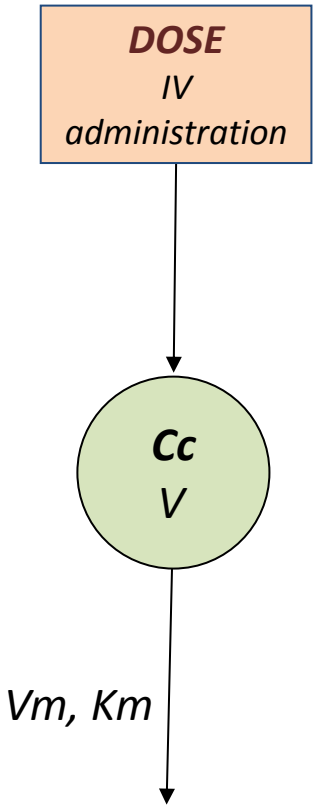
# *Non linear elimination*

**DESCRIPTION:**
PK model, IV administration,
nonlinear elimination, parameters (V, Vm, Km)

**INPUT:**
parameter = {V, Vm, Km}

**EQUATION:**
Cc = pkmodel(V, Vm, Km)

**OUTPUT:**
output = Cc



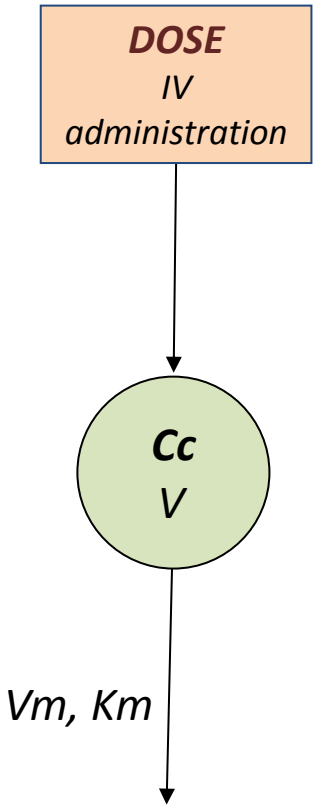

Non linear elimination can be defined using the function **pkmodel** with parameters ***Vm*** and ***Km***

**DESCRIPTION:**
PK model, IV administration,
nonlinear elimination, parameters (V, Vm, Km)

**INPUT:**
parameter = {V, Vm, Km}

**PK:**
compartment(cmt=1,concentration=Cc, volume=V)
iv(cmt=1)
elimination(cmt=1,Vm, Km)

**OUTPUT:**
output = Cc




Non linear elimination can also be defined with the PK macro **elimination** using parameters ***Vm*** and ***Km***

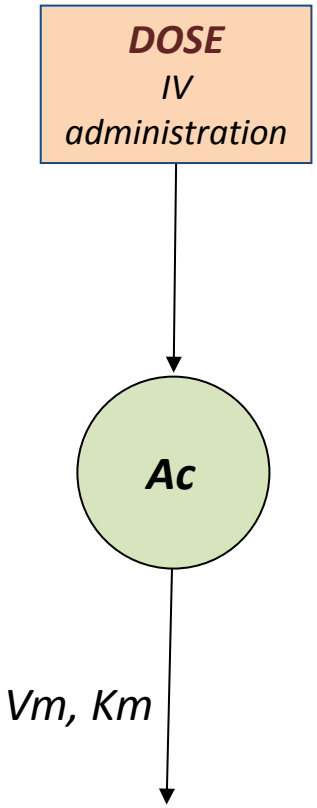
**DESCRIPTION:**
PK model, IV administration,
nonlinear elimination, parameters (V, Vm, Km)

**INPUT:**
parameter = {V, Vm, Km}

**PK:**
compartment(cmt=1,amount=Ac)
iv(cmt=1)

**EQUATION:**
ddt_Ac = -Vm*Ac/(V*Km+Ac)
Cc=Ac/V

**OUTPUT:**
output = Cc




Instead of using the PK macro **elimination**, the elimination can be defined in the block **EQUATION.**

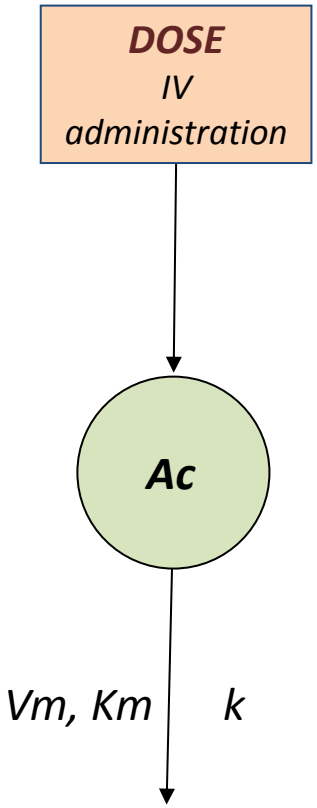
**DESCRIPTION:**
PK model, IV administration,
Combination of linear and nonlinear eliminations,

**INPUT:**
parameter = {V, Vm, Km, k}

**PK:**
compartment(cmt=1,amount=Ac)
iv(cmt=1)

**EQUATION:**
ddt_Ac = -Vm*Ac/(V*Km+Ac) - k*Ac
Cc=Ac/V

**OUTPUT:**
output = Cc




Complex user defined elimination processes that cannot be described with the PK macros should be described in the block **EQUATION.**

Here, the elimination process is a combination of linear and non linear eliminations: it is described with an ODE in the block **EQUATION.**

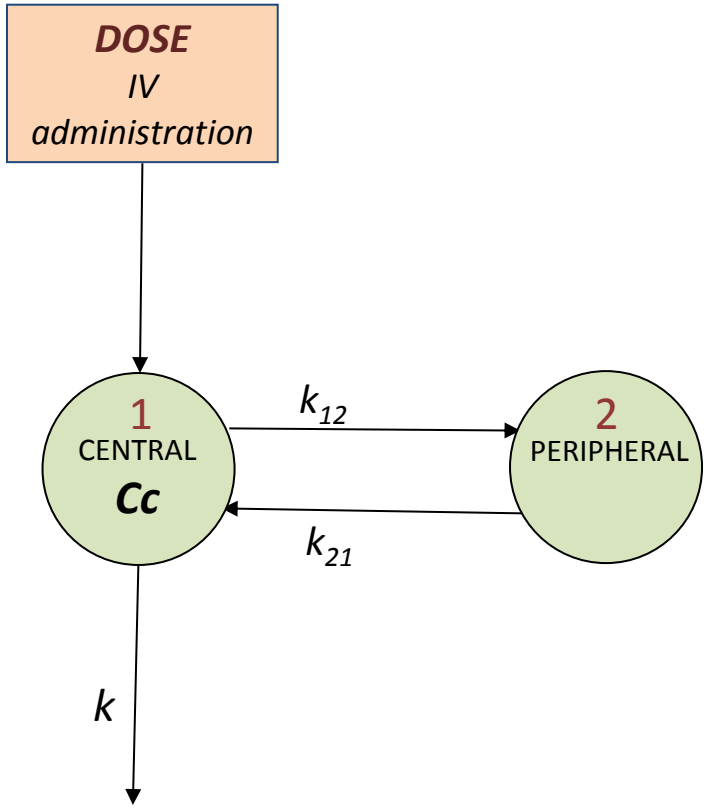
# *2 & 3 compartments models*

**DESCRIPTION:**
PK model, IV administration,
2 compartments,
linear elimination,

**INPUT:**
parameter = {V, k, k12, k21}

**EQUATION:**
Cc = pkmodel(V, k, k12, k21)

**OUTPUT:**
output = Cc



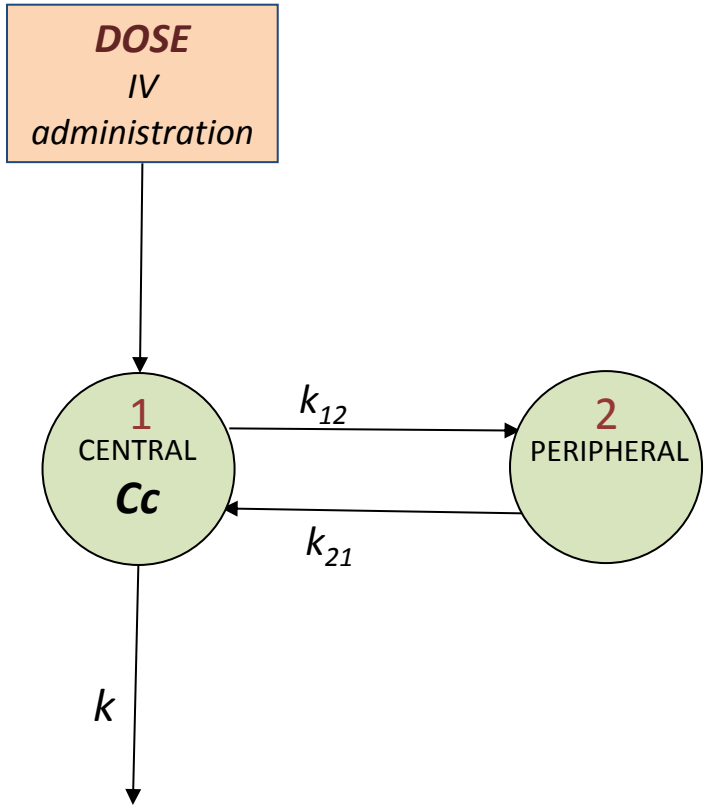

Function **pkmodel** introduces a peripheral compartment in the model when parameters ***k12*** and ***k21*** are used.

**DESCRIPTION:**
PK model, IV administration,
2 compartments,
linear elimination,

**INPUT:**
parameter = {V, k, k12, k21}

**PK:**
compartment(cmt=1,concentration=Cc, volume=V)
iv(cmt=1)
peripheral(k12, k21)
elimination(cmt=1,k)

**OUTPUT:**
output = Cc




PK macro **peripheral** can also be used to introduce a peripheral compartment in the model.

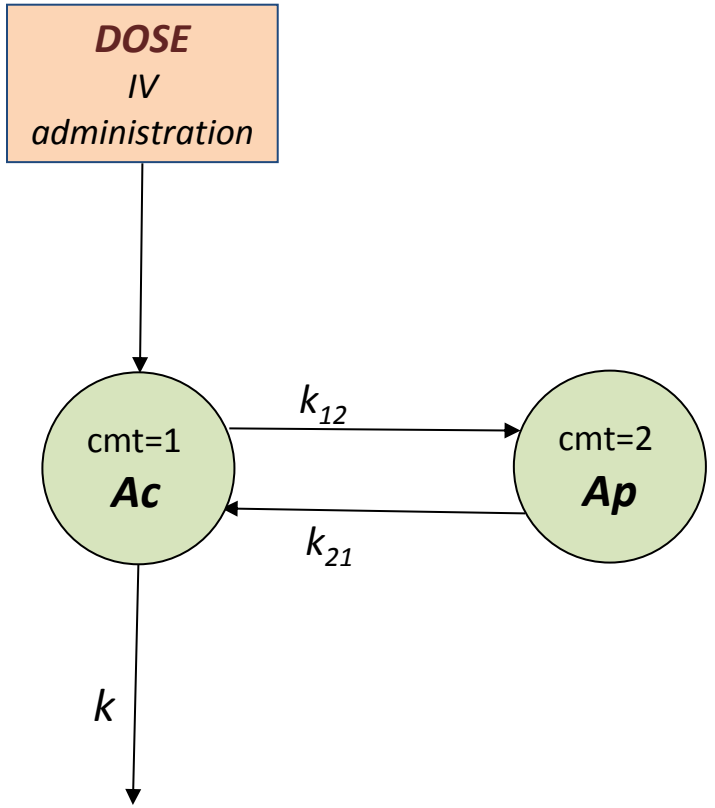
**DESCRIPTION:**
PK model, IV administration,
2 compartments,
linear elimination,

**INPUT:**
parameter = {V, k, k12, k21}

**PK:**
depot(target=Ac)

**EQUATION:**
ddt_Ac = -k12*Ac + k21*Ap - k*Ac
ddt_Ap = k12*Ac - k21*Ap
Cc = Ac/V

**OUTPUT:**
output = Cc



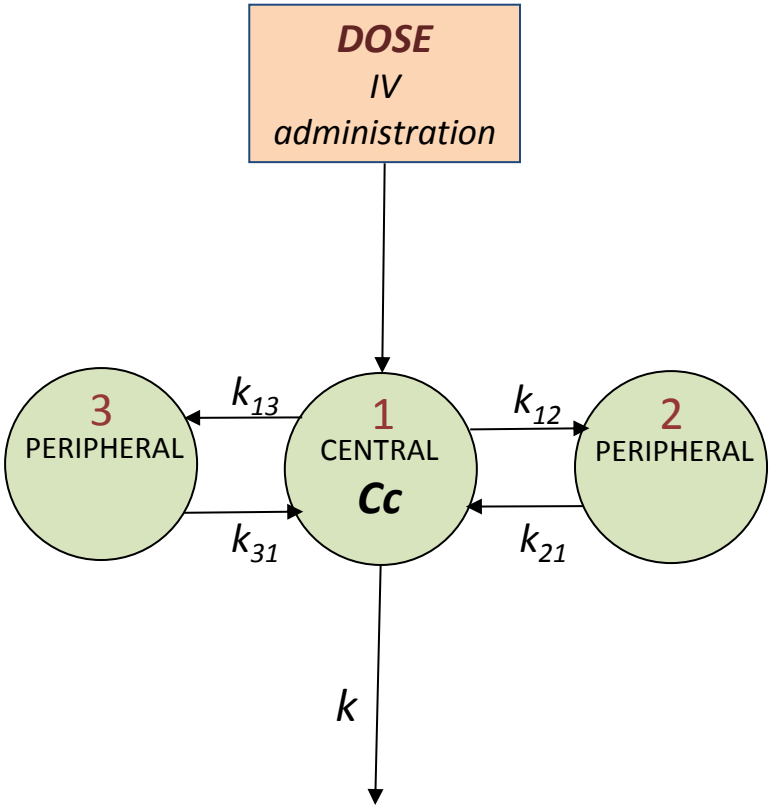

Transfers between the central and the peripheral compartments can be described with a system of (differential) equations in the block **EQUATION**.

**DESCRIPTION:**
PK model, IV administration,
3 compartments,
linear elimination,

**INPUT:**
parameter = {V, k, k12, k21, k13, k31}

**EQUATION:**
Cc = pkmodel(V, k, k12, k21, k13, k31)

**OUTPUT:**
output = Cc




Function **pkmodel** introduces two peripheral compartments in the model when parameters ***k12***, ***k21***, ***k13*** and ***k31*** are used.

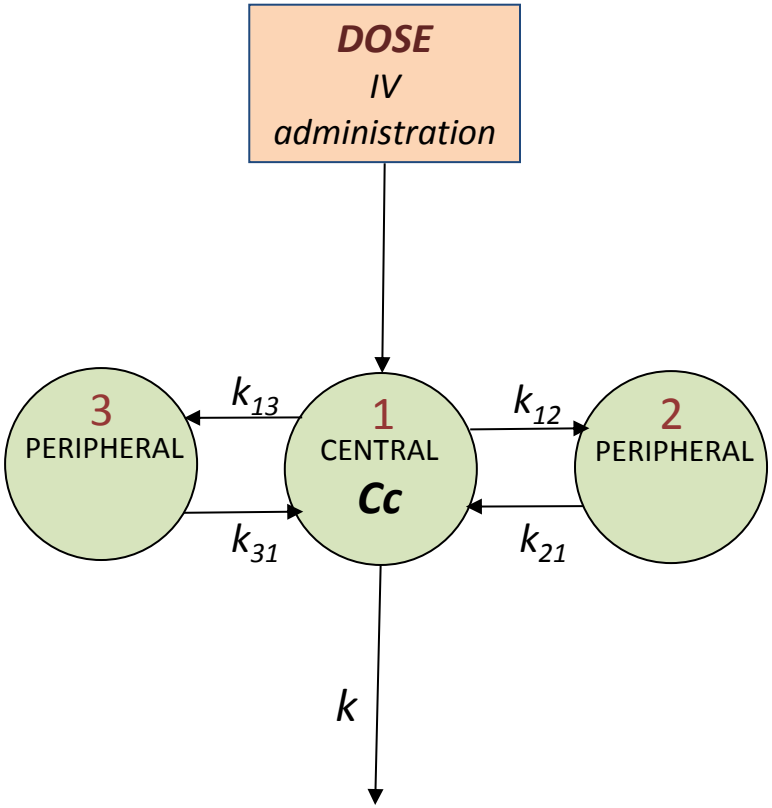
LIXOFT

**DESCRIPTION:**
PK model, IV administration,
3 compartments,
linear elimination,

**INPUT:**
parameter = {V, k, k12, k21, k13, k31}

**PK:**
compartment(cmt=1,concentration=Cc, volume=V)
iv(cmt=1)
peripheral(k12, k21)
peripheral(k13, k31)
elimination(cmt=1,k)

**OUTPUT:**
output = Cc




PK macro **peripheral** can also be used to introduce these two peripheral compartments in the model.

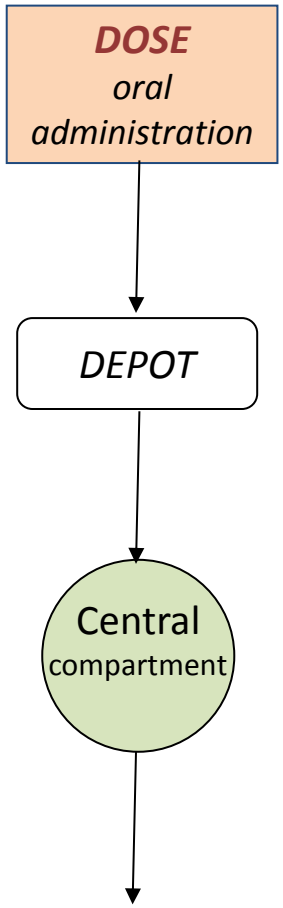
# MONOLIX 4.3

## MLXTRAN

## 2. MLXTRAN for PK models

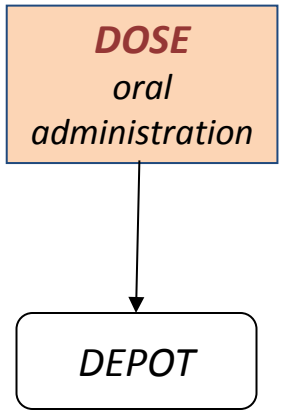
### 2.2 Oral administration





# *The data file*

| ID | TIME | AMT | Y |
|---|---|---|---|
| 1 | 0 | 500 | . |
| 1 | 2 | . | 48 |
| 1 | 6 | . | 32.8 |
| 1 | 12 | . | 18.1 |
| 1 | 18 | . | 6.46 |
| 1 | 24 | . | 3.06 |
| 2 | 0 | 500 | . |
| 2 | 2 | . | 29.5 |
| 2 | 6 | . | 41 |
| 2 | 12 | . | 25 |
| 2 | 18 | . | 16 |
| 2 | 24 | . | 5.69 |
| 3 | 0 | 500 | . |
| 3 | 2 | . | 21.5 |
| 3 | 6 | . | 28.9 |
| 3 | 12 | . | 25.3 |
| 3 | 18 | . | 8.28 |
| 3 | 24 | . | 6.58 |




The datafile only contains information about the administration, not about the absorption process which will be described in the model.

Then, the same datafile can be used with different absorption processes (zero-order, first order, sequential zero-order & first order,… )

For a unique type of administration, a unique depot compartment is assumed. Then, only the amount and the time of administration are required in the datafile.

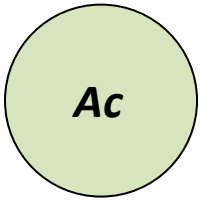
# *First order absorption process*

*6 different solutions for coding the same PK model*

**DESCRIPTION:**
PK model, oral administration, first order absorption
linear elimination, parameters (ka, V, k)
VERSION 1

**INPUT:**
parameter = {ka, V, k}

**PK:**
compartment(amount=Ac)



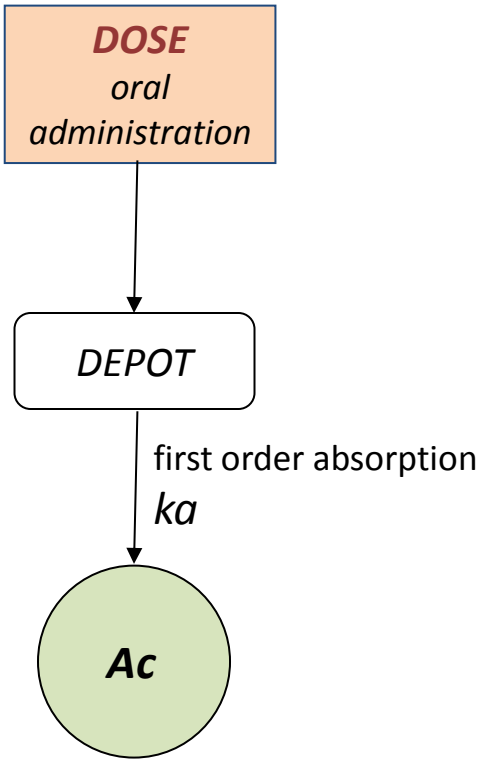

Block **PK** is used to define the PK model

– **compartment(amount=Ac)** creates a central compartment which amount is ***Ac***,

**DESCRIPTION:**
PK model, oral administration, first order absorption linear elimination, parameters (ka, V, k)
VERSION 1

**INPUT:**
parameter = {ka, V, k}

**PK:**
compartment(amount=Ac)
oral(ka)




Block **PK** is used to define the PK model

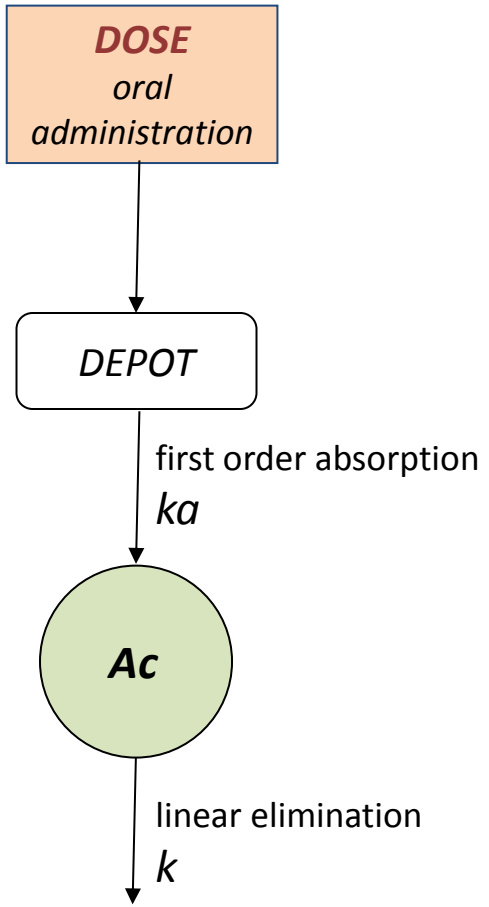
- **compartment(amount=Ac)** creates a central compartment which amount is **Ac**,
- **oral(ka)** indicates an oral administration and defines a first order absorption in the central compartment,

**DESCRIPTION:**
PK model, oral administration, first order absorption
linear elimination, parameters (ka, V, k)
VERSION 1

**INPUT:**
parameter = {ka, V, k}

**PK:**
compartment(amount=Ac)
oral(ka)
elimination(k)
Cc = Ac/V

**OUTPUT:**
output = Cc




Block **PK** is used to define the PK model

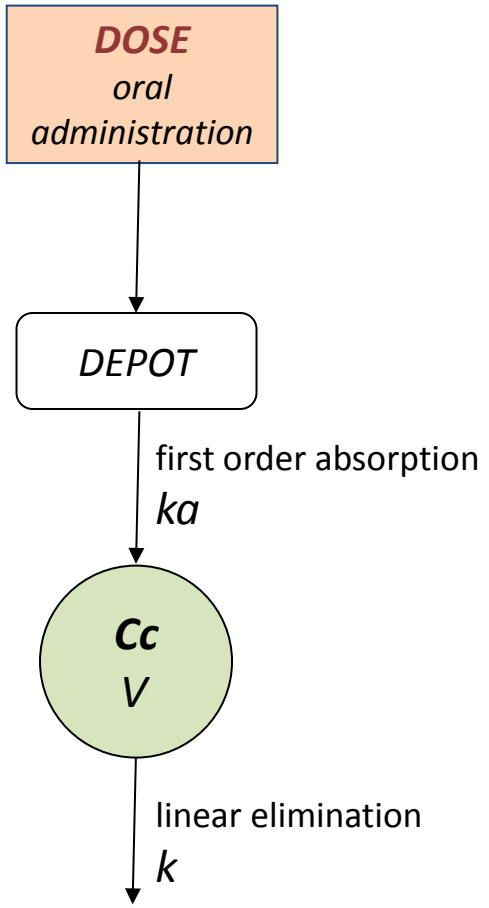
- **compartment(amount=Ac)** creates a central compartment which amount is **Ac**,
- **oral(ka)** indicates an oral administration and defines a first order absorption in the central compartment,
- **elimination(k)** defines a linear elimination from the central compartment with rate constant ***k***.

**DESCRIPTION:**
PK model, oral administration, first order absorption linear elimination, parameters (ka, V, k)
VERSION 2

**INPUT:**
parameter = {ka, V, k}

**EQUATION:**
Cc = pkmodel(ka, V, k)

**OUTPUT:**
output = Cc




Function **pkmodel** can be used to define most standard PK models.

The PK model is defined according to the arguments of function **pkmodel**.

Here, **pkmodel(ka, V, k)** assumes a first order absorption with constant rate ***ka*** and a linear elimination with rate constant ***k.***

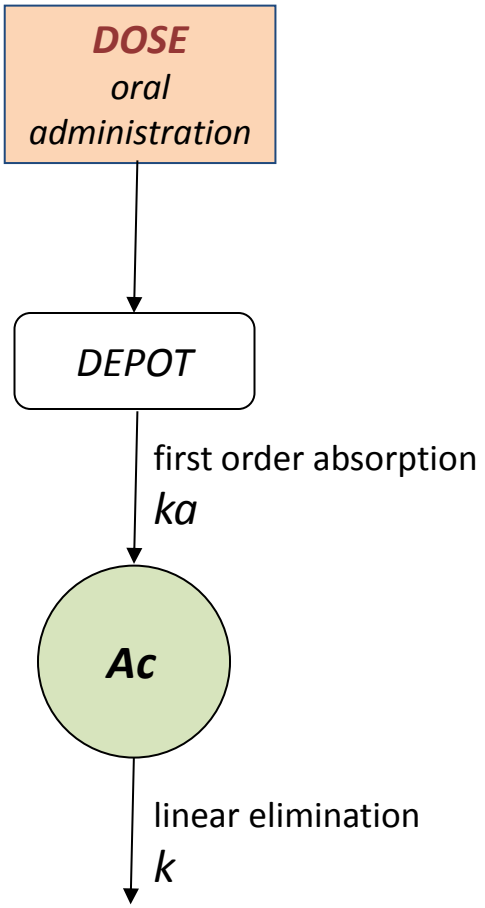
**DESCRIPTION:**
PK model, oral administration, first order absorption linear elimination, parameters (ka, V, k)
VERSION 3

**INPUT:**
parameter = {ka, V, k}

**PK:**
compartment(amount=Ac)
oral(ka)

**EQUATION:**
ddt_Ac = -k*Ac
Cc = Ac/V

**OUTPUT:**
output = Cc




Some components of the PK model can be described using equations in a block **EQUATION**.

Here,

- the absortion rate is defined by the PK macro **oral(ka)**
- the elimination rate is defined by the ODE **ddt_Ac = -k*Ac**

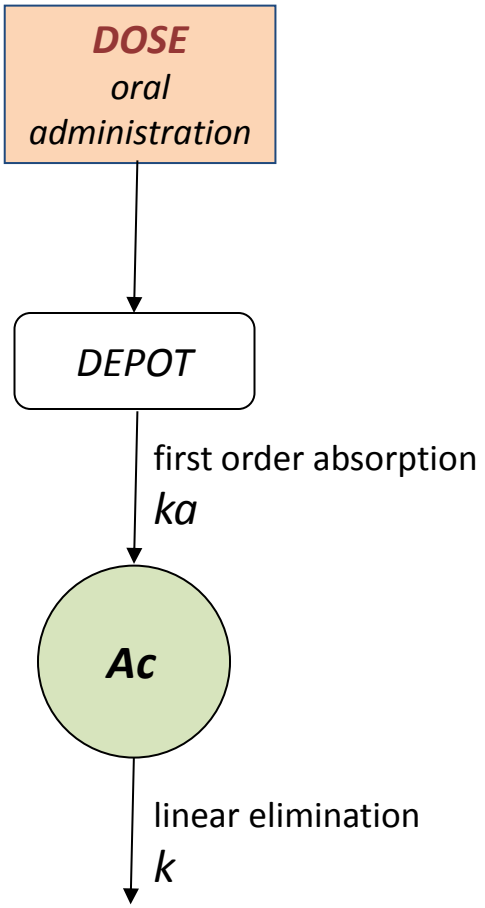
**DESCRIPTION:**
PK model, oral administration, first order absorption linear elimination, parameters (ka, V, k)
VERSION 3

**INPUT:**
parameter = {ka, V, k}

**PK:**
depot(target=Ac, ka)

**EQUATION:**
ddt_Ac = -k*Ac
Cc = Ac/V

**OUTPUT:**
output = Cc



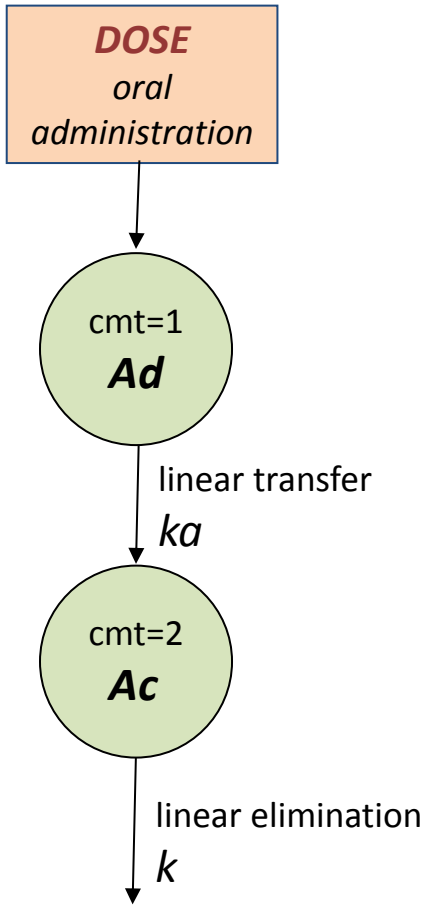

**compartment(cmt=1, amount=Ac)**
**oral(cmt=1, ka)**
and
**depot(target=Ac, ka)**
are equivalent

**DESCRIPTION:**
PK model, oral administration, first order absorption linear elimination, parameters (ka, V, k)
VERSION 4

**INPUT:**
parameter = {ka, V, k}

**PK:**
compartment(cmt=1, amount=Ad)
compartment(cmt=2, amount=Ac)
iv(cmt=1)
transfer(from=1, to=2, kt=ka)
elimination(cmt=2, k)
Cc = Ac/V

**OUTPUT:**
output = Cc




An oral administration can be described as an IV bolus in the depot compartment (cmt=1) and a linear transfer from the depot compartment (cmt=1) to the central compartment (cmt=2)

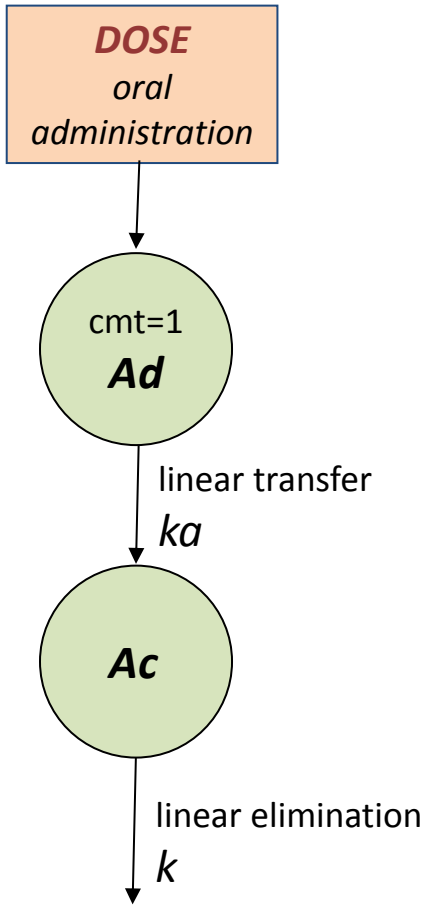
**DESCRIPTION:**
PK model, oral administration, first order absorption
linear elimination, parameters (ka, V, k)
VERSION 5

**INPUT:**
parameter = {ka, V, k}

**PK:**
compartment(cmt=1, amount=Ad)
iv(cmt=1)

**EQUATION:**
ddt_Ad = -ka*Ad
ddt_Ac = ka*Ad - k*Ac
Cc = Ac/V

**OUTPUT:**
output = Cc




Instead of using the PK macros, (differential) equations in the block **EQUATION** can be used to describe the transfer between compartments and the elimination from the central compartment.

Here, only the first compartment which receives the dose needs to be created with the PK macro **compartment.**

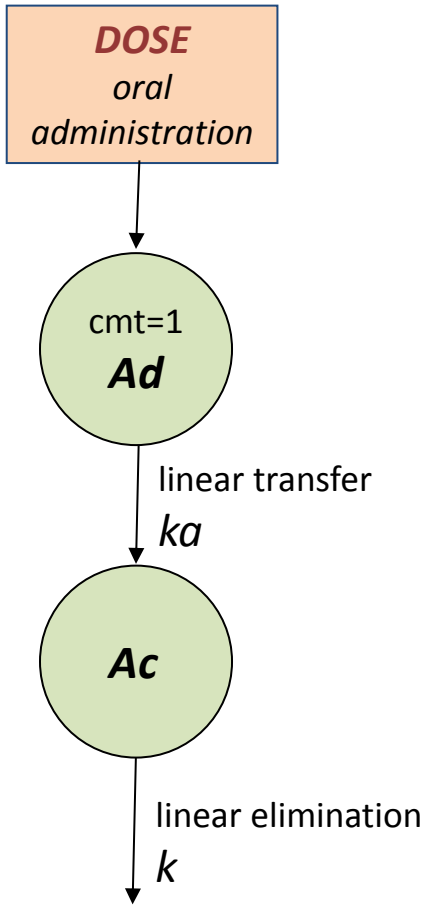
**DESCRIPTION:**
PK model, oral administration, first order absorption
linear elimination, parameters (ka, V, k)
VERSION 6

**INPUT:**
parameter = {ka, V, k}

**PK:**
depot(target=Ad)

**EQUATION:**
ddt_Ad = -ka*Ad
ddt_Ac = ka*Ad - k*Ac
Cc = Ac/V

**OUTPUT:**
output = Cc




Instead of using the PK macros **compartment** & **iv**, it is possible to consider the doses as source terms for the autonomous system defined with ODEs.

***depot(target=Ad)*** means that ***Ad*** is the target of the source term :
$Ad(tDose^{+}) = Ad(tDose^{-}) + amtDose$

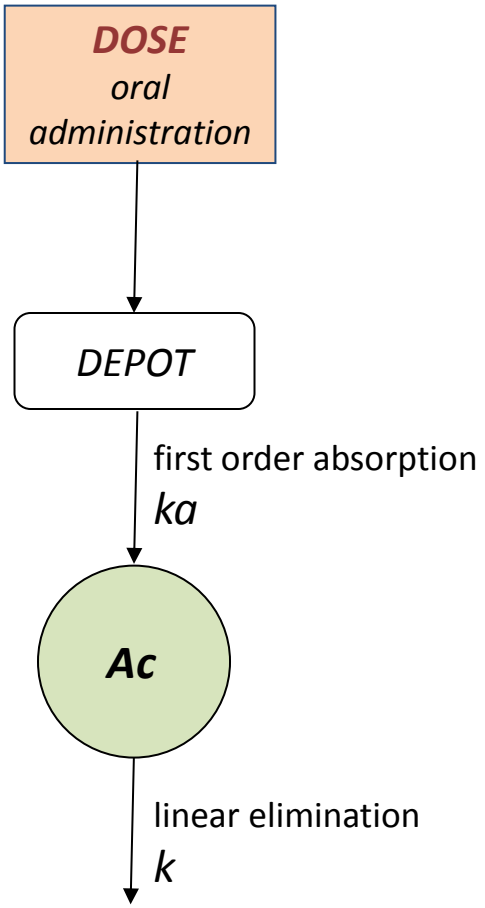
LIXOFT

**DESCRIPTION:**
PK model, oral administration, first order absorption
linear elimination, parameters (ka, V, k)
VERSION 7

**INPUT:**
parameter = {ka, V, k}

**EQUATION:**
dt = t - tDose
Cc = amtDose*ka/(V*(ka-k))*(exp(-k*dt) - exp(-ka*dt))

**OUTPUT:**
output = Cc




The analytical expression of **Cc** for a single dose administration can be used in the block **EQUATION**, **tDose** and **amtDose** are reserved keywords:

- **tDose** is the time of the last dose (if **tDose**=0 for all subjects, then it can be omitted).
- **amtDose** is the amount of drug administrated at time **tDose**.

LIXOFT

# *Some extensions:*

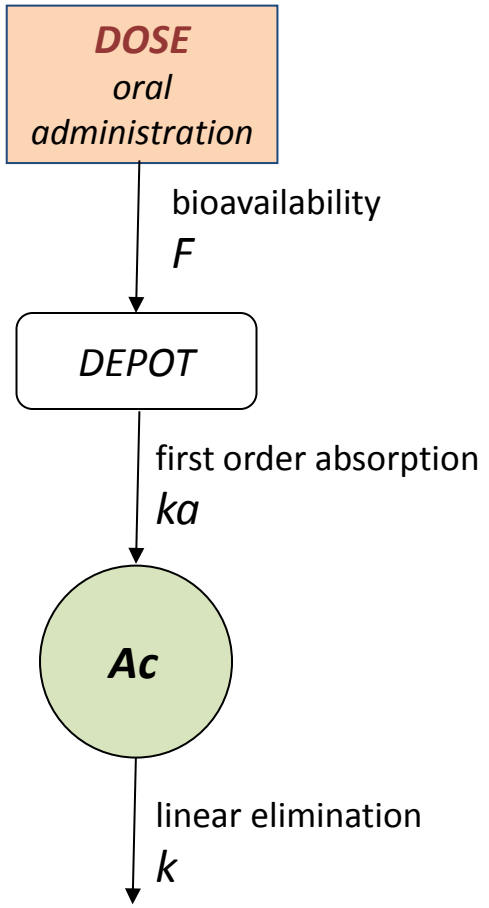
- *bioavailability*
- *lag-time*
- *transit compartment*
- *Non linear elimination*
- *Multiple compartments*

**DESCRIPTION:**
PK model, oral administration, bioavailability F, first order absorption, linear elimination,

**INPUT:**
parameter = {F, ka, V, k}

**PK:**
compartment(amount=Ac)
oral(ka, p=F)
elimination(k)
Cc = Ac/V

**OUTPUT:**
output = Cc




**p** is a reserved keyword used by the PK macro **absorption** and the function **pkmodel** to specify which fraction of the dose is absorbed.

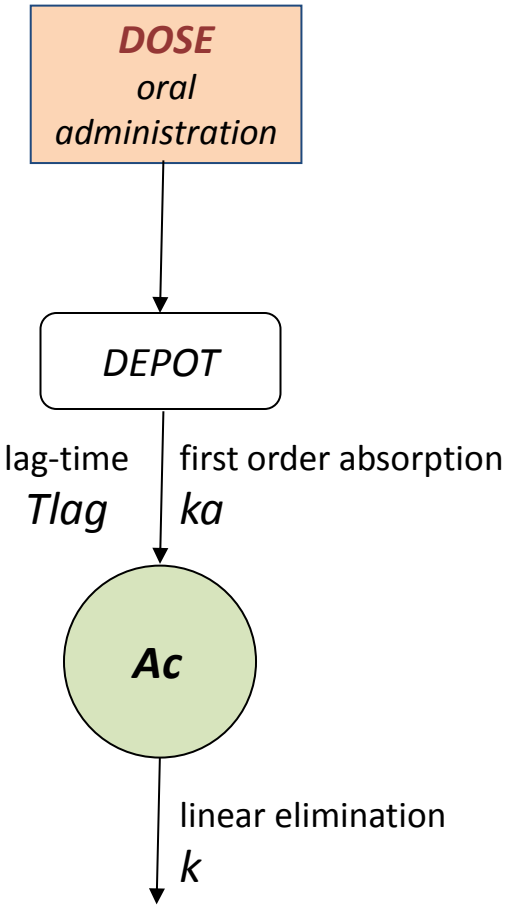
Thus, **oral(ka, p=F)** can be used to specify the bioavailability ***F***.

**DESCRIPTION:**
PK model, oral administration, lag time, first order absorption, linear elimination,

**INPUT:**
parameter = {Tlag, ka, V, k}

**PK:**
compartment(amount=Ac)
oral(Tlag, ka)
elimination(k)
Cc = Ac/V

**OUTPUT:**
output = Cc



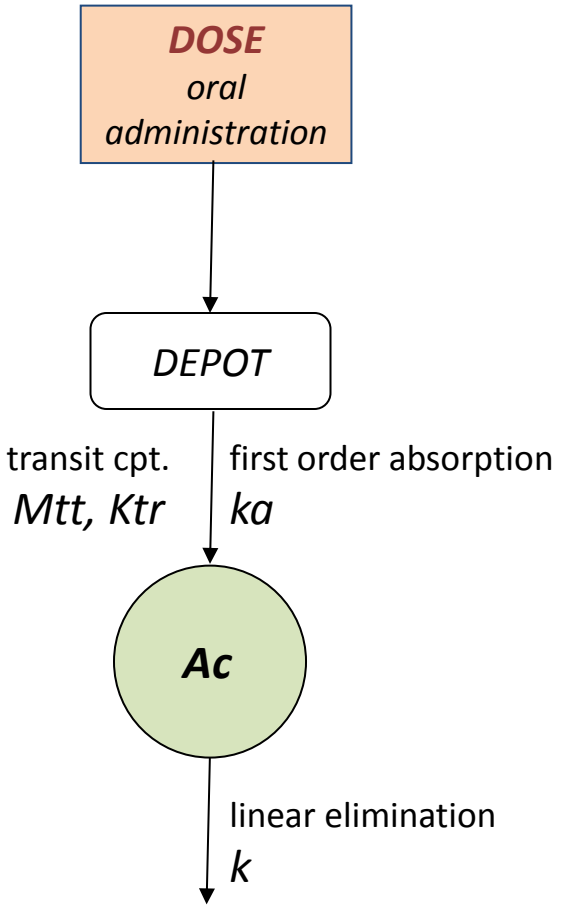

**Tlag** is a reserved keyword used by the PK macro **oral** and the function **pkmodel** to introduce a lag-time in the absorption process.

**DESCRIPTION:**
PK model, oral administration, transit compartment, first order absorption, linear elimination,

**INPUT:**
parameter = {Mtt, Ktr, ka, V, k}

**PK:**
compartment(amount=Ac)
oral(Mtt, Ktr, ka)
elimination(k)
Cc = Ac/V

**OUTPUT:**
output = Cc




**Mtt** and **Ktr** are reserved keyword used by the PK macro **oral** and the function **pkmodel** to introduce a transit compartment in the absorption process.

**Mtt** is the mean transit time and **Ktr** the transit rate constant.

**DESCRIPTION:**

PK model, oral administration, bioavailability F,
lag-time, first order absorption
non linear elimination,

**INPUT:**

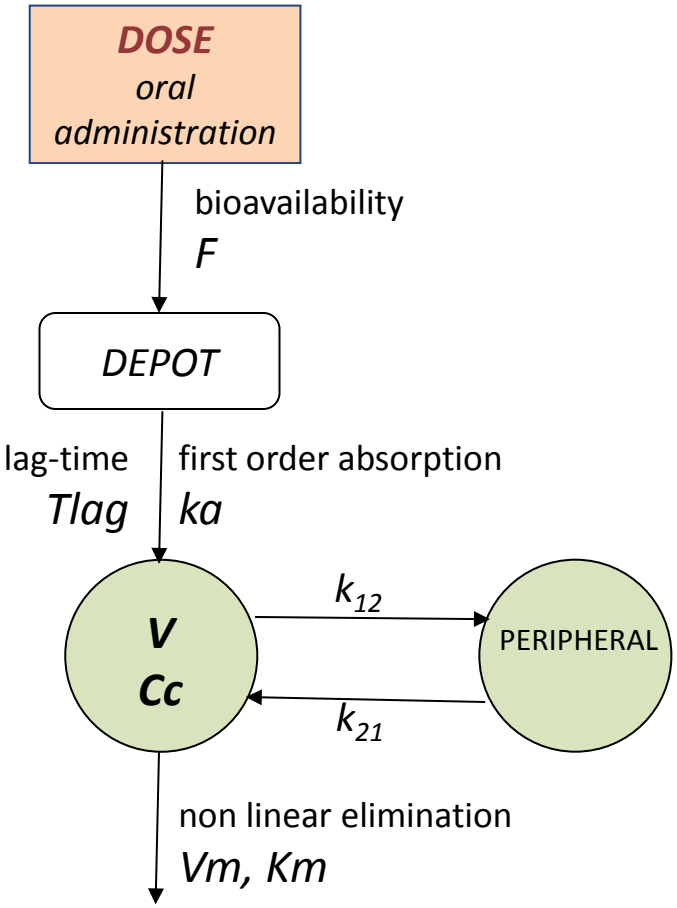
parameter = {F, Tlag, ka, V, k12, k21, Vm, Km}

**PK:**

compartment(concentration=Cc, volume=V)
oral(Tlag, ka, p=F)
peripheral(k12, k21)
elimination(Vm, Km)

**OUTPUT:**

output = Cc




The final PK model combines any absorption, distribution and elimination processes defined by the PK macros **oral, peripheral** and **elimination.**

**DESCRIPTION:**

PK model, oral administration, bioavailability F, lag-time, first order absorption non linear elimination,

**INPUT:**

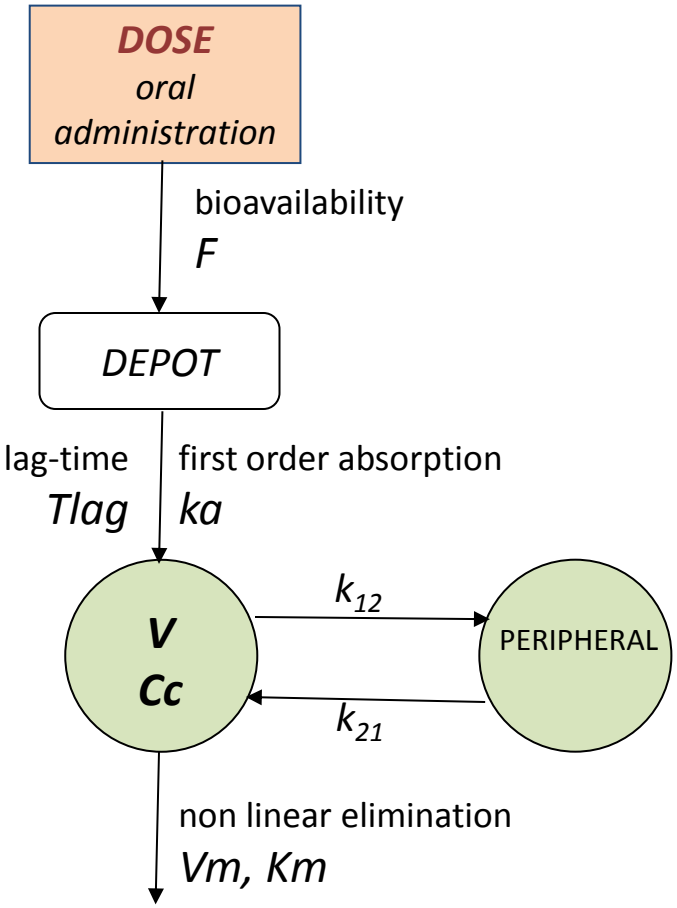
parameter = {F, Tlag, ka, V, k12, k21, Vm, Km}

**EQUATION:**

Cc = pkmodel(Tlag, ka, p=F, V, k12, k21, Vm, Km)

**OUTPUT:**

output = Cc




The final PK model can be equivalently defined using the **pkmodel** function.

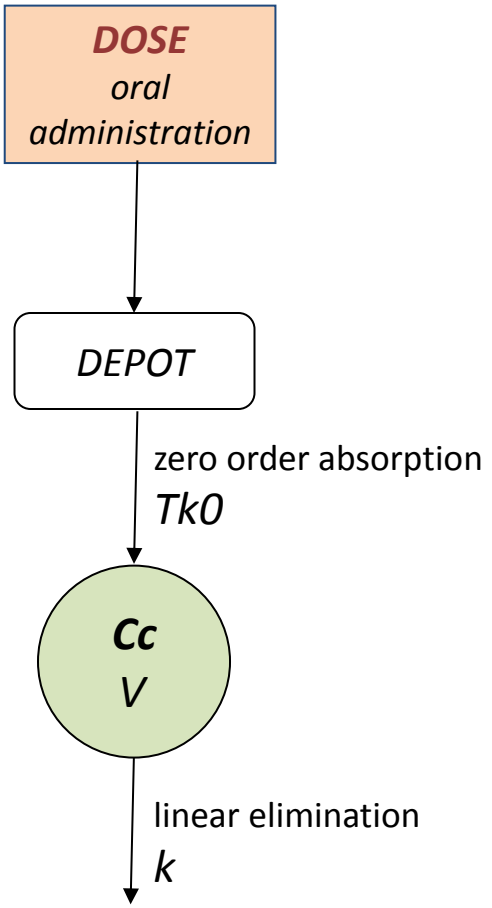
*Zero order absorption process*

**DESCRIPTION:**
PK model, oral administration, zero order absorption linear elimination, parameters (Tk0, V, k)

**INPUT:**
parameter = {Tk0, V, k}

**PK:**
compartment(concentration=Cc, volume=V)
oral(Tk0)
elimination(k)

**OUTPUT:**
output = Cc




**Tk0** is a reserved keyword used by the PK macro **oral** and the function **pkmodel** to specify the duration of a zero-order absorption process.

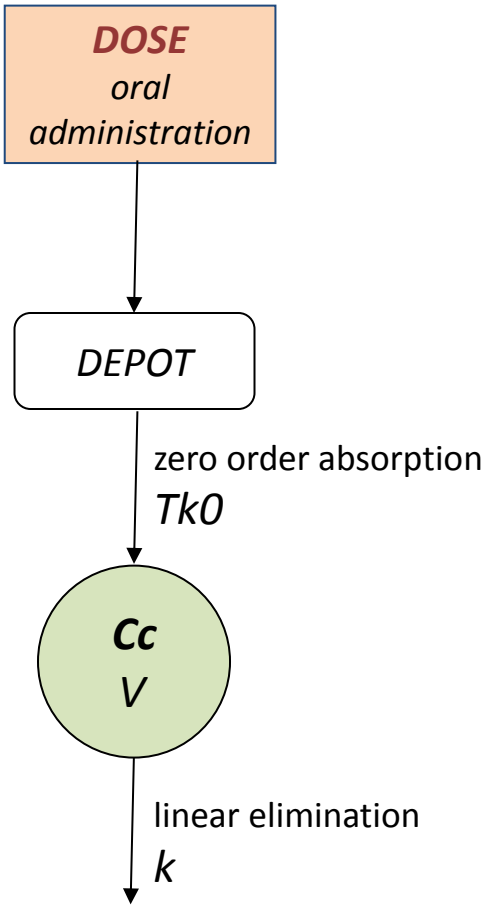
**Remark:** the structure of the datafile is the same for a first order absorption or a zero order absorption.

**DESCRIPTION:**
PK model, oral administration, zero order absorption linear elimination, parameters (Tk0, V, k)

**INPUT:**
parameter = {Tk0, V, k}

**EQUATION:**
Cc=pkmodel(Tk0, V, k)

**OUTPUT:**
output = Cc




**Tk0** is a reserved keyword used by the PK macro **oral** and the function **pkmodel** to specify the duration of a zero-order absorption process.

**Remark:** the structure of the datafile is the same for a first order absorption or a zero order absorption.

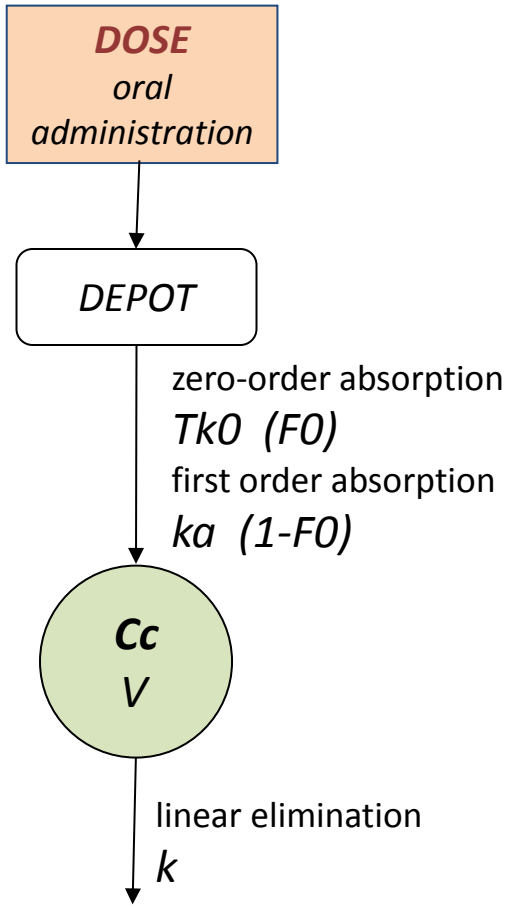
*Sequential zero order / first order absorption processes*

**DESCRIPTION:**
PK model, oral administration,
sequential zero-order & first order absorptions
linear elimination,

**INPUT:**
parameter = {F0, Tk0, ka, V, k}

**PK:**
compartment(concentration=Cc, volume=V)
oral(Tk0, p=F0)
oral(ka , Tlag=Tk0 , p=1-F0)
elimination(k)

**OUTPUT:**
output = Cc




PK macro **absorption** allows to easily describe complex absorption processes. Here,

- **oral(Tk0,p=Fr)** means that a fraction **Fr** is first absorbed with a zero-order process,
- **oral(ka, Tlag=Tk0, p=1-Fr)** means that the remaining fraction **1-Fr** is absorbed with a first order process when the zero-order process ends.

**Remark:** the structure of the datafile is the same for any absorption process.

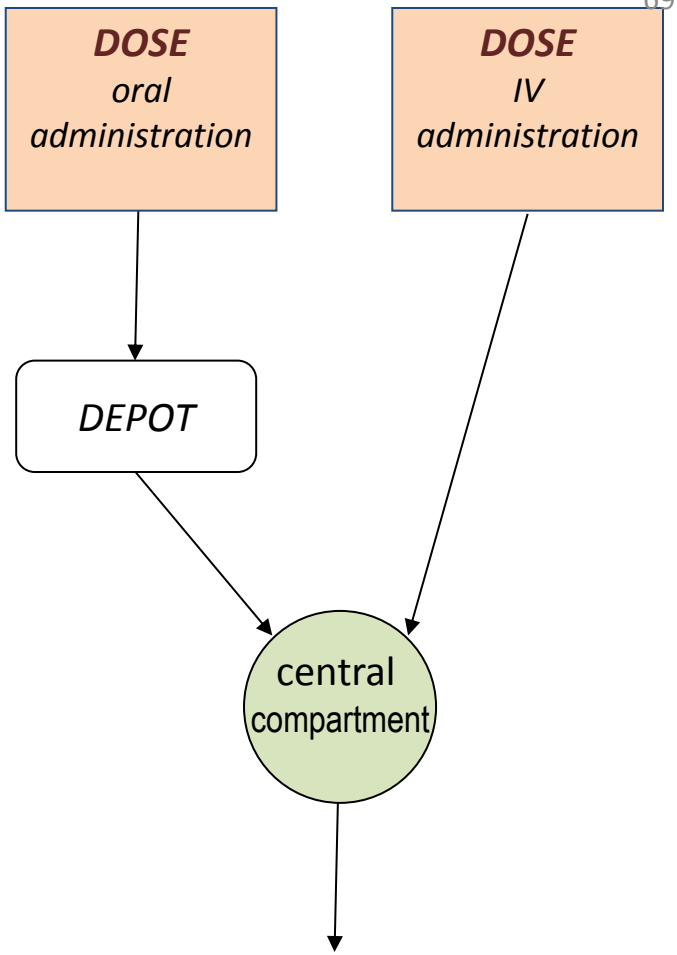
LIXOFT

# *MONOLIX 4.3*

# MLXTRAN

## 2. MLXTRAN for PK models

### 2.3 Complex administration



| Id | time | adm | amt | Y |
|---|---|---|---|---|
| 1 | 0 | 2 | 2.24 | . |
| 1 | 1 | . | . | 142 |
| 1 | 2 | . | . | 54.9 |
| 1 | 3 | . | . | 25.9 |
| 1 | 4 | . | . | 17.5 |
| 1 | 6 | 1 | 7 | . |
| 1 | 7 | . | . | 192 |
| 1 | 8 | . | . | 141 |
| 1 | 9 | . | . | 189 |
| 1 | 10 | . | . | 133 |
| 2 | 0 | 2 | 2.73 | . |
| 2 | 1 | . | . | 176 |
| 2 | 2 | . | . | 69.3 |
| 2 | 3 | . | . | 30.7 |
| 2 | 4 | . | . | 19.6 |
| 2 | 6 | 1 | 7 | . |
| 2 | 7 | . | . | 386 |
| 2 | 8 | . | . | 220 |
| 2 | 9 | . | . | 98.6 |
| 2 | 10 | . | . | 47.3 |

***DOSE***
*oral*
*administration*
**adm = 1**

***DOSE***
*IV*
*administration*
**adm = 2**

An additional column **adm** is used to specify the different types of administration.

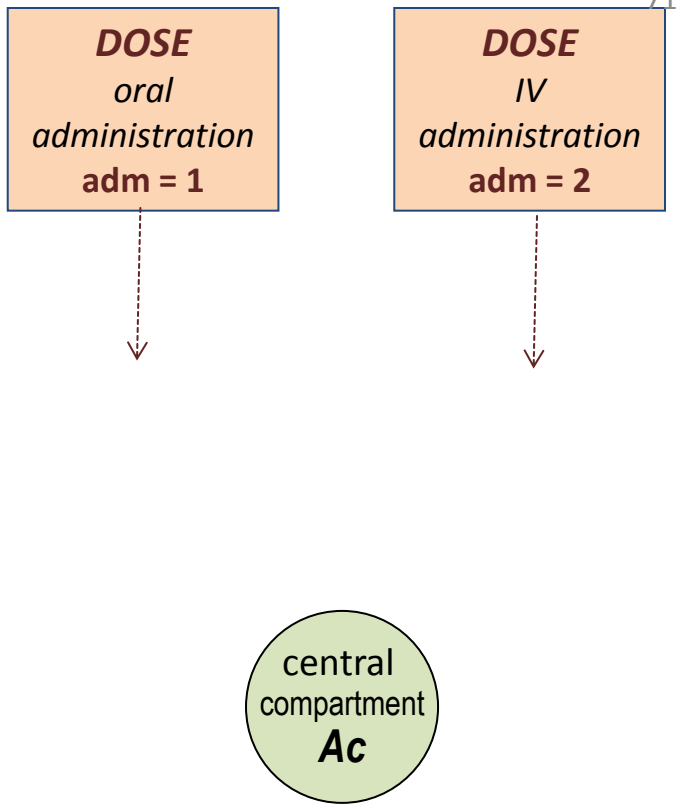
Here, **adm=1** indicates an oral administration and **adm=2** an IV bolus administration.

The datafile only contains information about the administration, not about the absorption process which will be described in the model.

**DESCRIPTION:**
PK model, combination of oral and IV administrations, first order absorption, linear elimination,

**INPUT:**
parameter = {F, ka, V, k}

**PK:**
compartment(amount=Ac)




Block **PK** is used to define the PK model

- **compartment(amount=Ac)** creates a central compartment which amount is ***Ac***,

LIXOFT

**DESCRIPTION:**

PK model, combination of oral and IV administrations, first order absorption, linear elimination,

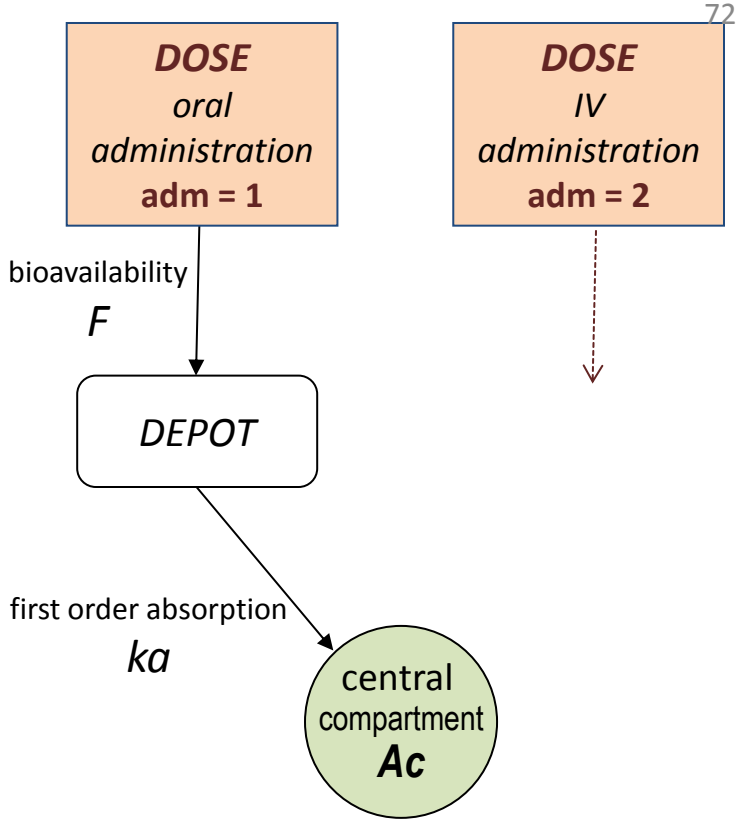
**INPUT:**

parameter = {F, ka, V, k}

**PK:**

compartment(amount=Ac)

oral(adm=1, ka, p=F)




Block **PK** is used to define the PK model

- **compartment(amount=Ac)** creates a central compartment which amount is ***Ac***,
- **oral(adm=1, ka, p=F)** indicates an oral administration from **adm=1** with a bioavailability **F** and defines a first order absorption in the central compartment.

**DESCRIPTION:**

PK model, combination of oral and IV administrations, first order absorption, linear elimination,

**INPUT:**

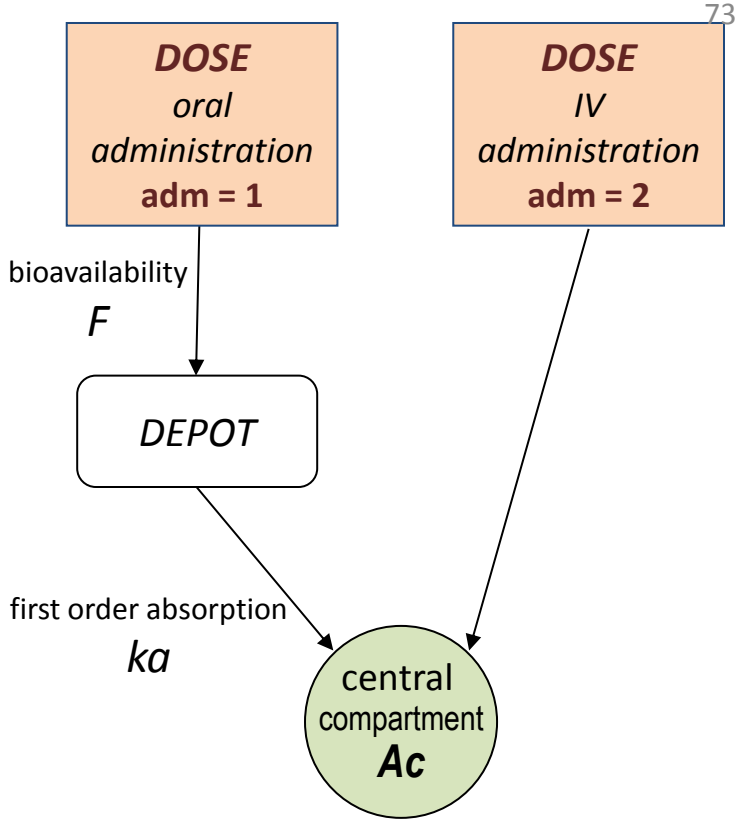
parameter = {F, ka, V, k}

**PK:**

compartment(amount=Ac)

oral(adm=1, ka, p=F)

iv(adm=2)




Block **PK** is used to define the PK model

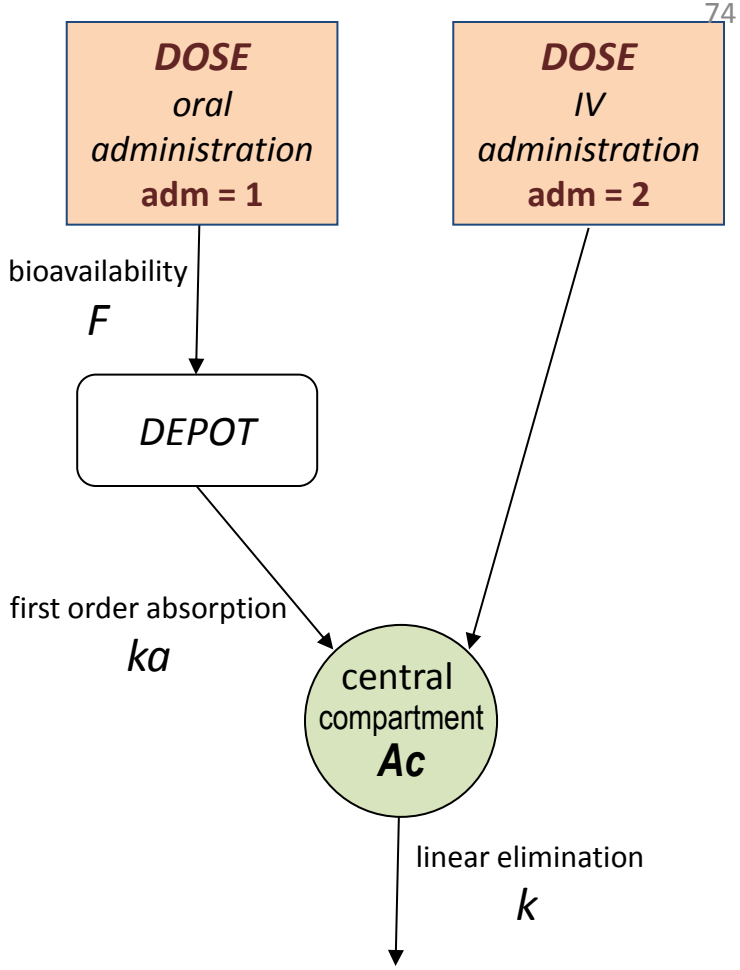
- **compartment(amount=Ac)** creates a central compartment which amount is **Ac**,
- **oral(adm=1, ka, p=F)** indicates an oral administration from **adm=1** with a bioavailability **F** and defines a first order absorption in the central compartment.
- **IV(adm=2)** indicates a IV administration from **adm=2**,

**DESCRIPTION:**
PK model, combination of oral and IV administrations, first order absorption, linear elimination,

**INPUT:**
parameter = {F, ka, V, k}

**PK:**
compartment(amount=Ac)
oral(adm=1, ka, p=F)
iv(adm=2)
elimination(k)
Cc = Ac/V

**OUTPUT:**
output = Cc




Block **PK** is used to define the PK model

- **compartment(amount=Ac)** creates a central compartment which amount is ***Ac***,
- **oral(adm=1, ka, p=F)** indicates an oral administration from **adm=1**, defines a first order absorption in the central compartment with a bioavailability **F**
- **IV(adm=2)** indicates a IV administration from **adm=2**,
- **elimination(k)** defines a linear elimination from the central compartment.

LIXOFT

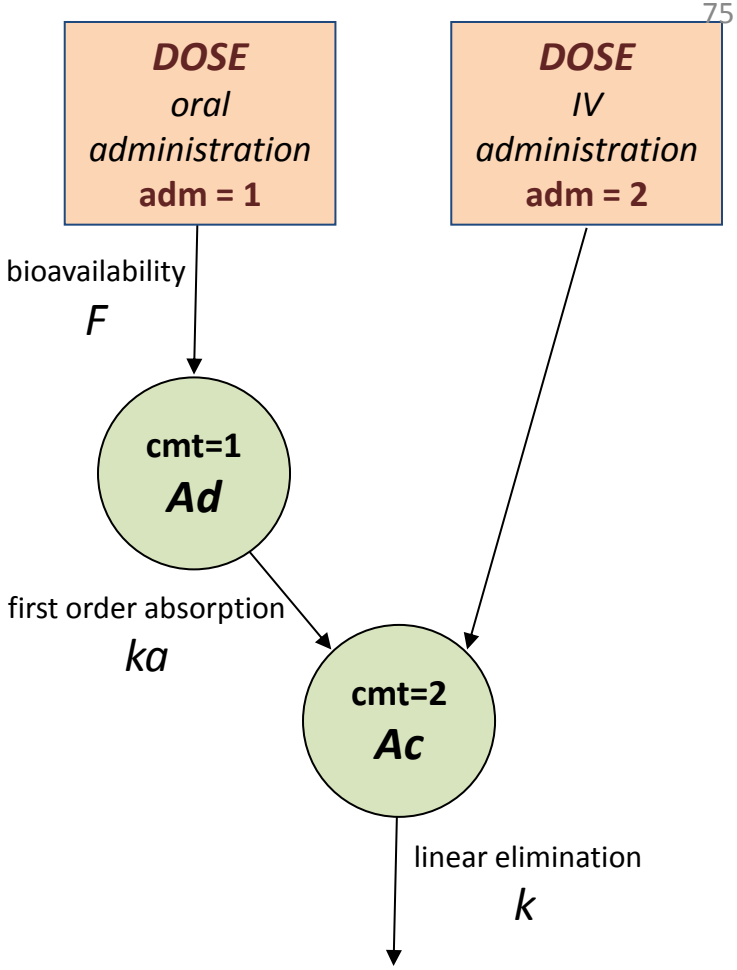
**DESCRIPTION:**
PK model, combination of oral and IV administrations, first order absorption, linear elimination,

**INPUT:**
parameter = {F, ka, V, k}

**PK:**
compartment(cmt=1, amount=Ad)
compartment(cmt=2, amount=Ac)
iv(adm=1, cmt=1, p=F)
iv(adm=2, cmt=2)

**EQUATION:**
ddt_Ad = -ka*Ad
ddt_Ac = ka*Ad - k*Ac
Cc=Ac/V

**OUTPUT:**
output = Cc




The same PK model can be described using a complete system of differential equations. Here block **PK** is used to create the compartments and associate the different administrations to the compartments.

- **compartment(cmt=1, amount=Ad)** creates a depot compartment which amount is ***Ad***,
- **compartment(cmt=2, amount=Ac)** creates a central compartment which amount is ***Ac***,
- **iv(adm=1, cmt=1, p=F)** indicates an IV bolus admin. from **adm=1** to **cmt=1** with a bioavailability **F**
- **iv(adm=2, cmt=2)** indicates an IV bolus administration from **adm=2** to **cmt=2**

LIXOFT

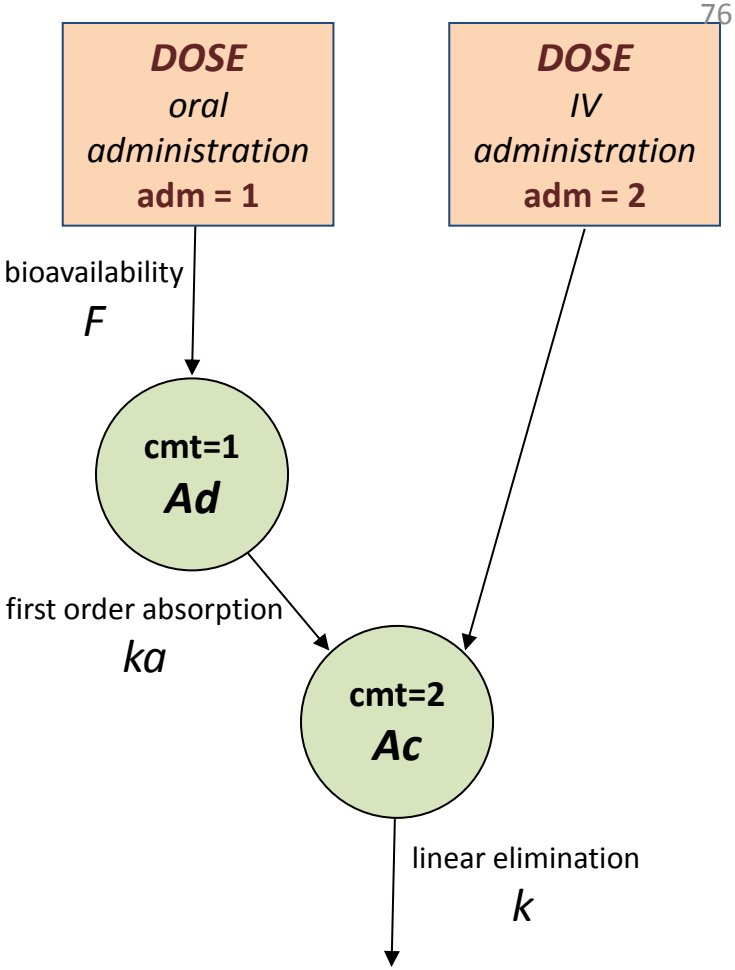
**DESCRIPTION:**
PK model, combination of oral and IV administrations, first order absorption, linear elimination,

**INPUT:**
parameter = {F, ka, V, k}

**PK:**
depot(adm=1, target=Ad, p=F)
depot(adm=2, target=Ac)

**EQUATION:**
ddt_Ad = -ka*Ad
ddt_Ac = ka*Ad - k*Ac
Cc=Ac/V

**OUTPUT:**
output = Cc

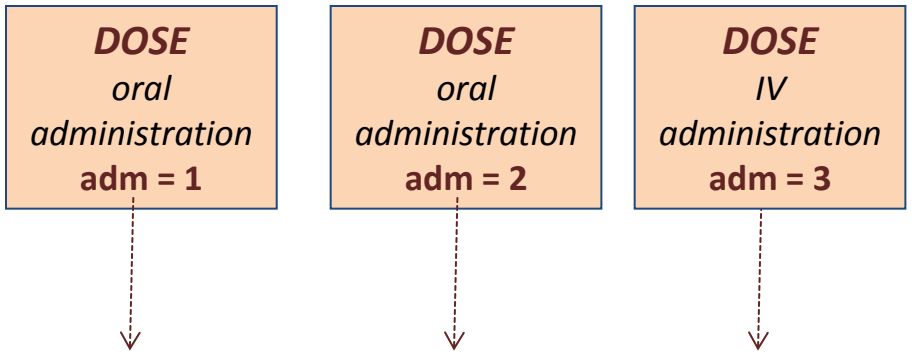



Instead of using the PK macros **compartment** & **iv**, it is possible to consider the doses as source terms of the autonomous system defined with ODEs.

**adm** and **type** are synonymous : they can be used equivalently.

LIXOFT

| Id | time | amt | Y | adm |
|---|---|---|---|---|
| 1 | 0 | 2 | . | 3 |
| 1 | 0.5 | . | 229 | . |
| 1 | 1 | . | 142 | . |
| 1 | 2 | . | 54.9 | . |
| 1 | 4 | . | 17.5 | . |
| 1 | 6 | 7 | . | 1 |
| 1 | 6.5 | . | 8.1 | . |
| 1 | 7 | . | 192 | . |
| 1 | 8 | . | 141 | . |
| 1 | 9 | . | 189 | . |
| 1 | 10 | . | 133 | . |
| 1 | 12 | 7 | . | 2 |
| 1 | 13 | . | 50 | . |
| 1 | 15 | . | 201 | . |
| 1 | 18 | . | 154 | . |



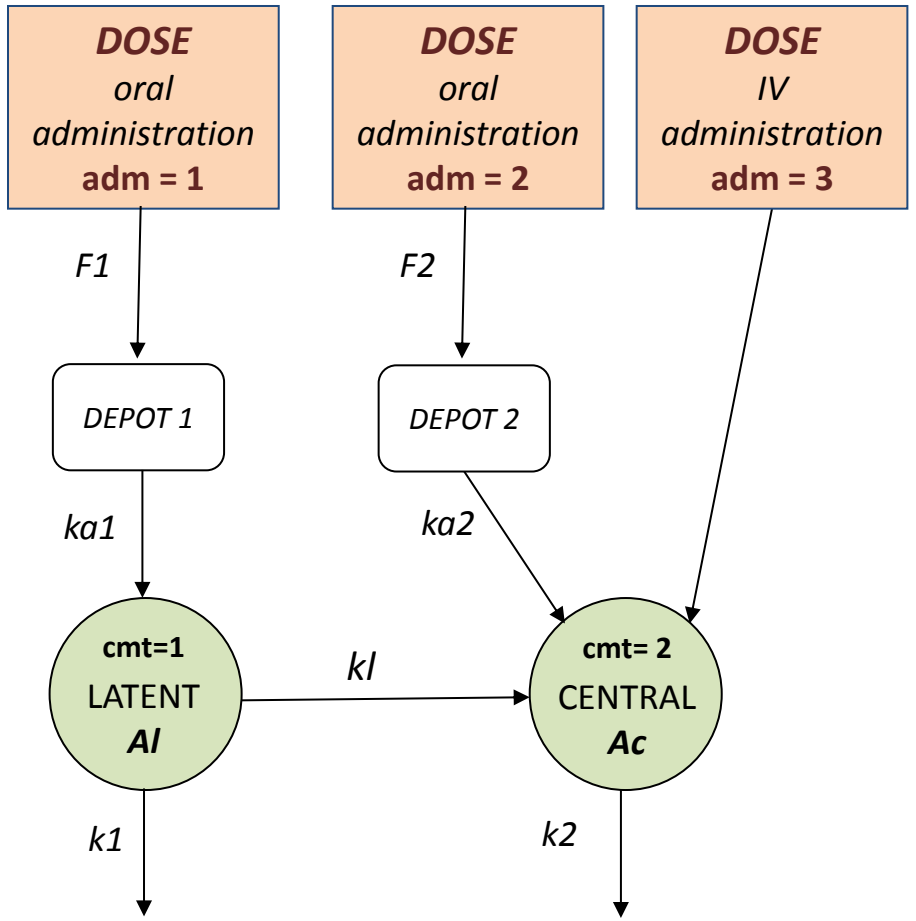

Extension to any combination of multiple oral and IV administrations is straightforward using the **adm** column in the data file.

**DESCRIPTION:**
PK model, combin. of oral and IV admin., latent compartment,

**INPUT:**
parameter = {F1, F2, ka1, ka2, kl, V, k1, k2}

**PK:**
compartment(cmt=1, amount=Al)
compartment(cmt=2, amount=Ac)
oral(adm=1, cmt=1, ka=ka1, p=F1)
oral(adm=2, cmt=2, ka=ka2, p=F2)
iv(adm=3, cmt=2)
transfer(from=1, to=2, kt=kl)
elimination(cmt=1, k=k1)
elimination(cmt=2, k=k2)
Cc = Ac/V

**OUTPUT:**
output = Cc



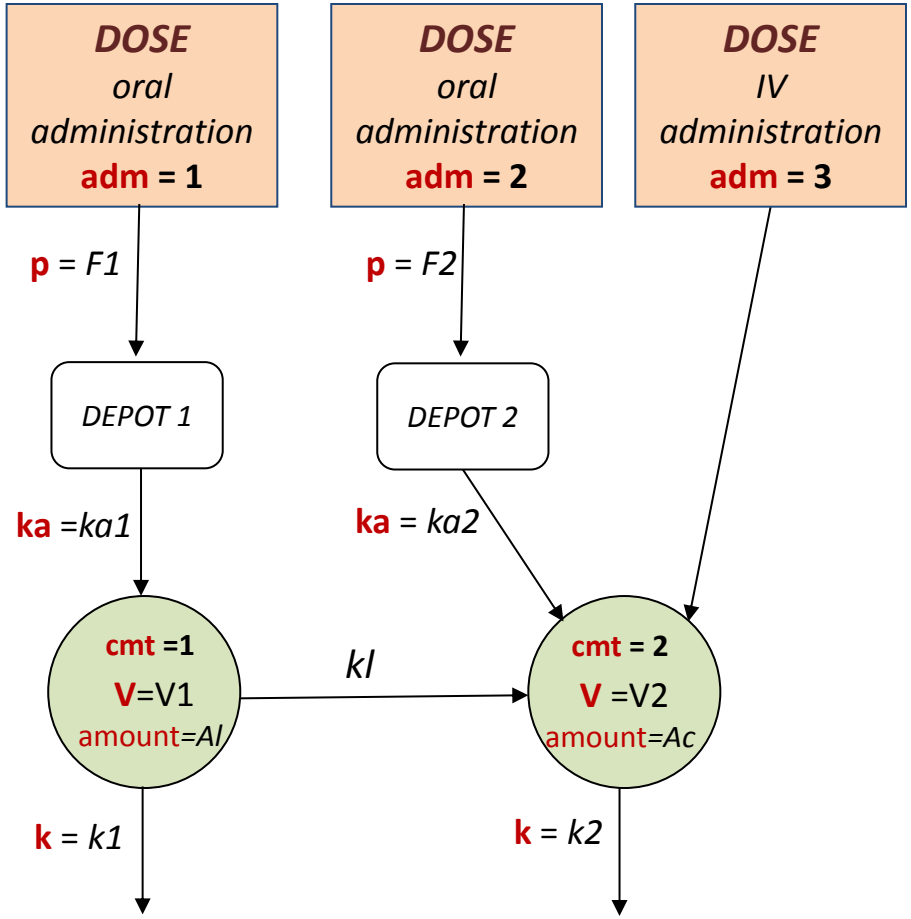

Description of complex PK models is then possible thanks to the use of the PK macros.

# MONOLIX 4.3

## MLXTRAN

## 2. MLXTRAN for PK models

### 2.4 PK parameters summary



## List of PK parameters:

| | |
|---|---|
| **adm** | Type of administration (link with the data file) |
| **cmt** | Compartment number (default =1) |
| **ka** | Absorption constant rate (first order absorption) |
| **Tko** | Absorption duration (zero order absorption) |
| **Tlag** | Lag time before absorption |
| **Mtt, Ktr** | Mean transit time & transit rate constant |
| **p** | Fraction of dose which is absorbed |
| **V** | Central compartment volume |
| **Cl** | Central compartment clearance |
| **Vm, Km** | Michaelis Menten elimination parameters |
| **k12, k21** | Transfer rate constants between compartments 1 (central) & 2 (peripheral) |
| **k13, k31** | Transfer rate constants between compartments 1 (central) & 3 (peripheral) |
| **kt** | Transfer rate constant between two compartments (used by **transfer**) |
| **from, to** | Source and target compartments (used by **transfer**) |
| **keo** | Effect compartment ransfer rate constant |
| **amount** | Amount in a compartment (used by **compartment**) |
| **concentration** | concentration in a compartment (volume of compartment **V** required) |

## PK macros and their input parameters

## Parameters for a call are matched by name, not by ordering

| iv | oral | elimination | peripheral | transfer |
|---|---|---|---|---|
| **adm** (default = 1)<br>**cmt** (default = 1) | **adm** (default = 1)<br>**cmt** (default = 1) | **cmt** (default = 1) | | **from**<br>**to** |
| | **ka** or **Tk0** | **k** or **Cl**<br>or (**Vm**, **Km**)<br>**V** | (**k12** , **k21**)<br>(**k13** , **k31**) | **kt** |
| | **Tlag** (default = 0)<br>or (**Mtt**, **Ktr**)<br>(default = 0) | | | |
| | **p** (default = 1) | | | |

**Required parameters**

**Optional parameters**

Remark: **oral** or **absorption** can be used indifferently.

**Input parameters of the pkmodel function:**

ka or Tk0
Tlag or (Mtt, Ktt )
p
V
k or Cl or (Km, Vm)
(k12, k21 )
(k13, k31 )
ke0

**Parameters for a call are matched by name, not by ordering**

**Output of the pkmodel function:**

Cc : concentration in the central compartment
Ce : concentration in the effect compartment

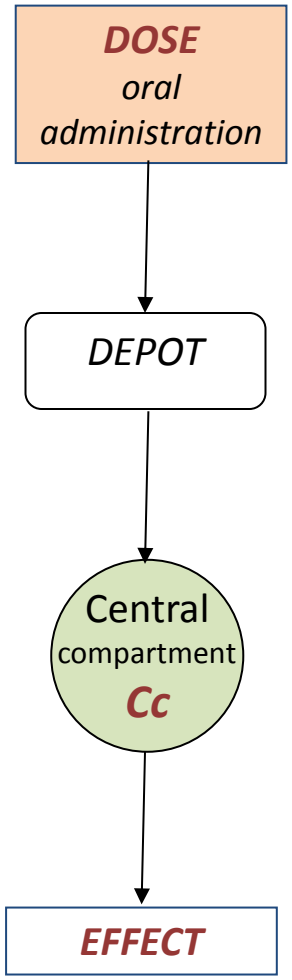
**Required parameters**
**Optional parameters**

# MONOLIX 4.3

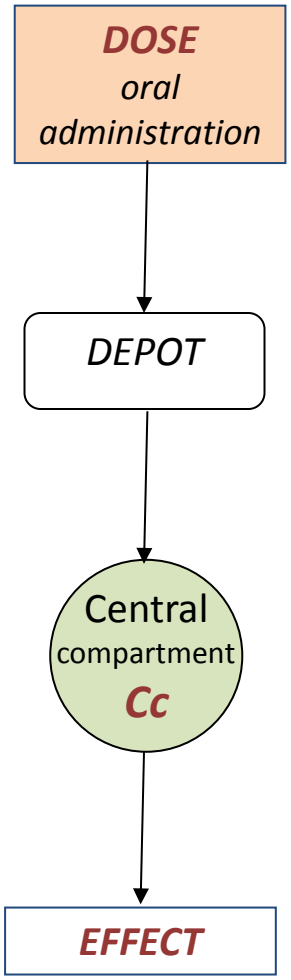
## MLXTRAN

## 3. MLXTRAN for PKPD models





| Id | TIME | AMT | Y | DVID |
|---|---|---|---|---|
| 1 | 0 | 100 | . | . |
| 1 | 0 | . | 100 | 2 |
| 1 | 24 | . | 9.2 | 1 |
| 1 | 24 | . | 49 | 2 |
| 1 | 36 | . | 8.5 | 1 |
| 1 | 36 | . | 32 | 2 |
| 1 | 48 | . | 6.4 | 1 |
| 1 | 48 | . | 26 | 2 |
| 1 | 72 | . | 4.8 | 1 |
| 1 | 72 | . | 22 | 2 |
| 1 | 96 | . | 3.1 | 1 |
| 1 | 96 | . | 28 | 2 |
| 1 | 120 | . | 2.5 | 1 |
| 1 | 120 | . | 33 | 2 |




The datafile contains an additional column **DVID** (or **YTYPE**) to specify if an observation is a PK data or a PD data

# *Immediate response models*

**DESCRIPTION:**
PK model for oral administration
Imax model

**INPUT:**
parameter = {ka, V, Cl, Imax, IC50, S0}

**EQUATION:**
Cc = pkmodel(ka, V, Cl)
E = S0*(1-Imax*Cc/(Cc+IC50))

**OUTPUT:**
output = {Cc, E}

In this example, both PK and PD models are defined in the block **EQUATION.**

We can use the function **pkmodel** for computing the concentration **Cc**.

There are 2 outputs for a PK/PD model.

**DESCRIPTION:**
PK model for oral administration
Imax model

**INPUT:**
parameter = {ka, V, Cl, Imax, IC50, S0}

**EQUATION:**
Cc = pkmodel(ka, V, Cl)
E = S0*(1-Imax*Cc/(Cc+IC50))

**OUTPUT:**
output = {Cc, E}

**DESCRIPTION:**
PK model for single oral administration
Imax model

**INPUT:**
parameter = {ka, V, Cl, Imax, IC50, S0}

**EQUATION:**
k = Cl/V
p1 = amtDose*ka/(V*(ka-k))
Cc = p1*(exp(-k*t) - exp(-ka*t))
E = S0*(1-Imax*Cc/(Cc+IC50))

**OUTPUT:**
output = {Cc, E}

In this example, both PK and PD models are defined in the block **EQUATION.**

We can use the function **pkmodel** for computing the concentration **Cc**.

There are 2 outputs for a PK/PD model.

For a single dose administration, the concentration **Cc** can be computed analytically instead of using the function **pkmodel**

*Effect compartment*

**DESCRIPTION:**
PK model for oral administration,
Effect compartment,
Imax model

**INPUT:**
parameter = {ka, V, Cl, ke0, Imax, IC50, S0}

**EQUATION:**
{Cc, Ce} = pkmodel(ka, V, Cl, ke0)
E= S0*(1-Imax*Ce/(Ce+IC50))

**OUTPUT:**
output = {Cc, E}

It is easy to add an effect compartment in the model, just by adding a second output to the function **pkmodel.**

Here, **Ce** is the concentration in the effect compartment.

**DESCRIPTION:**
PK model for oral administration,
Effect compartment,
Imax model

**INPUT:**
parameter = {ka, V, Cl, ke0, Imax, C50, S0}

**EQUATION:**
{Cc, Ce} = pkmodel(ka, V, Cl, ke0)
E= S0*(1-Imax*Ce/(Ce+C50))

**OUTPUT:**
output = {Cc, E}

**DESCRIPTION:**
PK model for single oral administration,
Effect compartment,
Imax model

**INPUT:**
parameter = {ka, V, Cl, ke0, Imax, IC50, S0}

**EQUATION:**
k = Cl/V
p1 = amtDose*ka/(V*(ka-k))
Cc = p1*(exp(-k*t) - exp(-ka*t))
ddt_Ce = -ke0*(Ce – Cc)
E = S0*(1-Imax*Ce/(Ce+IC50))

**OUTPUT:**
output = {Cc, E}

It is easy to add an effect compartment in the model, just by adding a second output to the function **pkmodel.**

Here, **Ce** is the concentration in the effect compartment.

For a single dose administration, the concentration **Cc** can be computed analytically instead of using the function **pkmodel**. Then, the concentration in the effect compartment is computed as the solution of a differential equation. When it is not specified, the initial value of an ODE is 0.

# *Indirect response models*

**DESCRIPTION:**
PK model for oral administration,
Use of pkmodel,
Indirect response model

**INPUT:**
parameter = {ka, V, Cl, Imax, IC50, Rin, kout}

**EQUATION:**
Cc = pkmodel(ka, V, Cl)
E_0 = Rin/kout
ddt_E= Rin*(1-Imax*Cc/(Cc+IC50)) - kout*E

**OUTPUT:**
output = {Cc, E}

In a turnover model, the effect **E** is function of the concentration **Cc** and is defined as the solution of an ODE.

Here, the initial value of **E** is different from 0 and must be defined as **E_0**

The concentration **Cc** can be computed using the function **pkmodel**

**DESCRIPTION:**
PK model for oral administration,
Use of pkmodel,
Indirect response model

**INPUT:**
parameter = {ka, V, Cl, Imax, IC50, Rin, kout}

**EQUATION:**
Cc = pkmodel(ka, V, Cl)
E_0 = Rin/kout
ddt_E= Rin*(1-Imax*Cc/(Cc+IC50)) - kout*E

**OUTPUT:**
output = {Cc, E}

**DESCRIPTION:**
PK model for oral administration,
Use of ODEs,
Indirect response model

**INPUT:**
parameter = {ka, V, Cl, Imax, IC50, Rin, kout}

**PK:**
compartment(cmt=1, amount=Ad)
iv(cmt=1)

**EQUATION:**
Cc = Ac/V
E_0 = Rin/kout
ddt_Ad = -ka*Ad
ddt_Ac = ka*Ad – Cl/V*Ac
ddt_E= Rin*(1-Imax*Cc/(Cc+IC50)) - kout*E

**OUTPUT:**
output = {Cc, E}

The concentration **Cc** and the effect **E** can also be defined together with a unique ODE system.

**DESCRIPTION:**
PK model for oral administration,
Use of pkmodel,
Indirect response model

**INPUT:**
parameter = {ka, V, Cl, Imax, IC50, Rin, kout}

**EQUATION:**
Cc = pkmodel(ka, V, Cl)
E_0 = Rin/kout
ddt_E= Rin*(1-Imax*Cc/(Cc+IC50)) - kout*E

**OUTPUT:**
output = {Cc, E}

**DESCRIPTION:**
PK model for single oral administration
Analytical solution of PK
Indirect response model

**INPUT:**
parameter = {ka, V, Cl, Imax, IC50, Rin, kout}

**EQUATION:**
k = Cl/V
p1 = amtDose*ka/(V*(ka-k))
Cc = p1*(exp(-k*t) - exp(-ka*t))
E_0 = Rin/kout
ddt_E= Rin*(1-Imax*Cc/(Cc+IC50)) - kout*E

**OUTPUT:**
output = {Cc, E}

For a single dose administration, the concentration **Cc** can be computed analytically instead of using an ODE or the function **pkmodel**

# *Error models*

**INPUT:**
parameter = {ka, V, Cl, Imax, IC50, Rin, kout}

**EQUATION:**
Cc = pkmodel(ka, V, Cl)
E_0 = Rin/kout
ddt_E= Rin*(1-Imax*Cc/(Cc+IC50)) - kout*E

**OBSERVATION:**
Concentration = {type=continuous, prediction=Cc, errorModel=proportional}

Effect = {type=continuous, prediction=E, errorModel=constant, autocorrelation=yes}

**OUTPUT:**
output = {Concentration, Effect}

**INPUT:**
parameter = {ka, V, Cl, Imax, IC50, Rin, kout}

**EQUATION:**
Cc = pkmodel(ka, V, Cl)
E_0 = Rin/kout
ddt_E= Rin*(1-Imax*Cc/(Cc+IC50)) - kout*E

**OUTPUT:**
output = {Cc, E}

For each continuous observation, the model can define the distribution of the observation, including an error model, or define only its prediction. The autocorrelation is disabled by default.

When the distribution of the observation is available, it must be the output of the model.

# *MONOLIX 4.3*

## MLXTRAN

## 4. MLXTRAN for discrete data models

# *Count data model*

**DESCRIPTION:**
count data model - Poisson distribution
P(Y=k) is defined

**INPUT:**
parameter = lambda

**OBSERVATION:**
Y = {
type = count
P(Y=k) = exp(-lambda + k*log(lambda) - factln(k))
}

**OUTPUT:**
output = Y

$$P(Y=k)=\frac{e^{-\lambda}\times\lambda^{k}}{k!}$$

The probability distribution of the count data **Y** is defined in the block **OBSERVATION,**

**output=Y** means that the model is used for describing the probability distribution of **Y**.

Then, this model can be used for estimation or for simulation.

Here, the probability distribution of the count data **Y** is defined by P(Y=k), for any k>=0.

**DESCRIPTION:**
count data model - Poisson distribution
log(P(Y=k)) is defined

**INPUT:**
parameter = lambda

**OBSERVATION:**
Y = {
type = count
log(P(Y=k)) = -lambda + k*log(lambda) - factln(k)
}

**OUTPUT:**
output = Y

$$\log\left(P(Y=k)\right) = -\lambda + k\log(\lambda) - \log(k!)$$

The probability distribution of the count data **Y** can equivalently be defined by log(P(Y=k)), for any k>=0

**DESCRIPTION:**
count data model – Generalized Poisson distribution

**INPUT:**
parameter = {dlt, lbd}

**OBSERVATION:**
Y = {
type = count,
log(P(Y=k)) = log(lbd) + (k-1)*log(lbd+k*dlt)
– lbd –k*dlt - factln(k)
}

**OUTPUT:**
output = Y

$$P(Y=k) = \frac{e^{-\lambda-k\delta}\,\lambda(\lambda+k\delta)^{k-1}}{k!}$$

More complex probability distributions can be defined, such as the Generalized Poisson distribution

**DESCRIPTION:**
count data model – zero-inflated Poisson distribution

**INPUT:**
parameter = {lambda, p0}

**OBSERVATION:**

```
Y = {
type = count,
if (k > 0)
   aux= log(1-p0) - lambda + k*log(lambda) - factln(k)
 else
   aux= log(p0+(1-p0)*exp(-lambda))
 end

 log(P(Y=k)) = aux
}
```

**OUTPUT:**
output = Y

$$P(Y=0) = p_0 + (1-p_0)e^{-\lambda}$$

$$\text{for } k \geq 1,$$

$$P(Y=k) = (1-p_0)\frac{e^{-\lambda}\,\lambda^k}{k!}$$

Or the zero-inflated Poisson distribution,

# *Categorical data model*

**DESCRIPTION:**
Categorical data model – Bernoulli distribution

**INPUT:**
parameter = p

**OBSERVATION:**
Y = {
type = categorical
categories = {0,1}
P(Y=1) = p
}

**OUTPUT:**
output = Y

$$Y \in \{0,1\}$$
$$P(Y=1) = p$$
$$P(Y=0) = 1-p$$

The probability distribution of the categorical data **Y** is defined in the block **OBSERVATION,**

Use **type=categorical** to specify that the data is of type « categorical »

Indicate with **categories=** the set of values taken by **Y.**

If **Y** takes K values, then *K*-1 probabilities are necessary to define the distribution of **Y.** Here, it is equivalent to define this binomial distribution with P(Y=1)=p or P(Y=0)=1-p.

**DESCRIPTION:**
Categorical data model – 3 categories

**INPUT:**
parameter = {a1, a2, a3}

**OBSERVATION:**
Y = {
type = categorical
categories = {1, 2, 3}
P(Y=1) = a1/(a1+a2+a3)
P(Y=2) = a2/(a1+a2+a3)
}

**OUTPUT:**
output = Y

$$Y \in \{1, 2, 3\}$$

$$P(Y = 1) = \frac{a_1}{a_1 + a_2 + a_3}$$

$$P(Y = 2) = \frac{a_2}{a_1 + a_2 + a_3}$$

$$P(Y = 3) = \frac{a_3}{a_1 + a_2 + a_3}$$

Here, **Y** takes 3 values, then two probabilities are needed to define its probability distribution.

In this example, P(Y=1) and P(Y=2) are defined.

**DESCRIPTION:**
Categorical data model – 3 categories

**INPUT:**
parameter = {a1, a2, a3}

**OBSERVATION:**
Y = {
type = categorical
categories = {1, 2, 3}
P(Y=1) = a1/(a1+a2+a3)
P(Y=3) = a3/(a1+a2+a3)
}

**OUTPUT:**
output = Y

$$Y \in \{1, 2, 3\}$$

$$P(Y = 1) = \frac{a_1}{a_1 + a_2 + a_3}$$

$$P(Y = 2) = \frac{a_2}{a_1 + a_2 + a_3}$$

$$P(Y = 3) = \frac{a_3}{a_1 + a_2 + a_3}$$

It is equivalent to define for example P(Y=1) and P(Y=3),

Obviously, the sum of the *K* probabilities must be equal to 1.

**DESCRIPTION:**
Ordered categorical data model – 3 categories
Cumulative probabilities

**INPUT:**
parameter = {a1, a2, a3}

**OBSERVATION:**
Y = {
type = categorical
categories = {1, 2, 3}
P(Y<=1) = a1/(a1+a2+a3)
P(Y<=2) = (a1+a2)/(a1+a2a31)
}

**OUTPUT:**
output = Y

$$Y \in \{1, 2, 3\}$$

$$P(Y = 1) = \frac{a_1}{a_1 + a_2 + a_3}$$

$$P(Y = 2) = \frac{a_2}{a_1 + a_2 + a_3}$$

$$P(Y = 3) = \frac{a_3}{a_1 + a_2 + a_3}$$

If **Y** is an ordered categorical data, it is possible to define the cumulative distribution function

*K* - 1 probabilities are needed to define the distribution of **Y**.

In this example, we use P(Y<=1) and P(Y<=2) to define the distribution of **Y**.

**DESCRIPTION:**
Ordered categorical data model – 3 categories
Tail probabilities

**INPUT:**
parameter = {a1, a2, a3}

**OBSERVATION:**
Y = {
type = categorical
categories = {1, 2, 3}
P(Y>1) = (a2+a3)/(a1+a2+a3)
P(Y>2) = a3/(a1+a2+a3)
}

**OUTPUT:**
output = Y

$$Y \in \{1, 2, 3\}$$

$$P(Y = 1) = \frac{a_1}{a_1 + a_2 + a_3}$$

$$P(Y = 2) = \frac{a_2}{a_1 + a_2 + a_3}$$

$$P(Y = 3) = \frac{a_3}{a_1 + a_2 + a_3}$$

We can equivalently define the distribution of **Y** with the tail distribution, here P(Y>1) and P(Y>2).

**DESCRIPTION:**
Ordered categorical data model – 3 categories
Logit – probabilities

**INPUT:**
parameter = {theta1, theta2}

**OBSERVATION:**
Y = {
type = categorical
categories = {1, 2, 3}
logit(P(Y<=1) )= theta1
logit(P(Y<=2) )= theta1+theta2
}

**OUTPUT:**
output = Y

$$Y \in \{1,2,3\}$$

$$P(Y \le 1) = \frac{1}{1+e^{-\theta_1}}$$

$$P(Y \le 2) = \frac{1}{1+e^{-\theta_1-\theta_2}}$$

$$P(Y \le 3) = 1$$

According to the parametrization, it can be convenient to define the distribution of **Y** using the logit of *K*-1 probabilities.

In this example, we use the logit of P(Y<=1) and P(Y<=2) to define the distribution of **Y**.

**DESCRIPTION:**
Ordered categorical data model – 3 categories
Logit – probabilities

**INPUT:**
parameter = {theta1, theta2}

**OBSERVATION:**
Y = {
type = categorical
categories = {1, 2, 3}
logit(P(Y>1) )= -theta1
logit(P(Y>2) )= -theta1-theta2
}

**OUTPUT:**
output = Y

$$Y \in \{1,2,3\}$$

$$P(Y \le 1) = \frac{1}{1+e^{-\theta_1}}$$

$$P(Y \le 2) = \frac{1}{1+e^{-\theta_1-\theta_2}}$$

$$P(Y \le 3) = 1$$

We can equivalently use the logit of P(Y>1) and P(Y>2) to define the distribution of **Y.**

# *Categorical data model with Markovian dependence*

**DESCRIPTION:**
Categorical data model – Markovian dependence

**INPUT:**
parameter = {p11, p21}

**OBSERVATION:**
Y = { type = categorical
categories = {1,2}
dependence = Markov
P(Y=1 | Y_p=1) = p11
P(Y=1 | Y_p=2) = p21
}

**OUTPUT:**
output = Y

$$Y_j \in \{1, 2\}$$

$$P(Y_j = 1 | Y_{j-1} = 1) = p_{11}$$

$$P(Y_j = 1 | Y_{j-1} = 2) = p_{21}$$

The conditional distributions $P(Y_j = k \mid Y_{j-1} = m)$ define the joint distribution of **Y** given $Y_1$.

Here, the « initial » distribution of $Y_1$ is not defined. It is assumed to be constant and does not contribute to the likelihood for estimating the population parameters.

For simulation, $P(Y_1 = 0) = P(Y_1 = 1) = 1/2$ is used.

`Y_p` holds for « previous » value of Y (*i.e.* $Y_{j-1}$)

**DESCRIPTION:**
Categorical data model – Markovian dependence

**INPUT:**
parameter = {p, p11, p21}

**OBSERVATION:**
Y = { type = categorical
categories = {1, 2}
dependence = Markov
P(Y_1=1) = p
P(Y=1 | Y_p=1) = p11
P(Y=1 | Y_p=2) = p21}

**OUTPUT:**
output = Y

$$Y_j \in \{1, 2\}$$

$$P(Y_1 = 1) = p$$

$$P(Y_j = 1 | Y_{j-1} = 1) = p_{11}$$

$$P(Y_j = 1 | Y_{j-1} = 2) = p_{21}$$

The conditional distributions $P(Y_j = k \mid Y_{j-1} = m)$ and the « initial » distribution of $Y_1$ define the joint distribution of **Y**.

In this example, $p = P(Y_1 = 1)$ is a parameter of the model.

**DESCRIPTION:**

Categorical data model – Markovian dependence
Continuous time

**INPUT:**

parameter = {q12, q21}

**OBSERVATION:**

Y = { type = categorical
categories = {1, 2}
dependence = Markov
transitionRate(1,2) = q12
transitionRate(2,1) = q21
}

**OUTPUT:**

output = Y

for any $0 \le s < t$, let

$$Q(s,t) = \left(q_{ij}(s,t)\right)_{1 \le i,j \le K}$$

$$P(s,t) = \left(p_{ij}(s,t)\right)_{1 \le i,j \le K}$$

$$p_{ij}(s,t) = P(Y(t) = j \,|\, Y(s) = i)$$

$$\frac{dP(s,t)}{dt} = Q(s,t)P(s,t)$$

$$\sum_{j=1}^{K} q_{ij}(s,t) = 0$$

The transition rates ($q_{ij}$) define the joint distribution of **Y**.

# *Time-to-event data model*

# Exact time of and right censored events

| ID | TIME | Y |
|---|---|---|
| 1 | 0 | 0 |
| 1 | 25 | 1 |
| 2 | 0 | 0 |
| 2 | 30 | 1 |
| 3 | 0 | 0 |
| 3 | 48 | 0 |
| 4 | 0 | 0 |
| 4 | 45 | 1 |
| 5 | 0 | 0 |
| 5 | 17 | 1 |
| 6 | 0 | 0 |
| 6 | 36 | 1 |
| 7 | 0 | 0 |
| 7 | 48 | 0 |

Single events

| ID | TIME | Y |
|---|---|---|
| 1 | 0 | 0 |
| 1 | 15 | 1 |
| 1 | 25 | 0 |
| 2 | 0 | 0 |
| 2 | 12 | 1 |
| 2 | 27 | 1 |
| 2 | 33 | 0 |
| 3 | 0 | 0 |
| 3 | 25 | 0 |
| 4 | 0 | 0 |
| 4 | 14 | 1 |
| 4 | 22 | 1 |
| 4 | 31 | 1 |
| 4 | 38 | 0 |

Repeated events

The same coding is used for single and repeated events:

- Y=1 means that the exact time of the event is known,
- Y=0 means that the event is right censored: the patient had not the event at that time,
- A record Y=0 at time $t_0$ is needed to define when we start observing. Here $t_0 = 0$.

**DESCRIPTION:**
Time-to-event data model
Constant hazard function

**INPUT:**
parameter = lambda

**OBSERVATION:**
Y = { type = event
hazard = 1/lambda
}

**OUTPUT:**
output = Y

$$h(t) = \frac{1}{\lambda}$$

$$P(T > t) = e^{-\frac{t}{\lambda}}$$

The probability distribution of the event data defined with the hazard function in the block **OBSERVATION,**

Use **type=event** to specify that the data is of type « event »,

**hazard** is a reserved keyword. Here, **hazard=lambda** means that the hazard is constant, *i.e.* the time to event has an exponential distribution.

**DESCRIPTION:**
Time-to-event data model
Weibull hazard function

**INPUT:**
parameter = {lambda, beta}

**OBSERVATION:**
Y = { type = event
hazard = (beta/lambda)*(t/lambda)^(beta-1)
}

**OUTPUT:**
output = Y

$$h(t) = \frac{\beta}{\lambda}\left(\frac{t}{\lambda}\right)^{\beta-1}$$

$$P(T > t) = e^{-\left(\frac{t}{\lambda}\right)^{\beta}}$$

**hazard** is a reserved keyword that can be used to define any complex hazard function.

# Interval censored events

| ID | TIME | Y |
|---|---|---|
| 1 | 0 | 0 |
| 1 | 20 | 0 |
| 1 | 25 | 1 |
| 2 | 0 | 0 |
| 2 | 25 | 0 |
| 2 | 30 | 1 |
| 3 | 0 | 0 |
| 3 | 50 | 0 |
| 4 | 0 | 0 |
| 4 | 40 | 0 |
| 4 | 45 | 1 |
| 5 | 0 | 0 |
| 5 | 60 | 0 |

Single event
(interval length = 5)

| ID | TIME | Y |
|---|---|---|
| 1 | 0 | 0 |
| 1 | 5 | 2 |
| 1 | 10 | 0 |
| 1 | 15 | 1 |
| 1 | 20 | 3 |
| 1 | 25 | 0 |
| 1 | 30 | 2 |
| 2 | 0 | 0 |
| 2 | 5 | 0 |
| 2 | 10 | 1 |
| 2 | 15 | 3 |
| 2 | 20 | 0 |
| 2 | 25 | 1 |
| 2 | 30 | 3 |

Repeated events
(interval length = 5)

| ID | Event |
|---|---|
| 1 | beetween 20 and 25 |
| 2 | beetween 25 and 30 |
| 3 | after 50 |
| 4 | beetween 40 and 45 |

| ID | Events |
|---|---|
| 1 | 2 events beetween 0 and 5<br>0 event beetween 5 and 10<br>1 event beetween 10 and 15<br>3 events beetween 15 and 20<br>0 event beetween 20 and 25<br>2 events beetween 25 and 30 |

**DESCRIPTION:**
Time-to-event data model
Constant hazard function

**INPUT:**
parameter = lambda

**OBSERVATION:**
Y = { type = event
eventType=intervalCensored,
maxEventNumber=1,
hazard = 1/lambda
}

**OUTPUT:**
output = Y

$$h(t) = \frac{1}{\lambda}$$

$$P(T > t) = e^{-\frac{t}{\lambda}}$$

Use **eventType=intervalCensored** to specify that the events are interval censored.

**maxEventNumber** is the maximum number of events that can occur per individual. An infinite number of events is assumed if **maxEventNumber** is not specified.

This information is required in an estimation context for properly computing the likelihood of the observations. No additional information is required for estimation.

**DESCRIPTION:**
Time-to-event data model
Constant hazard function

**INPUT:**
parameter = lambda

**OBSERVATION:**
Y = { type = event
eventType=intervalCensored,
maxEventNumber=3,
intervalLength=5,
rightCensoringTime=200,
hazard = 1/lambda
}

**OUTPUT:**
output = Y

$$h(t) = \frac{1}{\lambda}$$

$$P(T > t) = e^{-\frac{t}{\lambda}}$$

Some additional parameters can be defined for simulation

**intervalLength** is the length of the intervals ; default = righCensoringTime/10 (also used for VPCs).

**rightCensoringTime** is the length of the study ; default is the maximum of the times of observations available in the dataset (not used by Monolix, only for simulation).

# *Joint models*

| Id | TIME | AMT | Y | DVID |
|---|---|---|---|---|
| 1 | 0 | 100 | . | . |
| 1 | 4 | . | 9.2 | 1 |
| 1 | 8 | . | 5 | 2 |
| 1 | 12 | . | 8.5 | 1 |
| 1 | 18 | . | 6.4 | 1 |
| 1 | 24 | . | 2 | 2 |
| 2 | 0 | 120 | 26 | . |
| 2 | 4 | . | 4.8 | 1 |
| 2 | 8 | . | 3 | 2 |
| 2 | 12 | . | 3.1 | 1 |
| 2 | 18 | . | 2.5 | 1 |
| 2 | 14 | . | 0 | 2 |
| 3 | 0 | 80 | . | . |
| 3 | 4 | . | 5.7 | 1 |
| 3 | 8 | . | 4 | 2 |
| 3 | 12 | . | 3.8 | 1 |

A joint model is used for modelling simultaneously some continuous data (a biomarker for instance) and another type of data (event, count, categorical…)

The datafile contains an additional column **DVID** (or **YTYPE**) to specify the type of data.

In this example, DVID =1 is used for a continuous response and DVID =2 for count data.

**DESCRIPTION:**
Joint PK and count data model

**INPUT:**
parameter = {ka, V, Cl, ke0, lambda0, Imax, IC50}

**EQUATION:**
{Cc, Ce} = pkmodel(ka, V, Cl, ke0)
lambda=lambda0*(1 – Imax*Ce/(IC50+Ce))

**OBSERVATION:**
seizure = {
type = count
log(P(seizure=k)) = -lambda + k*log(lambda) - factln(k)
}

**OUTPUT:**
output = {Cc , seizure}

In this example, an effect compartment and an Imax model are used for modelling the Poisson intensity of the count data.

**DESCRIPTION:**
Joint PK and categorical data model

**INPUT:**
parameter = {ka, V, Cl, ke0, theta1, theta2, alpha, beta}

**EQUATION:**
{Cc, Ce} = pkmodel(ka, V, Cl, ke0)

**OBSERVATION:**
level = {
type = categorical
categories = {0, 1, 2}
logit(P(level<=0)) = theta1 + alpha*t + beta*Ce
logit(P(level<=1)) = theta1 + alpha*t + beta*Ce + theta2
}

**OUTPUT:**
output = {Cc , level}

In this example, the probability distribution of the categorical data is function of the time and the concentration in the effect compartment.

**DESCRIPTION:**
Joint PK and time to event data model

**INPUT:**
parameter = {ka, V, Cl, ke0, lambda0, Imax, IC50}

**EQUATION:**
{Cc, Ce} = pkmodel(ka, V, Cl, ke0)
lambda=lambda0*(1 - Imax*Ce/(IC50+Ce))

**OBSERVATION:**
hemorrhaging = { type = event, hazard = 1/lambda}

**OUTPUT:**
output = {Cc , hemorrhaging}

In this example, an effect compartment and an Imax model are used for modelling the risk of hemorrhaging.

**DESCRIPTION:**
Joint PK and time to event data model

**INPUT:**
parameter = {ka, V, Cl, ke0, lambda0, Imax, IC50}

**EQUATION:**
{Cc, Ce} = pkmodel(ka, V, Cl, ke0)
lambda=lambda0*(1 - Imax*Ce/(IC50+Ce))

**OBSERVATION:**

Concentration = { type = continuous, prediction = Cc,

errorModel = band(0, 10) }

hemorrhaging = { type = event, hazard = 1/lambda}

**OUTPUT:**
output = {Concentration, hemorrhaging}

In addition to its prediction, an error model is fixed for the concentration here, allowing us to define its whole distribution, as we did for the risk of hemorrhaging.

**DESCRIPTION:**

Joint PK, count data and time to event data model

**INPUT:**

parameter = {ka, V, Cl, ke0, lambda0, Imax, IC50, beta, theta1, theta2}

**EQUATION:**

{Cc, Ce} = pkmodel(ka, V, Cl, ke0)

lambda=lambda0*(1 – Imax*Ce/(IC50+Ce))

**OBSERVATION:**

hemorrhaging = { type = event, hazard = 1/lambda}

level = { type = categorical,  categories = {0, 1, 2}

logit(P(level<=0)) = theta1 + beta*Ce

logit(P(level<=1)) = theta1 + beta*Ce + theta2 }

**OUTPUT:**

output = {Cc , hemorrhaging, level}

A joint model can address simultaneously several types of data.

In this example, we model jointly PK data, time to event data and categorical data.

The distribution of several discrete data can be discribed in a same block **OBSERVATION**.

# MONOLIX 4.3

# MLXTRAN

## 5. Symbols reference

## List of symbols for blocks:

| | |
|---|---|
| **DESCRIPTION** | Block for title and free comments - example |
| **INPUT** | Block for inputs from the data and statistical model - example |
| **PK** | Block for PK function and macros - example |
| **EQUATION** | Block for explicit mathematical model - example |
| **OBSERVATION** | Block for random variables of observations - example |
| **OUTPUT** | Block for outputs - example |

## List of symbols for interface:

| | |
|---|---|
| **parameter** | List of individual parameters - example |
| **regressor** | List of regression values - example |
| **output** | List of outputs - example |
| **table** | List of additional outputs for tables |

## List of symbols for PK:

| | |
|---|---|
| **compartment** | Macro for compartment - example |
| **depot** | Macro for a deposit, where the doses are the source terms - example |
| **iv or input** | Macro for IV administration - example |
| **absorption or oral** | Macro for oral administration - example |
| **elimination** | Macro for elimination - example |
| **peripheral** | Macro for peripheral compartment - example |
| **transfer** | Macro for transfer - example |
| **cmt** | Compartment number - example |
| **target** | Target ODE component of the source term - example |
| **ka** | Absorption constant rate - example |
| **Tko** | Absorption duration - example |
| **Tlag** | Lag time before absorption - example |
| **Mtt, Ktr** | Mean transit time & transit rate constant - example |
| **p** | Fraction of dose which is absorbed - example |
| **V** | Central compartment volume for PK function - example |
| **Cl** | Central compartment clearance - example |
| **Vm, Km** | Michaelis Menten elimination parameters - example |

| | |
|---|---|
| **kij, kji** | Transfer rate constants between compartments **i** & **j** - example |
| **kt** | Transfer rate constant between two compartments - example |
| **from, to** | Source and target compartments - example |
| **keo** | Effect compartment transfer rate constant - example |
| **amount** | Amount in a compartment - example |
| **concentration** | Concentration in a compartment - example |
| **volume** | Central compartment volume - example |
| **pkmodel** | Function for standard PK models - example |
| **tDose** | Time of the last administered dose - example |
| **amtDose** | Amount of the last administered dose - example |
| **inftDose** | Infusion time of the last administered dose |

## List of symbols for ODE:

| | |
|---|---|
| **t** | First regression variable, denoted as continuous time |
| **ddt_**<component> | Derivative with respect to time **t** - example |
| <component>**_o** | Initial value - example |
| **to** or **t_o** | Initial time - example |
| **odeType** | ODE solver to use - example |
| **nonstiff** | Non stiff ODE solver |
| **stiff** | Stiff ODE solver - example |
| **linear** | Linear ODE solver |

134

## List of additional symbols for DDE:

| | |
|---|---|
| **delay** | Delayed value of a component of the system - example |

## List of symbols for observations:

| | |
|---|---|
| **type** | Type - example |
| **count** | Count data - example |
| **categorical** | Categorical data - example |
| **event** | Time-to-event data - example |
| **P** | Probability - example |
| **k** | Count value - example |
| **dependence** | dependence = Markov for Markovian dependence - example |
| **Y_p , Y_1** | previous (Y_p) and first (Y_1) observations example |
| **transitionRate** | rate of transition for Markov process - example |
| **categories** | List of categories - example |
| **intervalCensored** | interval censored events - example |
| **maxEventNumber** | maximum number of events - example |
| **intervalLength** | length of censoring interval - example |
| **rightCensoringTime** | duration of the study - example |
| **hazard** | Hazard function - example |
| **wsmm** | Within subject mixture model |
| **bsmm** | Between subject mixture model |

| | |
|---|---|
| **continuous** | Continuous data - example |
| **prediction** | Prediction - example |
| **errorModel** | Error model - example |
| **autocorrelation** | Autocorrelation of observations - example |
| **constant** | Constant error model $y = f + a\,e$ |
| **proportional** | Proportional error model $y = f + b\,f\,e$ |
| **combined1** | Combined error model $y = f + (a + b\,f)e$ |
| **combined2** | Combined error model $y = f + a\,e_1 + b\,f\,e_2$ |
| **proportionalc** | Proportional error model with power $y = f + b\,f^c\,e$ |
| **combined1c** | Combined error model with power $y = f + (a + b\,f^c)e$ |
| **combined2c** | Combined error model with power $y = f + a\,e_1 + b\,f^c\,e_2$ |
| **exponential** | Exponential error model $t(y) = \log(y)$ and $y = f\,e^{a\,e}$ |
| **logit** | Logit error model $t(y) = \log(y/(1-y))$ |
| **band(0, 10)** | Extended logit error model $t(y) = \log(y/(10-y))$ - example |
| **band(0, 100)** | Extended logit error model $t(y) = \log(y/(100-y))$ |

## List of symbols for operators:

| | |
|---|---|
| **+** | Addition or unary plus |
| **-** | Substraction or unary minus |
| ***** | Multiplication |
| **/** | Division |
| **^** | Power |
| **~ or !** | Logical *NOT* |
| **&& or &** | Logical *AND* |
| **\|\| or \|** | Logical *OR* |
| **==** | Equal to |
| **~= or !=** | Not equal to |
| **<** | Less than |
| **<=** | Less than or equal to |
| **>** | Greater than |
| **>=** | Greater than or equal to |

## List of symbols for conditionals:

| | |
|---|---|
| **if** *<condition>* | Weight following definitions with the indicator function of *<condition>* - example |
| **else** | Weight following definitions with the product of indicator functions of complements of all previous conditions - example |
| **elseif** *<condition>* | Weight following definitions with the product of indicator functions of *<condition>* and complements of all previous conditions |
| **end** | Terminate a conditional definitions - example |

## List of symbols for comments:

| | |
|---|---|
| ;*<line remainder>* | Comment. Any following text on the line is ignored |

## List of symbols for usual functions:

abs, sqrt, exp, log, log10, logit, sin, cos, tan, asin, acos, atan, sinh, cosh, tanh, floor, ceil, gammaln, factln, min, max, atan2, rem

## List of symbols for probability distribution functions:

betapdf, betacdf, chi2pdf, chi2cdf, exppdf, expcdf, evpdf, evcdf, fpdf, fcdf, gampdf, gamcdf, gpzpdf, gpzcdf, lognpdf, logncdf, normpdf, normcdf, raylpdf, raylcdf, tpdf, tcdf, unifpdf, unifcdf, wblpdf, wblcdf