

Package compilation for saemix 3.2 and basic run

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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

```
Reduce size of viral load simulation data (to 500 simulations) for CRAN
knitr::opts_chunk$set(root.dir = file.path(workDir, "saemix"))
setwd(file.path(workDir, "saemix"))

devtools::document(file.path(workDir, "saemix"))
```

```
i Updating saemix documentation
First time using roxygen2. Upgrading automatically...
Updating collate directive in /home/eco/work/saemix/versions/saemix3.2/saemix/DESCRIPTION
i Loading saemix
Loading required package: npde
Package saemix, version 3.2
please direct bugs, questions and feedback to emmanuelle.comets@inserm.fr

Writing NAMESPACE
Writing NAMESPACE
Writing readSaemix-methods.Rd
Writing showall-methods.Rd
Writing psi-methods.Rd
Writing initialize-methods.Rd
Writing print-methods.Rd
Writing show-methods.Rd
Writing summary-methods.Rd
Writing predict-methods.Rd
Writing plot-methods.Rd
Writing saemix.internal.Rd
Writing theo.saemix.Rd
Writing PD1.saemix.Rd
Writing oxboys.saemix.Rd
Writing cow.saemix.Rd
Writing yield.saemix.Rd
Writing toenail.saemix.Rd
Writing knee.saemix.Rd
Writing lung.saemix.Rd
Writing epilepsy.saemix.Rd
Writing rapi.saemix.Rd
Writing SaemixData-class.Rd
Writing extract-methods.Rd
Writing validate.names.Rd
Writing read-methods.Rd
Writing plot-SaemixData.Rd
Writing saemixData.Rd
Writing transform.Rd
Writing transformContCov.Rd
Writing transformCatCov.Rd
```

```

Writing subset.Rd
Writing SaemixModel-class.Rd
Writing sub-SaemixModel-method.Rd
Writing plot-SaemixModel.Rd
Writing predict.SaemixModel.Rd
Writing plot-SaemixModel-SaemixData-method.Rd
Writing saemixModel.Rd
Writing mydiag.Rd
Writing validate.covariance.model.Rd
Writing SaemixRes-class.Rd
Writing sub-SaemixRes-method.Rd
Writing resid.saemix.Rd
Writing fitted.saemix.Rd
Writing vcov.Rd
Writing SaemixObject-class.Rd
Writing saemixControl.Rd
Writing sub-SaemixObject-method.Rd
Writing saemix.predict.Rd
Writing plot-SaemixObject-ANY-method.Rd
Writing logLik.Rd
Writing coef.saemix.Rd
Writing replaceData.Rd
Writing createSaemixObject.Rd
Writing backward.procedure.Rd
Writing llis.saemix.Rd
Writing llgq.saemix.Rd
Writing forward.procedure.Rd
Writing fim.saemix.Rd
Writing map.saemix.Rd
Writing testnpde.Rd
Writing saemix.bootstrap.Rd
Writing bootstrap.data.Rd
Writing compare.saemix.Rd
Writing discreteVPC.Rd
Writing discreteVPCTTE.Rd
Writing conddist.saemix.Rd
Writing saemixPredictNewdata.Rd
Writing plotDiscreteData.Rd
Writing xbinning.Rd
Writing npdeSaemix.Rd
Writing saemix.plot.setoptions.Rd
Writing saemix.plot.select.Rd
Writing default.saemix.plots.Rd
Writing saemix.plot.data.Rd
Writing simulate.SaemixObject.Rd
Writing simulateDiscreteSaemix.Rd
Writing step.saemix.Rd
Writing saemix.Rd
Writing stepwise.procedure.Rd

```

```
roxygenise()
```

```
i Loading saemix
```

```
Package saemix, version 3.2
```

```

please direct bugs, questions and feedback to emmanuelle.comets@inserm.fr
Writing NAMESPACE
Writing NAMESPACE

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)

Installing package into '/home/eco/R-dev'
(as 'lib' is unspecified)

library(saemix)
library(testthat)

##
Attaching package: 'testthat'

The following object is masked from 'package:devtools':

```

```
##
test_file
```

## Running theopp example

```
?theo.saemix
```

```
No documentation for 'theo.saemix' in specified packages and libraries:
you could try '??theo.saemix'
```

```
?saemix
```

```
No documentation for 'saemix' in specified packages and libraries:
you could try '??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 (-)
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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: 0x55f3e8253b30>
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
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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
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```



```

8 1 319.992 9.05 6.89 79.6 1 0 0 1 1
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---- Model ----

Nonlinear mixed-effects model
Model function: One-compartment model with first-order absorption
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function(psi,id,xidep) {
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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: 0x55f3e8253b30>
Nb of parameters: 3
parameter names: ka V CL
distribution:
Parameter Distribution Estimated
[1,] ka log-normal Estimated
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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

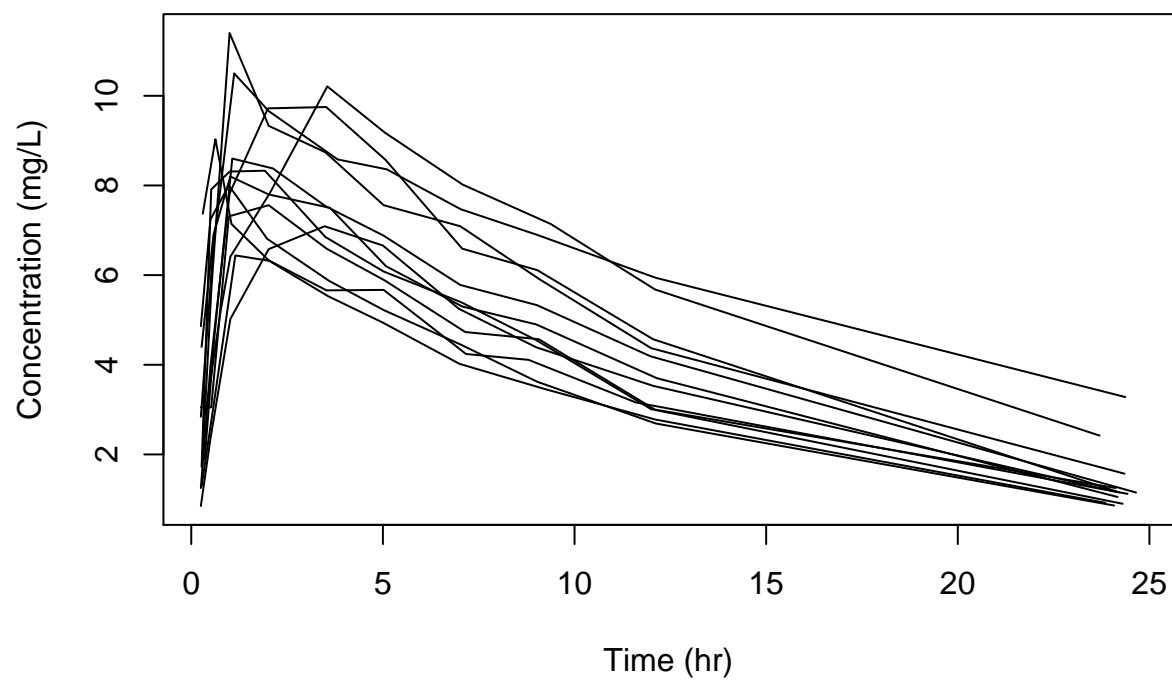
Object of class SaemixSimData
data simulated according to a non-linear mixed effect model
Characteristics of original data
number of subjects: 12
summary of response:
Min. 1st Qu. Median Mean 3rd Qu. Max.
0.850 3.513 5.665 5.447 7.325 11.400
Characteristics of simulated data
number of simulated datasets: 1000
summary of simulated response
Min. 1st Qu. Median Mean 3rd Qu. Max.

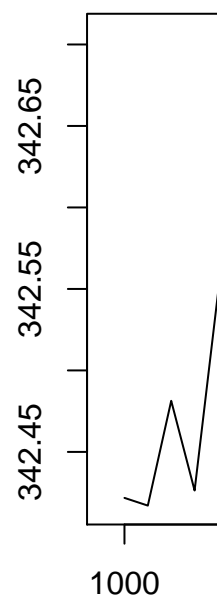
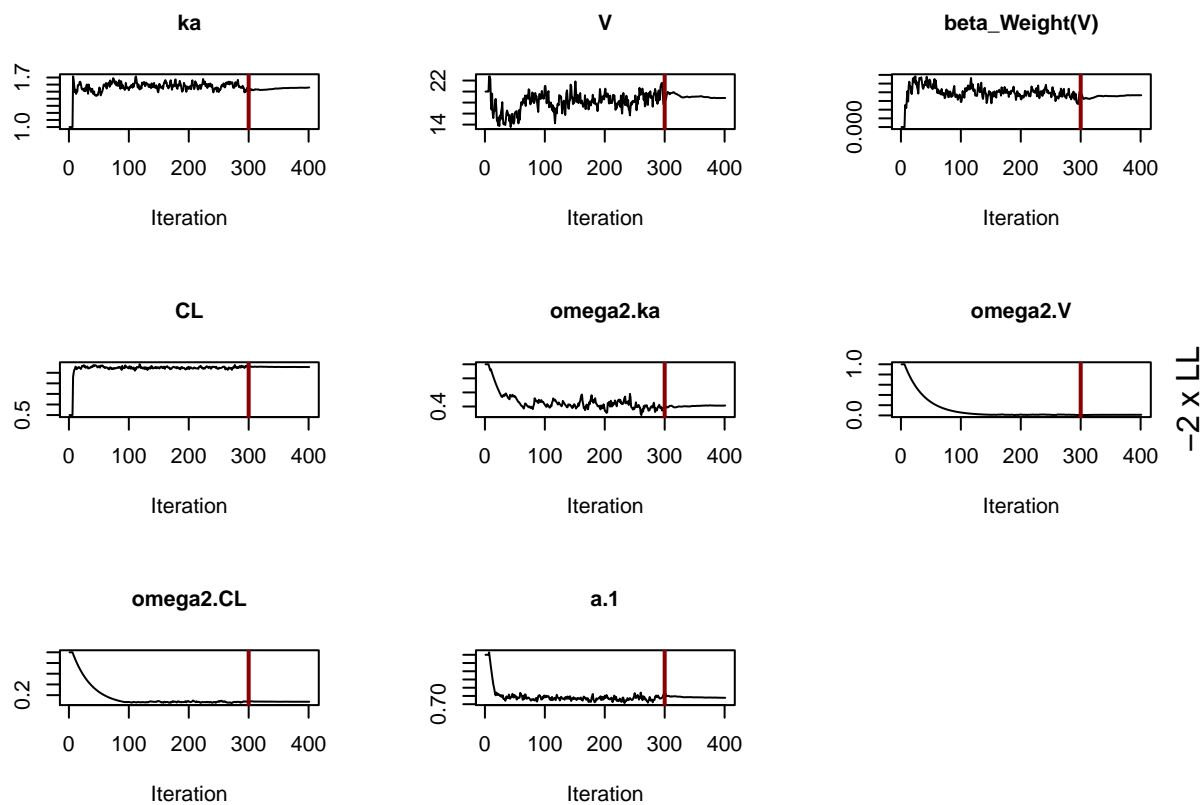
```

## -2.364 3.675 5.615 5.479 7.359 14.679

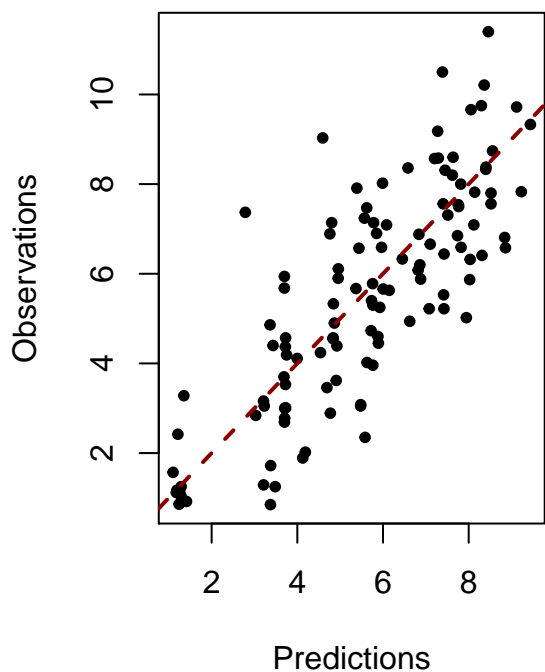
##		ka	V	CL
## 1	1.7863333	29.59934	1.681678	
## 2	1.9372081	31.98292	3.178891	
## 3	2.2543380	33.18598	2.854727	
## 4	1.2081689	31.53805	2.694492	
## 5	1.4877219	27.10964	2.399152	
## 6	1.0608154	38.09466	4.028817	
## 7	0.6907825	32.17493	3.280839	
## 8	1.3001684	34.17845	3.297077	
## 9	6.3284102	32.50705	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:

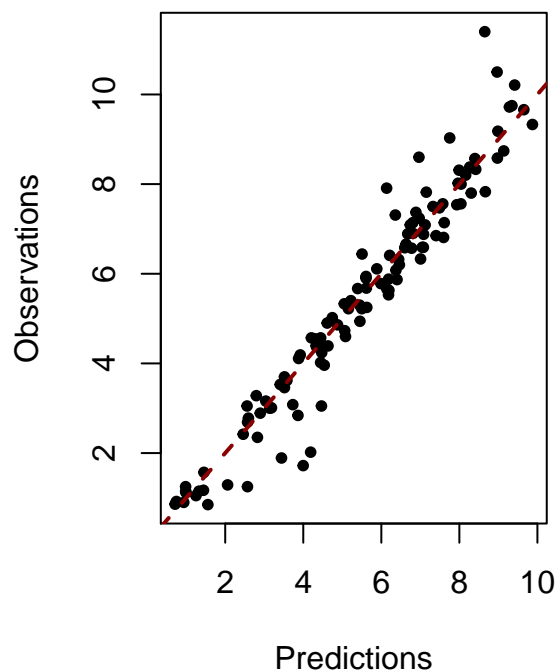




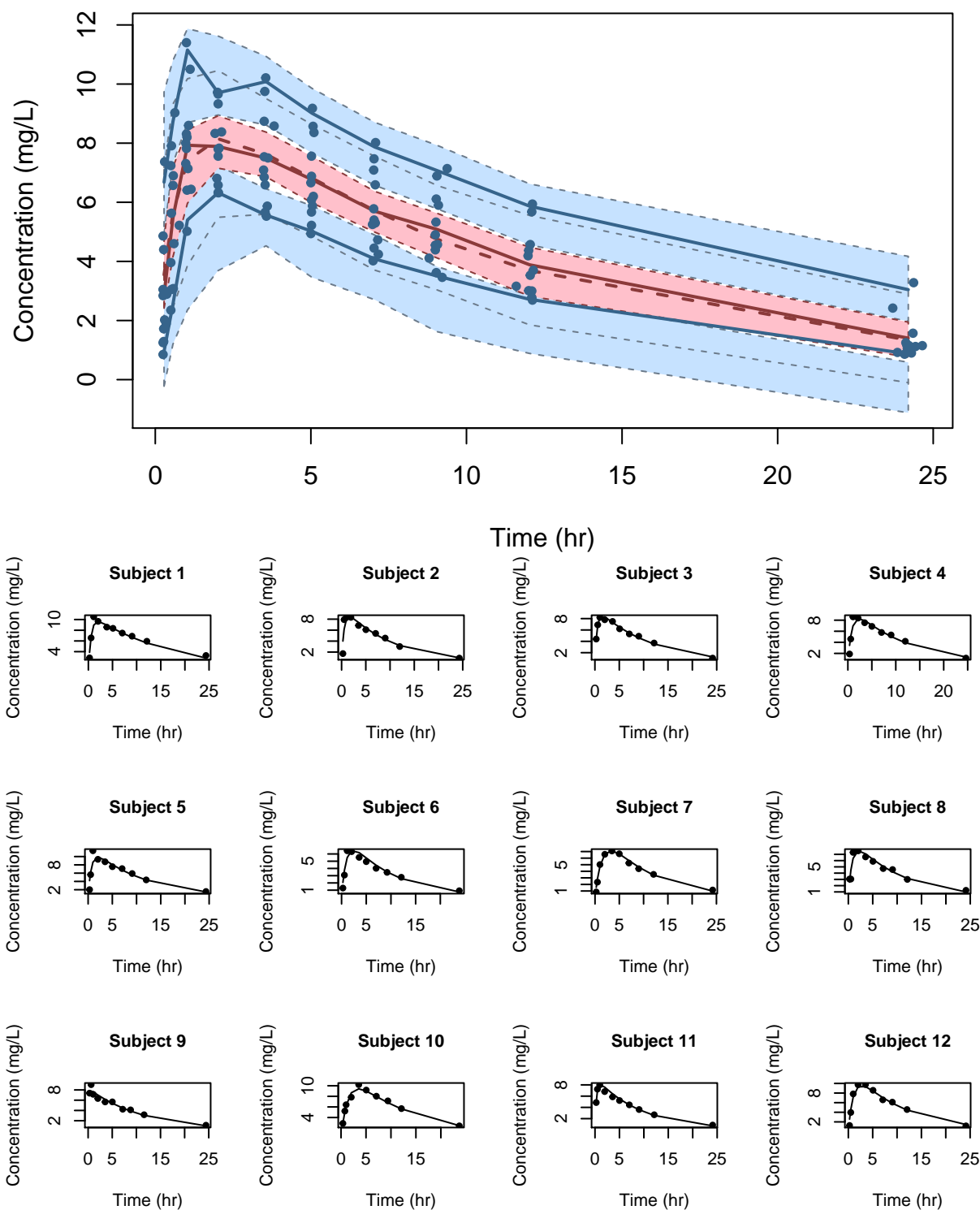
**Population predictions**



**Individual predictions, MAP**



## Visual Predictive Check



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

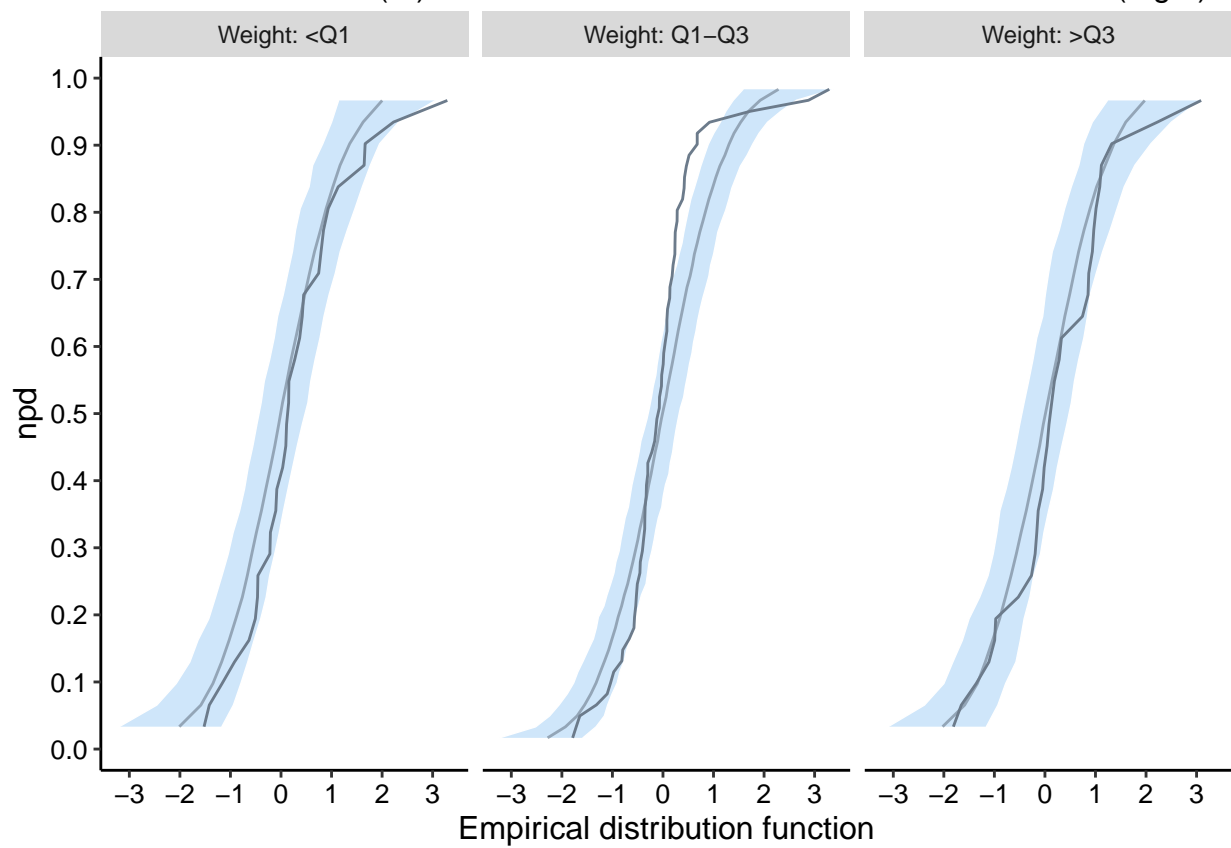
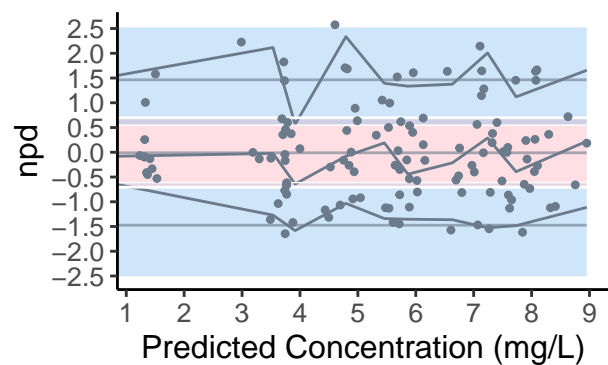
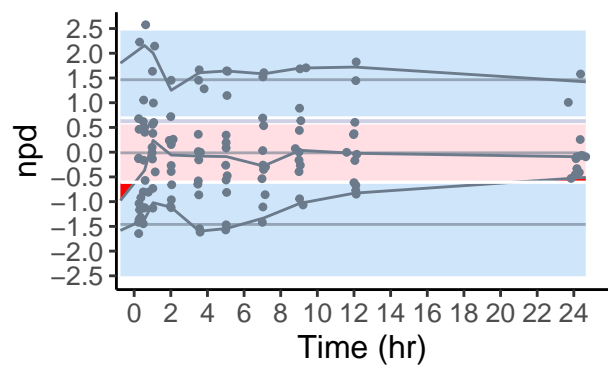
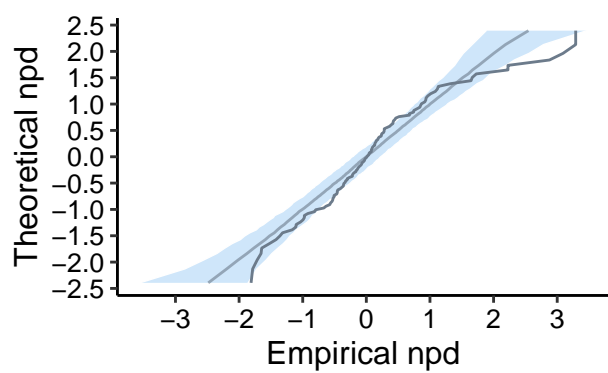
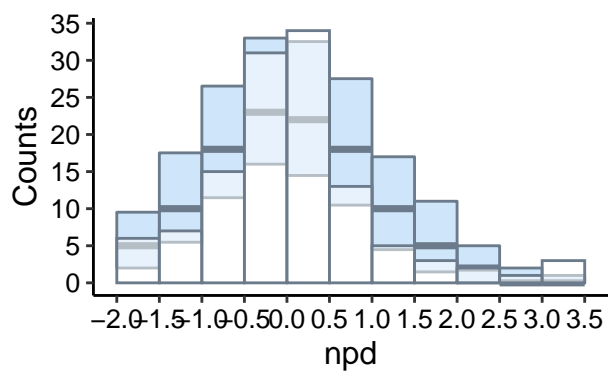
Warning in which(!is.na(as.integer(object@name.covariates))): NAs introduits
lors de la conversion automatique

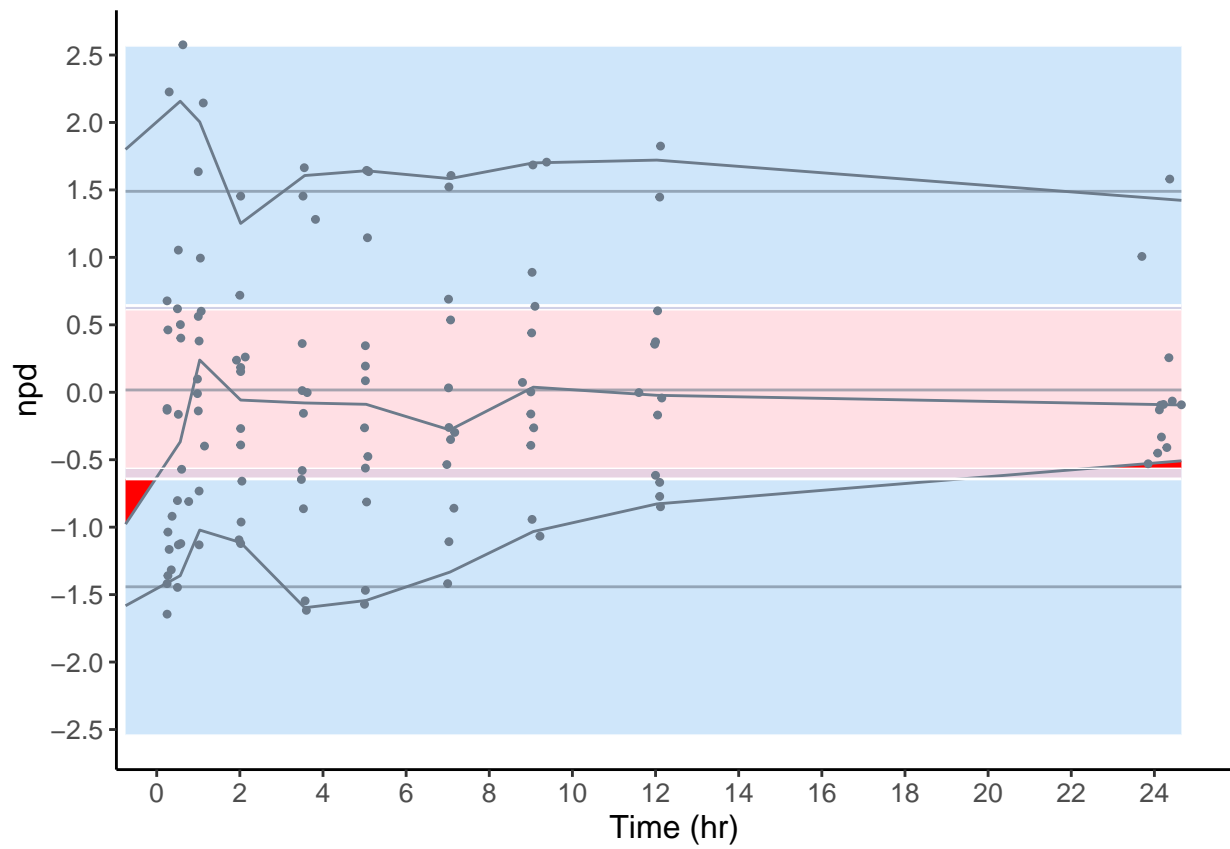
Distribution of npde :
nb of obs: 120
mean= 0.07365 (SE= 0.089)
variance= 0.9433 (SE= 0.12)
skewness= 0.9405
kurtosis= 1.958

Statistical tests (adjusted p-values):
t-test : 1
Fisher variance test : 1
SW test of normality : 3.94e-05 ***
Global test : 3.94e-05 ***

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

```





Bootstrap

## v Dev mode: OFF