Introduction to Simulx

slides courtesy: Laure Deyme

Simulation of a PK model using SimulX

- Simulx = function of the R package mlxR.
- Simulx allows to simulate complex models for longitudinal data by interfacing the C++ MlxLibrary with R.
- Implementing complex ODEs based mixed effects models becomes extremely easy using the model coding language Mlxtran.
- Developed by the Inria Xpop team

Useful website : http://simulx.webpopix.org/

PopPK publication

Read :

Terret et al. Dose and time dependencies of 5-fluorouracil pharmacokinetics. Clin Pharmacol Ther. 2000.

PATIENTS AND METHODS

Patients and treatment schedule. Twenty-one patients with an advanced, histologically proven colorectal carcinoma were studied. Written informed con-

by 5-fluorouracil by intravenous infusion for 10 minutes (400 mg/m^2 in 5% dextrose) and then continuous intravenous infusion (600 mg/m^2 in 5% dextrose) for 22 hours

Pharmacokinetic analysis. Plasma 5-fluorouracil levels were analyzed with the nonlinear mixed-effects modeling program (NONMEM,[25] version V, level 1.1) with the first-order method and the PREDPP package (University of California, San Francisco, Calif).[26] A proportional error model was used for the interpatient variables. A combination model (ie, additive plus proportional) was used for residual variability.

In the first phase of analysis, the data collected within the first 24-hour period of treatment (day 1) were used to test the different pharmacokinetic models: linear elimination (according to a rate constant [k_{10}]) and nonlinear elimination (according to the Michaelis-Menten parameters). For each of these models, one- (corre-

RESULTS

Pharmacokinetic model. Pharmacokinetic data of 5-fluorouracil were available in 21 patients. The data of 5-fluorouracil at day 1 were best described by a two-compartment model with a nonlinear elimination from the central compartment (Table II). No interindividual

PopPK publication

Collect :

Table III. Pharmacokinetic parameters of 5-fluorouracil at day 1

Parameters	*Mean (95% confidence interval)*	*Interindividual variability* (95% confidence interval)*
Central volume of distribution (L)	12.7 (9.6-15.8)	31% (11%-42%)
k_{12} (rate constant from central to peripheral volume) (h^{-1})	5.35 (3.32-7.38)	—†
k_{21} (rate constant from peripheral to central volume) (h^{-1})	5.69 (4.00-7.38)	27% (0%-43%)
V_{max} (maximum rate of elimination) ($mg \cdot h^{-1}$)	1390 (1213-1567)	20% (2%-28%)
K_m ($mg \cdot L^{-1}$)	5.57 (4.36-6.78)	22% (0%-36%)

*Coefficient of variation.
†Interindividual variability on k_{12} was fixed to zero.

PK model of 5 – FU in mlxtran

→.txt file

[LONGITUDINAL]
In the [LONGITUDINAL] sections the structural model and the error model are described.

The [LONGITUDINAL] section is mandatory for all Mlxtran models for Monolix, Mlxplore and Simulx.

input = { }
The input = { } list of the [LONGITUDINAL] section declares parameters

PK :
The PK: block permits to define PK models using macros, and to link the administration information of the data set with the model.

EQUATION :
The EQUATION: block is for mathematical equations including ODEs, DDEs and macros.

PK model of 5 – FU in mlxtran

[LONGITUDINAL]

→ **File: PKTerretFU.txt**

input = {V, k12, k21, Vm, Km**}**

PK :
Depot (target = Ac)

EQUATION :

ddt_Ac =
ddt_Ap =

Cc =

Simulation of 5-FU PK model using SimulX

New R Script :

- **setwd**("C:/Users/……./Desktop/simulx")

Change set working directory (setwd, in first line) with your pathway

- install.packages("mlxR")
- install.packages("ggplot2")

→ **R Script : FUTerretPK**

- library("ggplot2")
- library("mlxR")

- param <- c(, , , ,)
- adm <- list(time=c(,), amount=c(,), tinf=c(,))
- list.out <- list(name=“ ", time=seq(, , by=))

- pk.res <- simulx(model=“ .txt", parameter= , output= , treatment=)

- print(ggplot(data=pk.res$Cc, aes(x= , y=)) + geom_line(size=1))

- AUC <- exposure(model=“ .txt",parameter= , output= , treatment=)
- print(AUC)

PopPK model of Nivolumab

Table 1 PPK final model parameter estimates

Parameter[a] [units]	Estimate[b]	95% confidence interval[c]
Structural model parameters		
CL_{REF} [mL/h]	9.4	8.7 – 10
VC_{REF} [L]	3.63	3.5 – 3.75
Q_{REF} [mL/h]	32.1	25.9 – 37.4
VP_{REF} [L]	2.78	2.58 – 3.04
Interindividual variability model parameters		
ω^2_{CL}	0.123 (0.35)	0.106 – 0.143
ω^2_{VC}	0.123 (0.351)	0.0929 – 0.156
ω^2_{VP} [-]	0.258 (0.508)	0.197 – 0.315
ω^2_{EMAX}	0.0719 (0.268)	0.0488 – 0.119
ω_{CL}:ω_{VC}	0.0432 (0.352)	0.0344 – 0.0547
Residual error model parameters		
Proportional error [-]	0.215	0.203 – 0.229

BW, body weight; BPS, baseline performance status; CL, clearance; eGFR, estimated glomerular filtration rate; Q, inter-compartmental clearance; RAAS, Race (Asian); VC, volume of central compartment; VP, volume of peripheral compartment.

ment. The IIV parameters of the base model were specified by a lognormal model

Bajaj G, Wang X, Agrawal S, Gupta M, Roy A, Feng Y. Model-Based Population Pharmacokinetic Analysis of Nivolumab in Patients With Solid Tumors. CPT Pharmacomet Syst Pharmacol. 2017 Jan;6(1):58–66.

PopPK model of Nivolumab

[LONGITUDINAL]
input = {V1, V2, Q, CL}

PK:
depot(target = Ac)

EQUATION:

k12 =
k21 =
k10 =

ddt_Ac =
ddt_Ap =

Cc =

PopPK model of Nivolumab

[INDIVIDUAL]

The [INDIVIDUAL] section is used to define a probability distribution for model parameters. It is used to model inter-individual variability for given parameters.

It is only needed for models that have parameters with inter-individual variability.

input = { }

The input = { } list of the [INDIVIDUAL] section declares (typical, IIV, covariate) parameters

DEFINITION:

This block is used to definite probability distributions.

param = {distribution=… , typical = … , sd=…}

PopPK model of Nivolumab with IIV

```
[LONGITUDINAL]
input = {V1, V2, Q, CL}

PK:
depot(target = Ac)

EQUATION:

k12 =
k21 =
k10 =

ddt_Ac =
ddt_Ap =

Cc =

[INDIVIDUAL]

input= {V1_pop, V2_pop, Q_pop, CL_pop, omega_V1, omega_V2, omega_Q, omega_CL}

DEFINITION:

V1   = {distribution=,  typical = ,    sd=}
V2   = {distribution=,  typical = ,    sd=}
Q    = {distribution=,  typical = ,    sd=}
CL   = {distribution=,  typical = ,    sd=}
```

→ **File: pkpopnivolumab.txt**

→ **R script : nivolumabpkpop**

PopPK model of Nivolumab with IIV

```
library("ggplot2")
library("mlxR")

pop.param <- c(V1_pop  = ,  omega_V1  = ,
               V2_pop  = ,  omega_V2  = ,
               Q_pop   = ,  omega_Q   = ,
               cl_pop  = , omega_cl  = )
N = # number of Monte-Carlo simulations

trt1 <- list(time=c(, , ), amount=c(, ,)) # dose 1 = 240 mg
trt2 <- list(time=c(, , ), amount=c(, ,)) # dose 2 = 400 mg
g1  <- list(treatment = trt1, size=N, level='individual')
g2  <- list(treatment = trt2, size=N, level='individual')

res2 <- simulx(model= "pkpopnivolumab.txt",
               parameter= pop.param,
               group= list(g1,g2),
               output= list(name='Cc', time=seq(, , by= )))

prctilemlx(res2$Cc, number=2, level=90)
```

Data simulation of Nivolumab

Problem:

1) simulate a clinical trial with n=10 individuals with dose 240 mg administrated every 2 weeks starting at time 0, for 4 cycles, with a constant error model with parameter a=1.

For each patient:

- the predicted concentration every hour
- the observed concentration every 3 days

2) Same with dose 480 mg q4w for 2 cycles

3) Proportional error model

Data simulation of Nivolumab

```
[LONGITUDINAL]
input = {V1, V2, Q, CL,a}

PK:
depot(target = Ac)

EQUATION:
k12 =
k21 =
k10 =

ddt_Ac =
ddt_Ap =

Cc =

DEFINITION:
y1 = {distribution=, prediction=, sd= }
```

Demo : Simulation PKPD model

```
[LONGITUDINAL]
input={Tk0,V,Cl,kout,E0,IC50}

EQUATION:
C = pkmodel(Tk0, V, Cl)

E_0 = E0
kin = E0*kout
ddt_E = kin*(1-C/(C+IC50)) - kout*E
```

Per os administration
1-CPT PK, zero-order absorption
Linear elimination

Indirect effect model
In presence of drug → diminution

→ **File: pkpdsimulx.txt**

```
[INDIVIDUAL]
input={Tk0_pop,V_pop,Cl_pop,E0_pop,IC50_pop,kout_pop, omega_Tk0,omega_V,omega_Cl,omega_E0,omega_IC50,
       omega_kout}

DEFINITION:
Tk0   = {distribution=lognormal,   prediction=Tk0_pop,  sd=omega_Tk0}
V     = {distribution=lognormal,   prediction=V_pop,    sd=omega_V}
Cl    = {distribution=lognormal,   prediction=Cl_pop,   sd=omega_Cl}
E0    = {distribution=lognormal,   prediction=E0_pop,   sd=omega_E0}
IC50  = {distribution=lognormal,   prediction=IC50_pop, sd=omega_IC50}
kout  = {distribution=lognormal,   prediction=kout_pop, sd=omega_kout}
```

Demo : Simulation PKPD model

Source on Save

```r
setwd("C:/Users/Laure/Desktop")
install.packages("mlxR")
install.packages("ggplot2")

library("ggplot2")
library("mlxR")

N=400
adm.time <- seq(10,200,by=12)

trt3 <- list(time=adm.time, amount= 50)

pop.param    <- c(
  Tk0_pop    = 3,     omega_Tk0    = 0.2,
  V_pop      = 10,    omega_V      = 0.2,
  Cl_pop     = 1,     omega_Cl     = 0.2,
  E0_pop     = 10,   omega_E0     = 0.1,
  IC50_pop   = 3,     omega_IC50   = 0.1,
  kout_pop=0.4, omega_kout=0.1)
g3<- list(treatment = trt3, size=N, level='individual')
f <- list(name = c('C','E'),
          time = seq(0,250,by=2))
res <- simulx(model     = "pkpdsimulx.txt",
              parameter = pop.param,
              output    = f,group=g3)

prctilemlx(res$C)
prctilemlx(res$E)
```

→ **R script : simulxpkpd**

Demo : Simulation PKPD model