

Package compilation for saemix 3.2 and basic run

Emmanuelle Comets

16/08/2022

Copy files

```
cmd<-paste("rm -r ",file.path(workDir,"*"),sep="")
system(cmd)

dir.create(workDir)

## Warning in dir.create(workDir): '/home/eco/work/saemix/versions/saemix3.2'
## existe déjà

dir.create(file.path(workDir,"saemix"))

cmd<-paste("cp -rp ",file.path(saemixDir,"documentation","docsaem.pdf")," ",file.path(saemixDir,"inst",
system(cmd)

cmd<-paste("cp -rp ",file.path(saemixDir,"R")," ", file.path(workDir,"saemix","/"),sep="")
system(cmd)
cmd<-paste("cp -rp ",file.path(saemixDir,"data")," ", file.path(workDir,"saemix","/"),sep="")
system(cmd)
cmd<-paste("cp -rp ",file.path(saemixDir,"inst")," ", file.path(workDir,"saemix","/"),sep="")
system(cmd)
for(ifile in c("CHANGES","DESCRIPTION")) {
  cmd<-paste("cp ",file.path(saemixDir,ifile)," ", file.path(workDir,"saemix"),sep="")
  system(cmd)
}
cmd<-paste("cp ",file.path(saemixDir,"inst","CITATION")," ", file.path(workDir,"saemix","inst"),sep="")
system(cmd)
```

Compilation

- building on win-ftp
 - to specify when submitting Possibly mis-spelled words in DESCRIPTION: IAME (17:930) al (17:663) et (17:660) github (17:954) saemix (17:965)
 - removed: Found the following (possibly) invalid URLs: URL: <http://group.monolix.org/> From: DESCRIPTION Status: 403 Message: Forbidden
 - to change: no commas between keywords in R (maybe for vignettes)
 - previous version, solved now:

```
```\r}
Found the following \keyword or \concept entries
which likely give several index terms:
File 'backward.procedure.Rd':
 \keyword{backward,}
```

```

\keyword{selection,}
... (others)
...

```

- Examples with CPU or elapsed time > 5s user system elapsed rapi.saemix 47.006 0.096 47.115 cow.saemix 25.185 0.120 25.311 PD1.saemix 18.925 0.048 19.108 toenail.saemix 16.656 0.020 16.676 compare.saemix 9.152 0.020 9.171 theo.saemix 6.481 0.008 6.490 yield.saemix 5.419 0.016 5.435

```

setwd(workDir)
system("R CMD build saemix")

Test examples
if(testExamples)
 system("R CMD check --as-cran --run-donttest saemix_3.2.tar.gz") else
 system("R CMD check --as-cran saemix_3.2.tar.gz")

Reverse dependencies
cmd<-paste("cp ",file.path("/home/eco/work/saemix/versions/reverseDependencies/varTestnlme_1.3.0.tar.gz
system(cmd)

if(checkReverseDependencies) {
 # Check which packages depend on saemix
 package_dependencies(packages="saemix", reverse=TRUE)
 # TODO download these packages into workDir
}

if(installPackage) {
 # install saemix current version and check packages
 install.packages(pkgs=file.path(workDir,"saemix_3.2.tar.gz"),repos=NULL)
 #result <- check_packages_in_dir(workDir, revdep = list())
 result <- check_packages_in_dir(workDir, revdep = list("varTestnlme"))
 summary(result)
}

```

**Examples on CRAN** Examples with CPU or elapsed time > 5s user system elapsed rapi.saemix 32.510 0.092 32.602 cow.saemix 17.020 0.072 17.093 toenail.saemix 13.531 0.000 13.532 PD1.saemix 12.789 0.035 12.910 compare.saemix 6.331 0.016 6.347 theo.saemix 5.171 0.000 5.172

## Warnings

## Check

### Install package in development mode

```

dev_mode() # development mode

v Dev mode: ON

install.packages(pkgs=file.path(workDir,"saemix_3.2.tar.gz"),repos=NULL)

Installation du package dans '/home/eco/R-dev'
(car 'lib' n'est pas spécifié)

library(saemix)
library(testthat)

##

```

```
Attachement du package : 'testthat'
##
L'objet suivant est masqué depuis 'package:devtools':
##
test_file
```

## Running theopp example

```
?theo.saemix
```

```
Aucune documentation pour 'theo.saemix' n'a été trouvée dans les packages et les bibliothèques :
vous pourriez essayer '??theo.saemix'
```

```
?saemix
```

```
Aucune documentation pour 'saemix' n'a été trouvée dans les packages et les bibliothèques :
vous pourriez essayer '??saemix'
```

Run on the theophylline example

```
Object of class SaemixData
longitudinal data for use with the SAEM algorithm
Dataset theo.saemix
Structured data: Concentration ~ Dose + Time | Id
X variable for graphs: Time (hr)
covariates: Weight (kg), Sex (-)
reference class for covariate Sex : 0
Dataset characteristics:
number of subjects: 12
number of observations: 120
average/min/max nb obs: 10.00 / 10 / 10
First 10 lines of data:
Id Dose Time Concentration Weight Sex mdv cens occ ytype
1 1 319.992 0.25 2.84 79.6 1 0 0 1 1
2 1 319.992 0.57 6.57 79.6 1 0 0 1 1
3 1 319.992 1.12 10.50 79.6 1 0 0 1 1
4 1 319.992 2.02 9.66 79.6 1 0 0 1 1
5 1 319.992 3.82 8.58 79.6 1 0 0 1 1
6 1 319.992 5.10 8.36 79.6 1 0 0 1 1
7 1 319.992 7.03 7.47 79.6 1 0 0 1 1
8 1 319.992 9.05 6.89 79.6 1 0 0 1 1
9 1 319.992 12.12 5.94 79.6 1 0 0 1 1
10 1 319.992 24.37 3.28 79.6 1 0 0 1 1

Nonlinear mixed-effects model
Model function: One-compartment model with first-order absorption
Model type: structural
function(psi,id,xidep) {
dose<-xidep[,1]
tim<-xidep[,2]
ka<-psi[id,1]
V<-psi[id,2]
CL<-psi[id,3]
k<-CL/V
ypred<-dose*ka/(V*(ka-k))*(exp(-k*tim)-exp(-ka*tim))
return(ypred)
}
```

```

Nb of parameters: 3
parameter names: ka V CL
distribution:
Parameter Distribution Estimated
[1,] ka log-normal Estimated
[2,] V log-normal Estimated
[3,] CL log-normal Estimated
Variance-covariance matrix:
ka V CL
ka 1 0 0
V 0 1 0
CL 0 0 1
Error model: constant , initial values: a.1=1
Covariate model:
ka V CL
[1,] 0 1 0
[2,] 0 0 0
Initial values
ka V CL
Pop.CondInit 1.0 20 0.50
Cov.CondInit 0.1 0 -0.01

Nonlinear mixed-effects model fit by the SAEM algorithm

----- Data -----

Object of class SaemixData
longitudinal data for use with the SAEM algorithm
Dataset theo.saemix
Structured data: Concentration ~ Dose + Time | Id
X variable for graphs: Time (hr)
covariates: Weight (kg), Sex (-)
reference class for covariate Sex : 0
Dataset characteristics:
number of subjects: 12
number of observations: 120
average/min/max nb obs: 10.00 / 10 / 10
First 10 lines of data:
Id Dose Time Concentration Weight Sex mdv cens occ ytype
1 1 319.992 0.25 2.84 79.6 1 0 0 1 1
2 1 319.992 0.57 6.57 79.6 1 0 0 1 1
3 1 319.992 1.12 10.50 79.6 1 0 0 1 1
4 1 319.992 2.02 9.66 79.6 1 0 0 1 1
5 1 319.992 3.82 8.58 79.6 1 0 0 1 1
6 1 319.992 5.10 8.36 79.6 1 0 0 1 1
7 1 319.992 7.03 7.47 79.6 1 0 0 1 1
8 1 319.992 9.05 6.89 79.6 1 0 0 1 1
9 1 319.992 12.12 5.94 79.6 1 0 0 1 1
10 1 319.992 24.37 3.28 79.6 1 0 0 1 1

----- Model -----

Nonlinear mixed-effects model
Model function: One-compartment model with first-order absorption

```

```

Model type: structural
function(psi,id,xidep) {
dose<-xidep[,1]
tim<-xidep[,2]
ka<-psi[id,1]
V<-psi[id,2]
CL<-psi[id,3]
k<-CL/V
ypred<-dose*ka/(V*(ka-k))*(exp(-k*tim)-exp(-ka*tim))
return(ypred)
}
<bytecode: 0x55d129a226a0>
Nb of parameters: 3
parameter names: ka V CL
distribution:
Parameter Distribution Estimated
[1,] ka log-normal Estimated
[2,] V log-normal Estimated
[3,] CL log-normal Estimated
Variance-covariance matrix:
ka V CL
ka 1 0 0
V 0 1 0
CL 0 0 1
Error model: constant , initial values: a.1=1
Covariate model:
[,1] [,2] [,3]
Weight 0 1 0
Initial values
ka V CL
Pop.CondInit 1.0 20 0.50
Cov.CondInit 0.1 0 -0.01

---- Key algorithm options ----

Estimation of individual parameters (MAP)
Estimation of standard errors and linearised log-likelihood
Estimation of log-likelihood by importance sampling
Number of iterations: K1=300, K2=100
Number of chains: 5
Seed: 632545
Number of MCMC iterations for IS: 5000
Simulations:
nb of simulated datasets used for npde: 1000
nb of simulated datasets used for VPC: 100
Input/output
save the results to a file: FALSE
save the graphs to files: FALSE

---- Results ----

----- Fixed effects -----

Parameter Estimate SE CV(%) p-value

```

```

[1,] ka 1.5588 0.3071 19.7 -
[2,] V 18.8423 5.6328 29.9 -
[3,] beta_Weight(V) 0.0073 0.0042 58.0 0.085
[4,] CL 2.7717 0.2431 8.8 -
[5,] a.1 0.7389 0.0565 7.7 -

----- Variance of random effects -----

Parameter Estimate SE CV(%)
ka omega2.ka 0.414 0.1853 45
V omega2.V 0.012 0.0078 64
CL omega2.CL 0.077 0.0368 48

----- Correlation matrix of random effects -----

omega2.ka omega2.V omega2.CL
omega2.ka 1 0 0
omega2.V 0 1 0
omega2.CL 0 0 1

----- Statistical criteria -----

Likelihood computed by linearisation
-2LL= 341.3649
AIC = 357.3649
BIC = 361.2442
##
Likelihood computed by importance sampling
-2LL= 342.6478
AIC = 358.6478
BIC = 362.5271

Nonlinear mixed-effects model fit by the SAEM algorithm

----- Data -----

Object of class SaemixData
longitudinal data for use with the SAEM algorithm
Dataset theo.saemix
Structured data: Concentration ~ Dose + Time | Id
X variable for graphs: Time (hr)
covariates: Weight (kg), Sex (-)
reference class for covariate Sex : 0
Dataset characteristics:
number of subjects: 12
number of observations: 120
average/min/max nb obs: 10.00 / 10 / 10
First 10 lines of data:
Id Dose Time Concentration Weight Sex mdv cens occ ytype
1 1 319.992 0.25 2.84 79.6 1 0 0 1 1
2 1 319.992 0.57 6.57 79.6 1 0 0 1 1
3 1 319.992 1.12 10.50 79.6 1 0 0 1 1
4 1 319.992 2.02 9.66 79.6 1 0 0 1 1

```

```

5 1 319.992 3.82 8.58 79.6 1 0 0 1 1
6 1 319.992 5.10 8.36 79.6 1 0 0 1 1
7 1 319.992 7.03 7.47 79.6 1 0 0 1 1
8 1 319.992 9.05 6.89 79.6 1 0 0 1 1
9 1 319.992 12.12 5.94 79.6 1 0 0 1 1
10 1 319.992 24.37 3.28 79.6 1 0 0 1 1

---- Model ----

Nonlinear mixed-effects model
Model function: One-compartment model with first-order absorption
Model type: structural
function(psi,id,xidep) {
dose<-xidep[,1]
tim<-xidep[,2]
ka<-psi[id,1]
V<-psi[id,2]
CL<-psi[id,3]
k<-CL/V
ypred<-dose*ka/(V*(ka-k))*(exp(-k*tim)-exp(-ka*tim))
return(ypred)
}
<bytecode: 0x55d129a226a0>
Nb of parameters: 3
parameter names: ka V CL
distribution:
Parameter Distribution Estimated
[1,] ka log-normal Estimated
[2,] V log-normal Estimated
[3,] CL log-normal Estimated
Variance-covariance matrix:
ka V CL
ka 1 0 0
V 0 1 0
CL 0 0 1
Error model: constant , initial values: a.1=1
Covariate model:
[,1] [,2] [,3]
Weight 0 1 0
Initial values
ka V CL
Pop.CondInit 1.0 20 0.50
Cov.CondInit 0.1 0 -0.01

---- Key algorithm options ----

Estimation of individual parameters (MAP)
Estimation of standard errors and linearised log-likelihood
Estimation of log-likelihood by importance sampling
Number of iterations: K1=300, K2=100
Number of chains: 5
Seed: 632545
Number of MCMC iterations for IS: 5000
Simulations:

```

```

nb of simulated datasets used for npde: 1000
nb of simulated datasets used for VPC: 100
Input/output
save the results to a file: FALSE
save the graphs to files: FALSE

----- Results -----

----- Fixed effects -----

Warning in .local(x, ...): NAs introduits lors de la conversion automatique

Parameter Estimate SE CV(%) p-value
[1,] ka 1.5588 0.3071 19.7 -
[2,] V 18.8423 5.6328 29.9 -
[3,] beta_Weight(V) 0.0073 0.0042 58.0 0.085
[4,] CL 2.7717 0.2431 8.8 -
[5,] a.1 0.7389 0.0565 7.7 -

----- Variance of random effects -----

Parameter Estimate SE CV(%)
ka omega2.ka 0.414 0.1853 45
V omega2.V 0.012 0.0078 64
CL omega2.CL 0.077 0.0368 48

----- Correlation matrix of random effects -----

omega2.ka omega2.V omega2.CL
omega2.ka 1 0 0
omega2.V 0 1 0
omega2.CL 0 0 1

----- Statistical criteria -----

Likelihood computed by linearisation
-2LL= 341.3649
AIC = 357.3649
BIC = 361.2442
##
Likelihood computed by importance sampling
-2LL= 342.6478
AIC = 358.6478
BIC = 362.5271

Object of class SaemixSimData
data simulated according to a non-linear mixed effect model
Characteristics of original data
number of subjects: 12
summary of response:
Min. 1st Qu. Median Mean 3rd Qu. Max.
0.850 3.513 5.665 5.447 7.325 11.400
Characteristics of simulated data

```

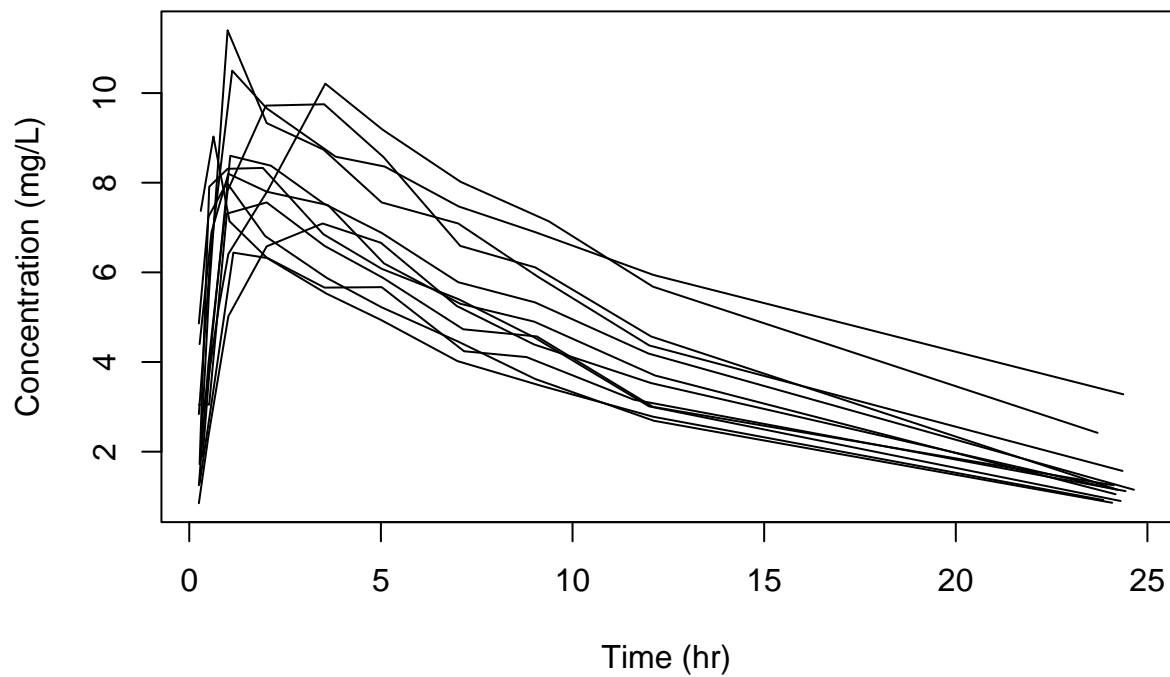


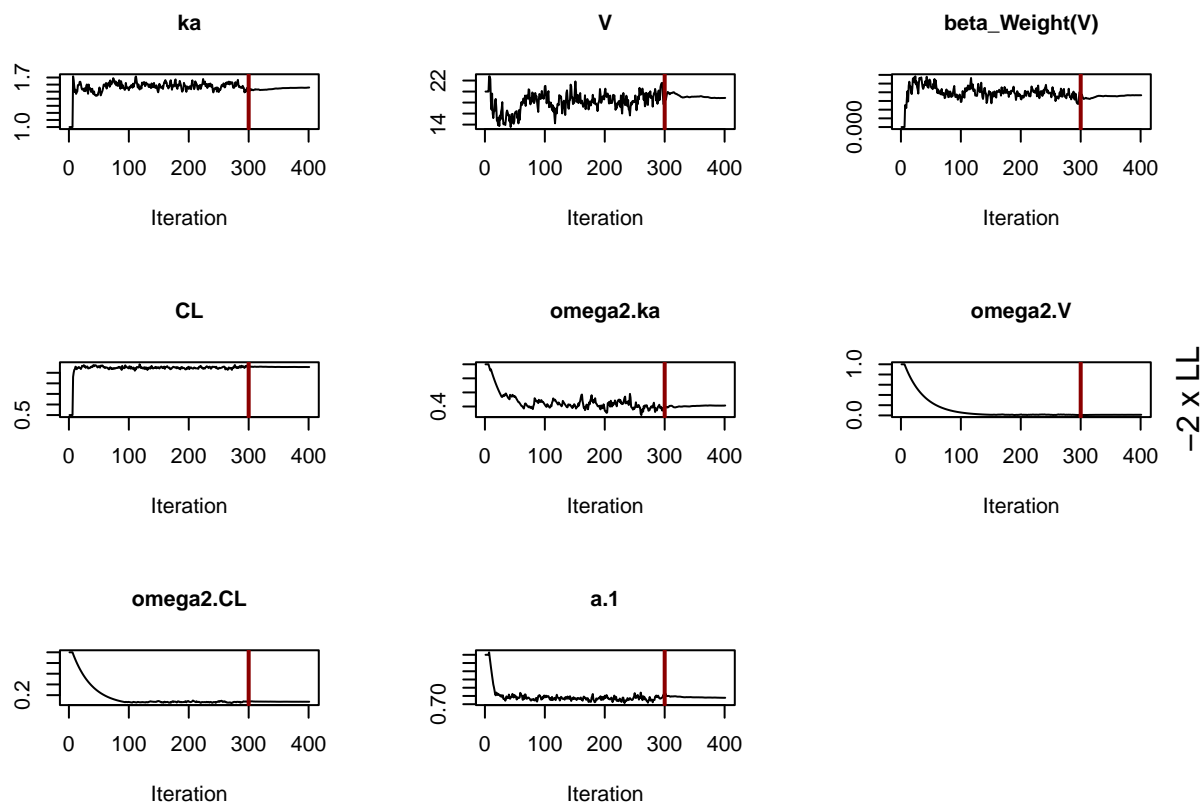
```
number of simulated datasets: 1000
summary of simulated response
Min. 1st Qu. Median Mean 3rd Qu. Max.
-2.364 3.675 5.615 5.479 7.359 14.679
```

```
ka V CL
1 1.7863333 29.59934 1.681678
2 1.9372081 31.98292 3.178891
3 2.2543380 33.18598 2.854727
4 1.2081689 31.53805 2.694492
5 1.4877219 27.10964 2.399152
6 1.0608154 38.09466 4.028817
7 0.6907825 32.17493 3.280839
8 1.3001684 34.17845 3.297077
9 6.3284102 32.50705 2.832542
10 0.7559841 26.58247 1.891913
11 3.1478359 35.17647 3.763632
12 0.9503826 26.06740 2.424328
```

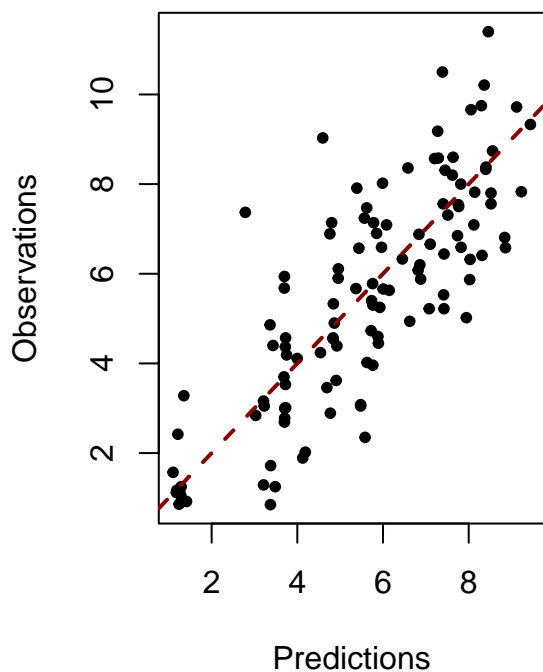
Plot results:

```
Simulating data using nsim = 1000 simulated datasets
Computing WRES and npde ..
```

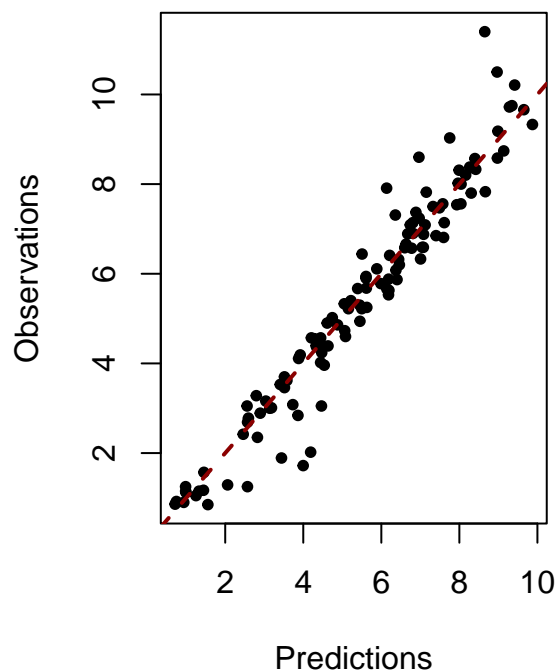




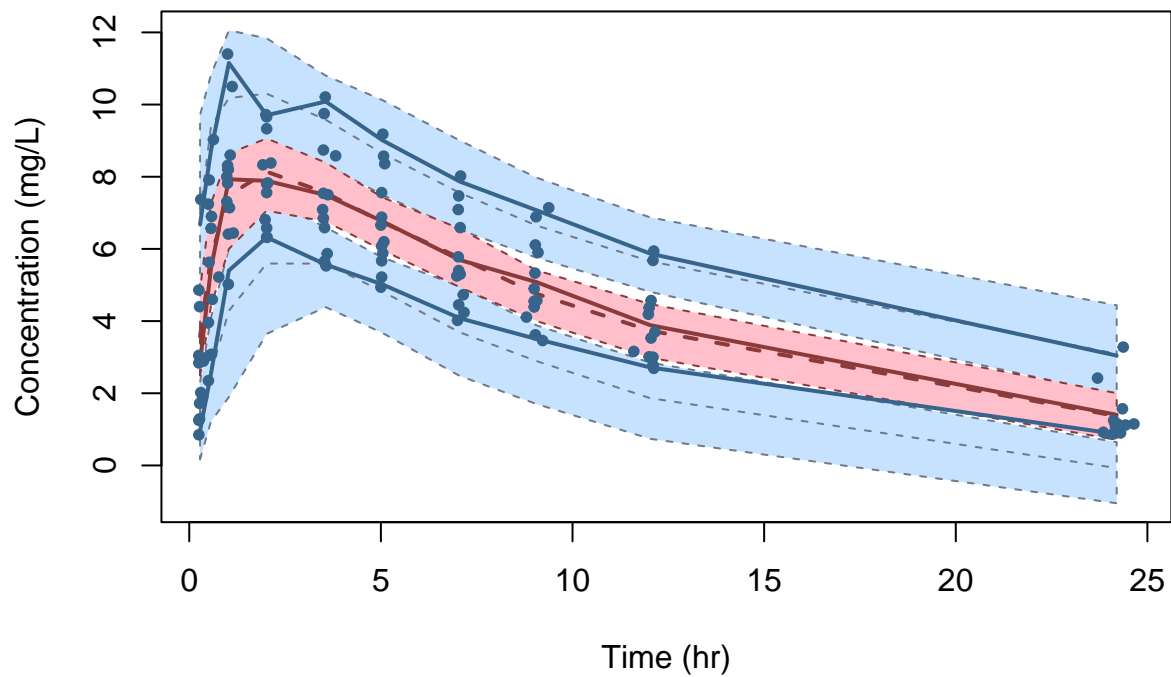
**Population predictions**



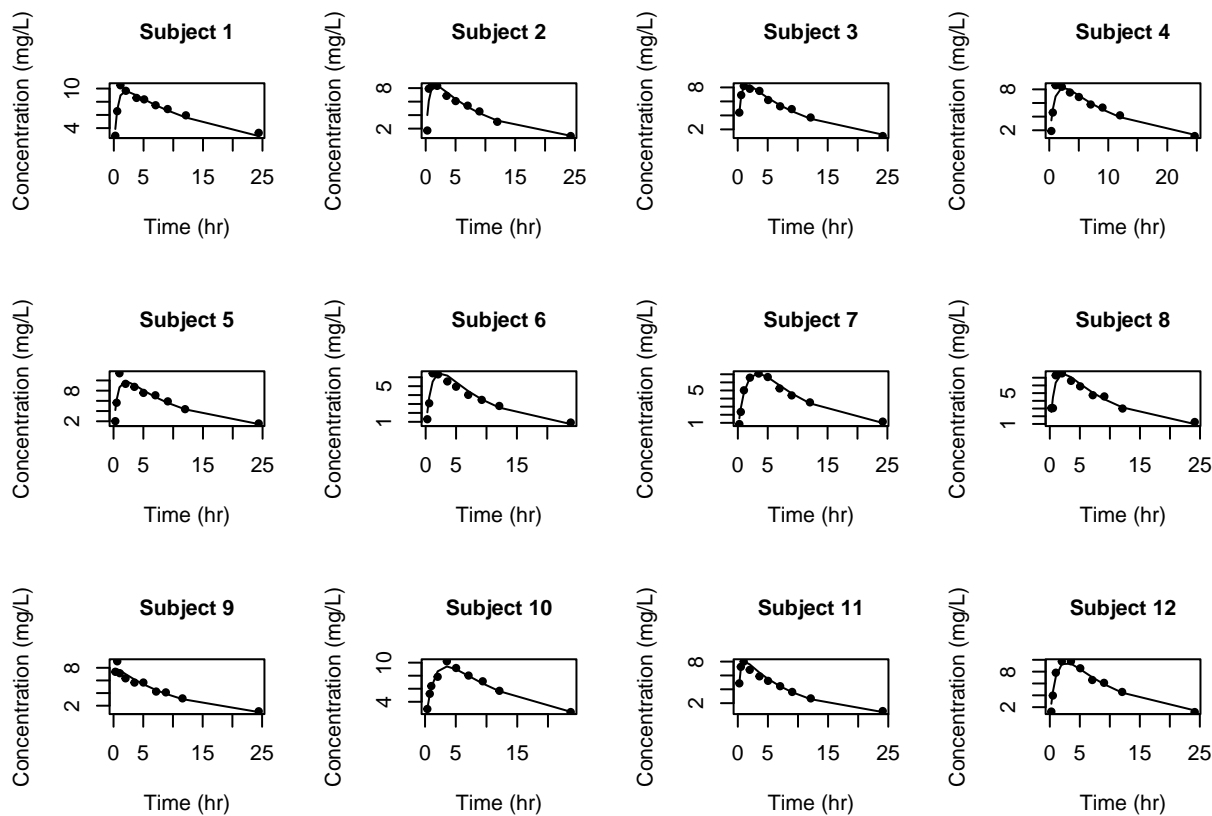
**Individual predictions, MAP**



## Visual Predictive Check



## Computing WRES and npde ..



## Computing WRES and npde ..

```

Please use npdeSaemix to obtain VPC and npde

Warning in read(x, dat, detect = detect, verbose = verbose): NAs introduits lors
de la conversion automatique

Warning in read(x, dat, detect = detect, verbose = verbose): NAs introduits lors
de la conversion automatique

Warning in read(x, dat, detect = detect, verbose = verbose): NAs introduits lors
de la conversion automatique

Warning in read(x, dat, detect = detect, verbose = verbose): NAs introduits lors
de la conversion automatique

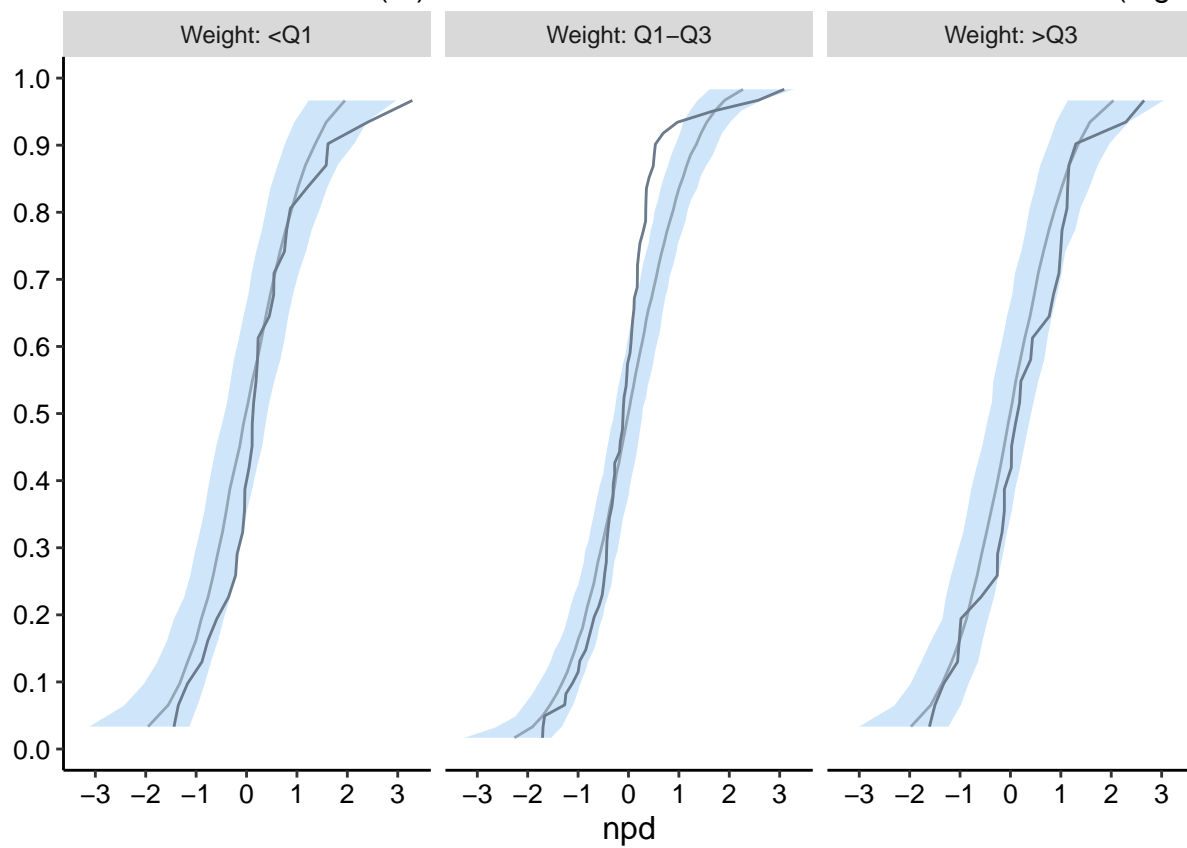
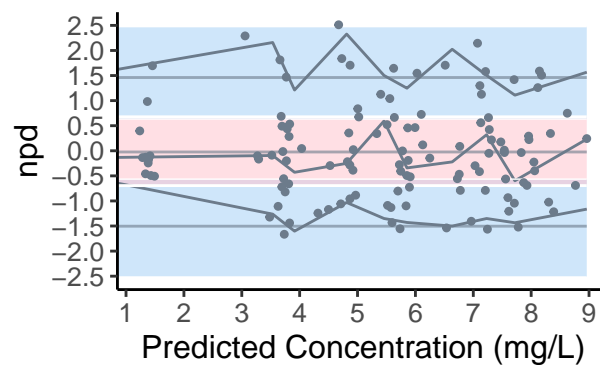
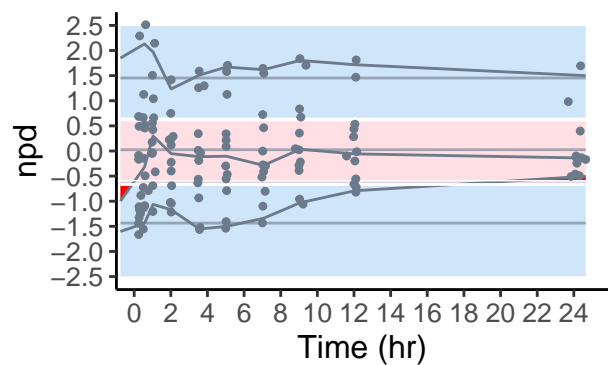
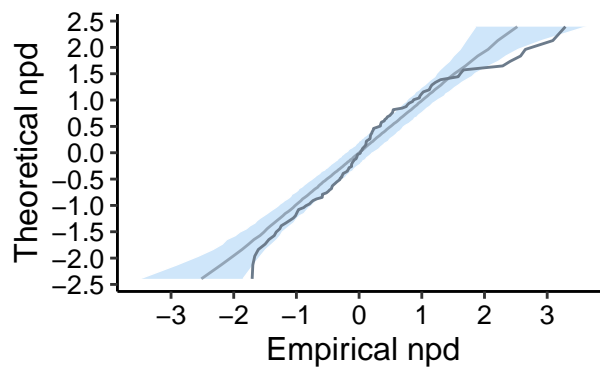
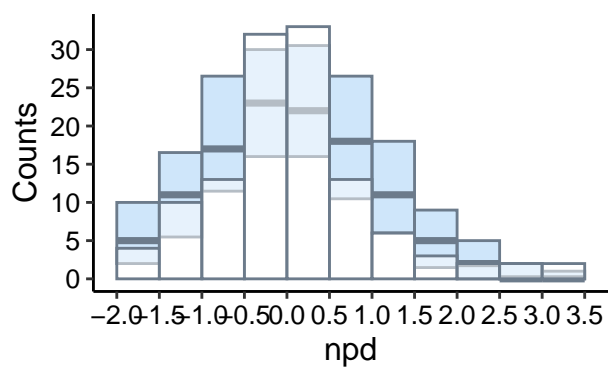
Warning in which(!is.na(as.integer(object@name.covariates))): NAs introduits
lors de la conversion automatique

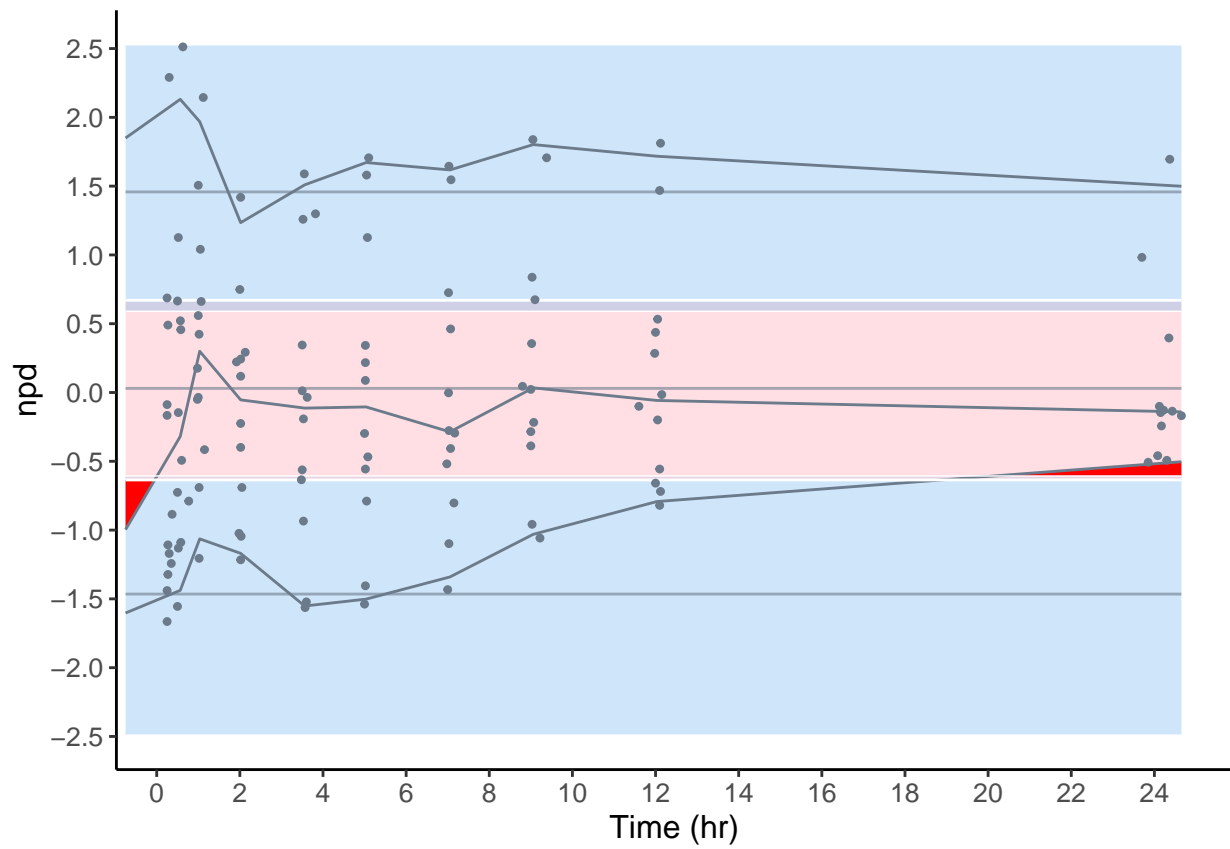
Distribution of npde :
nb of obs: 120
mean= 0.07039 (SE= 0.087)
variance= 0.9023 (SE= 0.12)
skewness= 0.8593
kurtosis= 1.542

Statistical tests (adjusted p-values):
t-test : 1
Fisher variance test : 1
SW test of normality : 0.000231 ***
Global test : 0.000231 ***

Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1

```





Bootstrap

## v Dev mode: OFF