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Author Emmanuelle Comets, Karl Brendel, Thi Huyen Tram Nguyen, France Mentre.

Maintainer Emmanuelle Comets <emmanuelle.comets@inserm.fr>

Description Routines to compute normalised prediction distribution errors, a metric designed to evaluate non-linear mixed effect models such as those used in pharmacokinetics and pharmacodynamics

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`npde-package` *Normalised prediction distribution errors for nonlinear mixed-effect models*

Description

Routines to compute normalised prediction distribution errors, a metric designed to evaluate non-linear mixed effect models such as those used in pharmacokinetics and pharmacodynamics

Details

Package:	npde
Type:	Package
Version:	2.0
Date:	2012-08-15
License:	GPL version 2 or later

See the documentation for npde or autonpde for details. A comprehensive user manual is provided in the inst directory of the package, along with a document illustrating the different graphs and graphical options. Please refer to these two guides for details, and send all comments and bug reports to Emmanuelle Comets (<emmanuelle.comets@bichat.inserm.fr>).

Author(s)

Emmanuelle Comets, Karl Brendel and France Mentre

Maintainer: Emmanuelle Comets <emmanuelle.comets@bichat.inserm.fr>

References

K. Brendel, E. Comets, C. Laffont, C. Laveille, and F. Mentre. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. *Pharmaceutical Research*, 23:2036–49, 2006.

E. Comets, K. Brendel, and F. Mentre. Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: the npde add-on package for R. *Computer Methods and Programs in Biomedicine*,90:154–66, 2008.

E. Comets, K. Brendel, and F. Mentre. Model evaluation in nonlinear mixed effect models, with applications to pharmacokinetics. *Journal de la Societe Francaise de Statistique*,151:106–28, 2010.

T.H. Nguyen, E. Comets, and F. Mentre. Extension of NPDE for evaluation of nonlinear mixed effect models in presence of data below the quantification limit with applications to HIV dynamic model. *Journal of Pharmacokinetics and Pharmacodynamics*, in press, 2012.

Examples

```
data(theopp)
data(simtheopp)

# Calling autonpde with dataframes

# x<-autonpde(theopp,simtheopp,1,3,4,boolsave=FALSE)
# x$npde
```

`dist.pred.sim` *Compute distribution of pd/npde using simulations*

Description

This function is used to built the distribution of pd/npde using the simulations under the model. The default is to build only the distribution of pd, and to sample from N(0,1) when building the distribution of npde under the null hypothesis.

Usage

```
dist.pred.sim(npdeObject,nsamp, ...)
```

Arguments

npdeObject	an object returned by a call to npde or autonpde
nsamp	number of datasets (defaults to 100 or to the number of replications if it is smaller)
...	additional arguments. Currently only the value of calc.pd and calc.npde may be passed on, and will override their corresponding value in the "options" slot of npdeObject

Value

an object of class NpdeObject; the ["results"] slot will contain pd and/or npde for a sample of the simulated datasets (depending on whether calc.pd/calc.npde are), stored in pd.sim and/or npde.sim

Author(s)

Emmanuelle Comets <emmanuelle.comets@bichat.inserm.fr>

References

K. Brendel, E. Comets, C. Laffont, C. Laveille, and F. Mentre. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. *Pharmaceutical Research*, 23:2036–49, 2006.

See Also

npde, autonpde

Examples

```
data(theopp)
data(simtheopp)
x<-autonpde(theopp,simtheopp,1,3,4,boolsave=FALSE)
# Use random samples from N(0,1) to obtain a prediction interval on the empirical cdf of the npde
plot(x,plot.type="ecdf",bands=TRUE,approx.pi=TRUE)
# defaults to computing the pd and npde for 100 simulated datasets (in the theophylline example, this uses all the
x<-dist.pred.sim(x)
# Use the npde from the simulated datasets to obtain a prediction interval on the empirical cdf
plot(x,plot.type="ecdf",bands=TRUE,approx.pi=FALSE)
```

---

gof.test *Test on npde or pd*

Description

Performs a global test on npde (default) or pd

Usage

```
gof.test.NpdeObject(object, which = "npde",
  parametric = TRUE, ...)
```

Arguments

object	an object (currently has methods for types numeric, NpdeRes and NpdeObject)
which	whether the tests should be performed for npde (default), pd or npd (normalised pd)
parametric	whether parametric or non-parametric tests should be applied
...	additional arguments passed on to the function; special arguments are na.action, which controls how to handle NAs in the results (na.action), verbose (if FALSE, suppresses printing of the results) and covsplit which requests the tests to be performed split by categories or quantiles of the data. If covsplit is TRUE, continuous covariates will be split in 3 categories (<Q1, Q1-Q3, >Q3) (see details in the PDF documentation), but this behaviour can be overriden by passing the argument ncat=XXX where XXX is the number of categories to divide the continuous covariates in.

Details

If object is an NpdeObject and an argument covsplit=TRUE is given in ..., in addition to the global descriptive statistics and tests, tests will be performed for each covariate in which.cov. This argument can be set in ...; barring an explicit specification, the component which.cov of the prefs slot for a NpdeObject object will be used. The default value is which.cov="all", which produces tests for each covariate in the dataset. Two additional dataframes will then be present:

cov.stat descriptive statistics and test p-values split by covariate and by categories

cov.p.value p-values split by covariate; for each covariate, two tests are performed: the first test is a correlation test for continuous covariates and a Chi-square test for categorical covariates; the second test is defined using the p-values of the global tests split by each category, and appling a Bonferroni correction to obtain an overall p-value (see PDF documentation for details)

The p.value elements is a named vector with four components:

p.mean p-value for the mean test (Wilcoxon test if parametric=FALSE, Student test if parametric=TRUE)

p.var p-value for the variance test (parametric=FALSE, Fisher test if parametric=TRUE)

p.dist p-value for the distribution test (XXX if parametric=FALSE, XXX if parametric=TRUE)

p.global p-value for the global test (combination of the mean, variance and distribution tests with a Bonferroni correction)

Value

A list with the following elements:

mean mean

se.mean standard error of the mean

var variance

se.var standard error on variance

kurtosis kurtosis (see kurtosis)

skewness skewness (see skewness)

p.value p-values for several tests (see below)

References

K. Brendel, E. Comets, C. Laffont, C. Laveille, and F.Mentre. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. *Pharmaceutical Research*, 23:2036–49, 2006.

K. Brendel, E. Comets, C. Laffont, and F.Mentre. Evaluation of different tests based on observations for external model evaluation of population analyses. *Journal of Pharmacokinetics and Pharmacodynamics*, 37:49–65, 2010.

See Also

kurtosis, skewness

Examples

```
data(theopp)
```

---

kurtosis *Kurtosis*

Description

Computes the kurtosis.

Usage

```
kurtosis(x)
```

Arguments

x	a numeric vector containing the values whose kurtosis is to be computed. NA values are removed in the computation.

Details

If $N = \text{length}(x)$, then the kurtosis of x is defined as:

$$Nsum_i(x_i - \text{mean}(x))^4(sum_i(x_i - \text{mean}(x))^2)^(- 2) -$$

Value

The kurtosis of x.

References

G. Snedecor, W. Cochran. *Statistical Methods*, Wiley-Blackwell, 1989

Examples

```
x <- rnorm(100)
kurtosis(x)
```

---

npde *Compute normalised prediction distribution errors*

Description

These functions compute normalised prediction distribution errors (npde) and optionally prediction discrepancies (pd). npde asks the user the name and structure of the files containing the data, using pdemenu, while autonpde takes these variables and others as arguments.

Usage

```
autonpde(namobs, namsim, iid, ix, iy, imdv = 0, icens =
  0, icov = 0, iipred = 0, boolsave = TRUE, namsav =
  "output", type.graph = "eps", verbose = FALSE,
  calc.npde=TRUE, calc.pd=TRUE, decorr.method =
  "cholesky", cens.method = "cdf", units =
  list(x="",y=""), detect=FALSE, ties=TRUE)
```

Arguments

namobs	name of the file containing the observed data, or a dataframe containing the observed data (in both cases, the column containing the various data required for the computation of the pde can be set using the arguments iid,ix and iy below)
namsim	name of the file containing the simulated data, or a dataframe containing the simulated data (the program will assume that subject ID are in column 1 and simulated Y in column 3, see User Guide)
iid	name/number of the column in the observed data containing the patient ID; if missing, the program will attempt to detect a column named id
ix	name/number of the column in the observed data containing the independent variable (X); ; if missing, the program will attempt to detect a column named X
iy	name/number of the column in the observed data containing the dependent variable (Y); if missing, the program will attempt to detect a column with the response

imdv	name/number of the column containing information about missing data (MDV), defaults to 0 (column not present)
icens	name/number of the column containing information about censored data (cens), defaults to 0 (column not present)
icov	name/number of the column(s) containing covariate information defaults to 0 (no covariates)
iipred	name/number of the column(s) with individual predictions (ipred), defaults to 0 (individual predictions not available)
units	a list with components x, y and cov (optional), specifying the units respectively for the predictor (x), the response (y), and the covariates (a vector of length equal to the number of covariates). Units will default to (-) if not given.
detect	a boolean controlling whether automatic recognition of columns in the dataset is on, defaults to FALSE
boolsave	a boolean (TRUE if graphs and results are to be saved to a file, FALSE otherwise), defaults to TRUE
namsav	name of the files to which results are to be saved (defaults to "output", which will produce a file called output.eps (if the default format of postscript is kept, see type.graph) for the graphs and a file called output.npde for the numerical results (see value)
type.graph	type of graph (one of "eps","jpeg","png","pdf"), defaults to postscript ("eps")
calc.npde	a boolean (TRUE if npde are to be computed, FALSE otherwise), defaults to TRUE
calc.pd	a boolean (TRUE if pd are to be computed, FALSE otherwise), defaults to TRUE
cens.method	a character string indicating the method used to handle censored data (see npde.cens.method) defaults to cdf
decorr.method	a character string indicating the method used to decorrelate observed and simulated data in the computation of npde (see npde.decorr.method) defaults to cholesky
ties	a boolean (if FALSE, the distributions of pd and npde are smoothed by jittering the values so that there are no ties), defaults to TRUE
verbose	a boolean (TRUE if messages are to be printed as each subject is processed, FALSE otherwise), defaults to FALSE

Details

Both functions compute the normalised prediction distribution errors (and/or prediction discrepancies) in the same way. npde is an interactive function whereas autonpde takes all required input as arguments.

When the computation of npde fails because of numerical problems, error messages are printed out, then pd are computed instead and graphs of pd are plotted so that the user may evaluate why the computation failed.

The function also prints out the characteristics of the distribution of the npde (mean, variance, skewness and kurtosis) as well as the results of the statistical tests applied to npde. In addition, if boolsave is TRUE, two files are created:

results file the numerical results are saved in a file with extension .npde (the name of which is given by the user). The file contains the components id, xobs, ypred, npde, pd stored in columns

graph file the graphs are saved to a file with the same name as the results file, and with extension depending on the format.

Value

An object of class NpdeObject

Author(s)

Emmanuelle Comets <emmanuelle.comets@bichat.inserm.fr>

References

K. Brendel, E. Comets, C. Laffont, C. Laveille, and F. Mentre. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. *Pharmaceutical Research*, 23:2036–49, 2006.

See Also

npde.graphs, gof.test

Examples

```
data(theopp)
data(simtheopp)

# Calling autonpde with dataframes

x<-autonpde(theopp,simtheopp,1,3,4,boolsave=FALSE)
x

# Calling autonpde with names of files to be read from disk

write.table(theopp,"theopp.tab",quote=FALSE,row.names=FALSE)
write.table(simtheopp,"simtheopp.tab",quote=FALSE,row.names=FALSE)
x<-autonpde(namobs="theopp.tab", namsim="simtheopp.tab", iid = 1,
ix = 3, iy = 4, imdv=0, boolsave = FALSE)

head(x["results"]["res"])
```

---

npde.cens.method *Method used to handle censored data*

Description

Specifies the method used to handle censored data (data below the limit of quantification LOQ)

Details

More details can be found in the PDF documentation.

Value

The following methods are available in the npde library:

omit pd and npde for censored data will be set to NA

cdf for an observation ycens_ij under the LOQ, a pd_ij will be imputed in the uniform distribution [0-pLOQ_ij] where pLOQ_ij is the probability that y_ij is below LOQ, according to the model; the predictive distribution will then be used to obtain a corresponding y*_ij. This is also performed for all simulated data, and the npde are then computed on the completed dataset containing the observed y_ij for the uncensored data and the y*_ij imputed for the censored data. This method is the default.

ipred an observation ycens_ij is replaced by the individual prediction according to the model (ipred, which must be present in the dataset). Simulated data are left untouched.

ppred an observation ycens_ij is replaced by the population prediction according to the model. Simulated data are left untouched.

loq an observation ycens_ij is replaced by the value of the LOQ. Simulated data are left untouched.

References

K. Brendel, E. Comets, C. Laffont, C. Laveille, and F. Mentre. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. *Pharmaceutical Research*, 23:2036–49, 2006.

---

npde.decorr.method *Method used to decorrelate vectors*

Description

Specifies the method used to decorrelate observed and simulated data

Details

More details can be found in the PDF documentation.

Value

Decorrelation requires computing the square root of the inverse of the individual variance-covariance matrix Vi. The following methods are available in the npde library:

cholesky decorrelation is performed through the Cholesky decomposition (default)

inverse decorrelation is performed by inverting Vi through the `eigen` function

polar the singular-value decomposition (`svd`) is used

References

K. Brendel, E. Comets, C. Laffont, C. Laveille, and F. Mentre. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. *Pharmaceutical Research*, 23:2036–49, 2006.

`npde.graphs` *Save the graphs for a NpdeObject object to a file*

Description

Save the graphs to a file on disk

Arguments

`object`	a NpdeObject object
`...`	optional arguments to replace options in object

Details

The following options can be changed by passing the appropriate arguments: namsav (string giving the root name of the files, an extension depending on the type of graph will be added), namgr (string giving the full name of the file), type.graph (one of "eps", "pdf", "jpeg", "png")

References

K. Brendel, E. Comets, C. Laffont, C. Laveille, and F.Mentre. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. *Pharmaceutical Research*, 23:2036–49, 2006.

`npde.save` *Save the results contained in a NpdeObject object to a file*

Description

Save the results to a table on disk

Arguments

`object`	a NpdeObject object
`...`	optional arguments to replace options in object

Details

The following options can be changed by passing the appropriate arguments: namsav (string giving the root name of the files, an extension .npde will be added), nameres (string giving the full name of the file)

References

K. Brendel, E. Comets, C. Laffont, C. Laveille, and F.Mentre. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. *Pharmaceutical Research*, 23:2036–49, 2006.

`npdeControl` *Set options for an NpdeObject*

Description

Set, replace and check options for an NpdeObject

Usage

```
npdeControl(boolsave = TRUE, namsav = "output",
  type.graph = "eps", verbose = FALSE, calc.npde = TRUE,
  calc.pd = TRUE, decorr.method = "cholesky", cens.method
  = "omit", ties = TRUE, sample = FALSE)
```

Arguments

`boolsave`	whether to save the results (a file containing the numerical results and a file with the graphs)
`namsav`	the root name of the files to save to (the file with the results will be named ROOTNAME.npde and the graphs will be saved to ROOTNAME.format where format is given by the type.graph argument)
`type.graph`	type of graph to save to (one of "eps", "pdf", "jpeg", "png")
`verbose`	a boolean; if TRUE, a message is printed as the computation of the npde begins for each new subject
`calc.pd`	a boolean; TRUE to compute pd
`calc.npde`	a boolean; TRUE to compute npde
`decorr.method`	the method used to decorrelate simulated and observed data (see `npde.decorr.method`)
`cens.method`	the method used to handle censored data (see `npde.cens.method`)
`ties`	if FALSE, a smoothing will be applied to prediction discrepancies to avoid ties
`sample`	if TRUE, the test on the pd will be performed after randomly sampling only pd per subject

npdeData *Creates a NpdeData object*

Description

This function is used to create a NpdeData object, representing a longitudinal data structure, and fill it with data from a dataframe or a file on disk

Usage

```
npdeData(name.data,header=TRUE,sep="",na.strings=c(".","NA"),name.group,
  name.predictor,name.response,
  name.covariates,name.cens,name.miss,name.ipred,
  units=list(x="",y="",covariates=c()),detect=TRUE,verbose=FALSE)
```

Arguments

name.data	name of the file containing the observed data, or a dataframe containing the observed data
sep	field separator (for files on disk)
na.strings	strings to be considered as indicating NA
header	boolean indicating whether the file has a header (mandatory if detect is TRUE)
name.group	name/number of the column in the observed data containing the patient ID (if missing and detect is TRUE, columns named id, subject or sujet (regardless of case) will be assumed to contain this information)
name.predictor	name/number of the column in the observed data containing the independent variable X (if missing and detect is TRUE, columns named xobs, time, dose, x, temps, tim (regardless of case) will be assumed to contain this information)
name.response	name/number of the column in the observed data containing the dependent variable Y (if missing and detect is TRUE, columns named yobs, response, resp, conc, concentration (regardless of case) will be assumed to contain this information)
name.miss	name/number of the column containing information about missing data (MDV) (if missing and detect is TRUE, column called mdv or miss (regardless of case) will be assumed to contain this information)
name.cens	name/number of the column containing information about censored data (cens) (if missing and detect is TRUE, column with a name containing cens (regardless of case) will be assumed to contain this information)
name.covariates	name/number of the column(s) containing covariate information (optional)
name.ipred	name/number of the column(s) with individual predictions (ipred) (if missing and detect is TRUE, column with a name containing ipred (regardless of case) will be assumed to contain this information)

units	a list with components x, y and cov (optional), specifying the units respectively for the predictor (x), the response (y), and the covariates (a vector of length equal to the number of covariates). Units will default to (-) if not given.
detect	a boolean controlling whether automatic recognition of columns in the dataset is on, defaults to TRUE
verbose	whether to print warning messages, defaults to FALSE (set to TRUE to check how data is being handled)

Value

an object of class NpdeData

Author(s)

Emmanuelle Comets <emmanuelle.comets@bichat.inserm.fr>

References

K. Brendel, E. Comets, C. Laffont, C. Laveille, and F. Mentre. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. *Pharmaceutical Research*, 23:2036–49, 2006.

See Also

npde, autonpde

Examples

```
data(theopp)

x<-npdeData(theopp) # Automatic detection
print(x)
x<-npdeData(theopp,name.group="ID",name.predictor="Time",name.response="Conc",
name.covariates=c("Wt"),units=list(x="hr",y="mg/L",covariates="kg")) # Explicit
print(x)
plot(x)
```

NpdeData-class *Class "NpdeData" representing the structure of the longitudinal data*

Description

A longitudinal data structure

Objects from the Class

NpdeData objects are typically created by calls to npdeData and contain the following slots:

name.data character string giving the name of the dataset

name.group character string giving the name of the grouping term (ID)

name.predictor character string giving the name of the predictor (X)

name.response character string giving the name of the response (Y)

name.cens character string giving the name of the censoring indicator

name.mdv character string giving the name of the missing data indicator

name.covariates vector of character string giving the name(s) of the covariates

name.ipred character string giving the name of the individual predictions

units (optional) a list with the units for X, Y, and covariates

data a dataframe containing the data

N number of subjects

ntot.obs total number of non-missing observations

nind.obs vector of size N giving the number of non-missing observations for each subject

ind index of non-missing observations

icens index of censored observations (non-missing)

not.miss a vector of boolean indicating for each observation whether it is missing (FALSE) or available (TRUE)

loq the censoring value

Methods

npdeData(name.data): Create a new NpdeData object from dataset name.data

print(npde.data): Prints a summary of object npde.data

show(npde.data): Prints a short summary of object npde.data

showall(npde.data): Prints a detailed summary of object npde.data

plot(npde.data): Plots the data in npde.data. More details can be found in plot.NpdeData

summary(npde.data): Returns a summary of object npde.data in list format

set.plotoptions(npde.data): Sets options for graphs of npde.data (internal method used in plots)

See Also

npde, autonpde, plot.NpdeData

Examples

```
methods(class="NpdeData")

showClass("NpdeData")
```

NpdeObject-class *Class "NpdeObject"*

Description

An object of class NpdeObject

Objects from the Class

NpdeObject objects are typically created by calls to npde or autonpde. They contain the following slots:

data an object of class NpdeData, containing the observed data

sim.data an object of class NpdeSimData, containing the simulated data

res an object of class NpdeRes, containing the results

options a list of options

prefs a list of graphical preferences for the plots

Methods

print(x): Prints a summary of object

show(x): Prints a short summary of object

showall(x): Prints a detailed summary of object

plot(x): Diagnostic and other plots. More details can be found in plot.NpdeObject

summary(x): Returns a summary of object x in list format

gof.test(x, which="npde", parametric=TRUE, ...): Returns goodness-of-fit tests

set.plotoptions(x): Sets options for graphs (internal method used in plots)

See Also

npde, autonpde, NpdeData, NpdeSimData, NpdeRes, gof.test

Examples

```
methods(class="NpdeObject")

showClass("NpdeObject")
```

NpdeSimData-class *Class "NpdeSimData" representing the structure of the longitudinal data*

Description

A longitudinal data structure, with simulated data

Objects from the Class

NpdeSimData objects are created by associating an NpdeData object with matching simulated data, and they contain the following slots.

name.simdata character string giving the name of the dataset

nrep number of replications)

datsim a dataframe containing the simulated data, with columns: idsim (subject id), irsim (replication index), xsim (simulated x), ysim (simulated response). After a call to npde or autonpde, an additional column ydsim (decorrelated replicated data) will be added.

Methods

print(npde.simdata): Prints a summary of object npde.simdata

show(npde.simdata): Prints a short summary of object npde.simdata

showall(npde.simdata): Prints a detailed summary of object npde.simdata

See Also

npde, autonpde

Examples

```
showClass("NpdeSimData")
```

plot.NpdeData *Plots a NpdeData object*

Description

Plots the data in a NpdeData object

Usage

```
## S3 method for class 'NpdeData'
plot(x, y, ...)
```

Arguments

x	a NpdeData object
y	unused, here for compatibility with the base plot function
...	additional graphical parameters to be passed on to the plot

Details

The default plot is a spaghetti plot of all the data, with a line joining the observations for each subject. If censored data is present, it is shown with a different symbol and colour.

References

K. Brendel, E. Comets, C. Laffont, C. Laveille, and F.Mentre. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. *Pharmaceutical Research*, 23:2036–49, 2006.

See Also

set.plotoptions

Examples

```
data(theopp)

x<-npdeData(theopp,name.group="ID",name.predictor="Time",name.response="Conc",
name.covariates=c("Wt"),units=list(x="hr",y="mg/L",covariates="kg"))
plot(x)
```

---

plot.NpdeObject *Plots a NpdeObject object*

Description

Plots the data and diagnostic plots in a NpdeObject object

Usage

```
  ## S3 method for class 'NpdeObject'
plot(x, y, ...)
```

Arguments

x	a NpdeObject object
y	unused, here for compatibility with the base plot function
...	additional graphical parameters, which when given will supersede graphical preferences stored in the object

Details

The default plot

References

K. Brendel, E. Comets, C. Laffont, C. Laveille, and F.Mentre. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. *Pharmaceutical Research*, 23:2036–49, 2006.

See Also

`set.plotoptions`

Examples

```
data(theopp)
data(simtheopp)

x<-autonpde(theopp,simtheopp,iid="ID",ix="Time", iy="Conc", boolsave=FALSE)
plot(x)
```

`set.plotoptions` *Set graphical preferences*

Description

This function is used to set options for graphs

Usage

```
set.plotoptions(object, ...)
```

Arguments

`object`	an object of class NpdeData or NpdeObject
`...`	arguments to replace default arguments (currently ignored)

Details

See documentation for a list of available options.

Value

a list of options for graphs

Author(s)

Emmanuelle Comets <emmanuelle.comets@bichat.inserm.fr>

See Also

npde, autonpde

---

showall *Brief summary of an object*

Description

Prints a brief summary of an object

Usage

```
showall.NpdeData(object)
```

Arguments

object	an object

---

simtheopp *Simulated data for the computation of normalised prediction distribution errors*

Description

The simtheopp dataset contains 100 simulations using the design of dataset theopp. These simulations are used to compute npde. The control file used to perform the simulations can be found in the subdirectory 'doc' within the library npde.

Usage

```
simtheopp
```

Format

This data frame contains the following columns:

ID an ordered factor with levels 1, ..., 12 identifying the subject on whom the observation was made. The ordering is first by simulation then by increasing time.

xsim time since drug administration when the sample was drawn (hr).

ysim simulated theophylline concentration (mg/L).

Details

See theopp for a description of the original dataset.

The simulated data was obtained using the software *NONMEM*. A one-compartment model was fit to the data. An exponential interindividual variability was assumed for the three parameters (absorption rate constant ka, volume of distribution V and clearance CL) and a combined additive and proportional residual error model was usd. The estimated parameters were then used to simulate 100 datasets with the same structure as the original dataset. Thus, for each observation in the original dataset, the simulated dataset contains 100 simulations under the model used for the estimation.

This dataset is provided so that users can figure out what type of data is needed for the computation of prediction distribution errors. More information can be found in the User Guide distributed along with this package, which contains a run-through of the theophylline example.

Source

Boeckmann, A. J., Sheiner, L. B. and Beal, S. L. (1994), *NONMEM Users Guide: Part V*, NONMEM Project Group, University of California, San Francisco.

See Also

theopp

Examples

```
data(simtheopp)

# Plotting the simulated data for subject 1 in the first simulation
plot(ysim[2:12]~xsim[2:12],data=simtheopp,xlab="Time after dose (hr)",
ylab="Theophylline concentration (mg/L)",type="l",
main="Example of simulated data for subject 1")

# Plotting a 90% prediction interval for the observations in theopp
# using the simulated data in simtheopp
# note : differences in doses between subjects are not taken into account
data(theopp)
xpl<-c(0,0.25,0.5,1,2,3.5,5,7,9,12,24)
xpl1<-list(c(0,0.1),c(0.2,0.4),c(0.5,0.65),c(0.9,1.2),c(1.9,2.2),c(3.4,4),
c(4.9,5.2),c(6.9,7.2),c(8.8,9.4),c(11.5,12.2),c(23.7,24.7))

ypl<-cbind(xpl=xpl,binf=xpl,median=xpl,bsup=xpl)
for(i in 1:(length(xpl))) {
  vec<-simtheopp$ysim[simtheopp$xsim>=xpl1[[i]][1] &simtheopp$xsim<=xpl1[[i]][2]]
  ypl[i,2:4]<-quantile(vec,c(0.05,0.5,0.95))
}
plot(Conc~Time,data=theopp,xlab="Time after dose (hr)",
ylab="Theophylline concentration (mg/L)")
lines(ypl[,1],ypl[,3],lwd=2)
lines(ypl[,1],ypl[,2],lty=2)
lines(ypl[,1],ypl[,4],lty=2)
```

`simvirload` *Simulated data for the computation of normalised prediction distribution errors, viral load example*

Description

The `simvirload` dataset contains 1000 simulations using the design of dataset `virload`. These simulations are used to compute npde.

Usage

```
simvirload
```

Format

This data frame contains the following columns:

ID an ordered factor with levels `1`, ..., `50` identifying the subject on whom the observation was made. The ordering is first by simulation then by increasing time.

xsim time (day).

ysim simulated viral loads, in base 10 log-scale (cp/L).

Details

See `virload` for a description of the original dataset.

The simulated data was obtained using the software *R*, as described in Nguyen et al. (2011).

Source

Goujard, C., Barrail-Train, A., Duval, X., Nembot, G., Panhard, X., Savic, R., Descamps, D., Vrijens, B., Taburet, A., Mentre, F., and the ANRS 134 study group (2010). Virological response to atazanavir, ritonavir and tenofovir/emtricitabine: relation to individual pharmacokinetic parameters and adherence measured by medication events monitoring system (MEMS) in naive HIV-infected patients (ANRS134 trial). *International AIDS Society 2010*, Abstr WEPE0094.

Nguyen, T., Comets, E., Mentre, F. (2010). Prediction discrepancies (pd) for evaluation of models with data under limit of quantification. *20th meeting of the population approach group in Europe (PAGE), Athens, Greece*. Abstr 2182.

See Also

`virload`

skewness *Skewness*

Description

Computes the skewness.

Usage

```
skewness(x)
```

Arguments

x	a numeric vector containing the values whose skewness is to be computed. NA values are removed in the computation.

Details

If $N = \mathrm{length}(x)$, then the skewness of x is defined as

$$N^{-1}\mathrm{sd}(x)^{-3}\sum_i (x_i - \mathrm{mean}(x))^3.$$

Value

The skewness of x.

References

G. Snedecor, W. Cochran. *Statistical Methods*, Wiley-Blackwell, 1989

Examples

```
x <- rnorm(100)
skewness(x)
```

theopp *Pharmacokinetics of theophylline*

Description

The theopp data frame has 132 rows and 5 columns of data from an experiment on the pharmacokinetics of theophylline.

Usage

```
theopp
```

Format

This data frame contains the following columns:

ID an ordered factor with levels 1, ..., 12 identifying the subject on whom the observation was made. The ordering is by Time at which the observation was made.

Dose dose of theophylline administered orally to the subject (mg).

Time time since drug administration when the sample was drawn (hr).

Conc theophylline concentration in the sample (mg/L).

Wt weight of the subject (kg).

Details

Boeckmann, Sheiner and Beal (1994) report data from a study by Dr. Robert Upton of the kinetics of the anti-asthmatic drug theophylline. Twelve subjects were given oral doses of theophylline then serum concentrations were measured at 11 time points over the next 25 hours. In the present package *npde*, we removed the data at time 0.

These data are analyzed in Davidian and Giltinan (1995) and Pinheiro and Bates (2000) using a two-compartment open pharmacokinetic model.

These data are also available in the library `datasets` under the name `Theoph` in a slightly modified format and including the data at time 0. Here, we use the file in the format provided in the *NONMEM* installation path (see the User Guide for that software for details).

Source

Boeckmann, A. J., Sheiner, L. B. and Beal, S. L. (1994), *NONMEM Users Guide: Part V*, NONMEM Project Group, University of California, San Francisco.

Davidian, M. and Giltinan, D. M. (1995) *Nonlinear Models for Repeated Measurement Data*, Chapman & Hall (section 5.5, p. 145 and section 6.6, p. 176)

Pinheiro, J. C. and Bates, D. M. (2000) *Mixed-effects Models in S and S-PLUS*, Springer (Appendix A.29)

Examples

```
data(theopp)
str(theopp)

#Plotting the theophylline data
plot(Conc~Time,data=theopp,xlab="Time after dose (hr)",
ylab="Theophylline concentration (mg/L)")
```

`virload` *Simulated HIV viral loads in HIV patients*

Description

This is simulated data, based on real data obtained in a phase II clinical trial supported by the French Agency for AIDS Research, the COPHAR 3-ANRS 134 trial (Goujard et al., 2010). The original study included 35 patients, who received a once daily dose containing atazanavir (300 mg), ritonavir (100 mg), tenofovir disoproxil (245 mg) and emtricitabine (200 mg) during 24 weeks. Viral loads were measured 6 times over a treatment period of 24 weeks (day 0, 28, 56, 84, 112, 168).

The datasets were generated in a simulation study designed to evaluate the new method proposed to handle BQL data (Nguyen et al., 2011). Data was simulated using a simple bi-exponential HIV dynamic model describing the two-phase decline of viral load during anti-retroviral treatment.

The `virload` data frame has 300 rows and 4 columns of data. The dataset was then censored at two different LOQ levels (LOQ=20 or 50~copies/mL) to generate two datasets containing different proportions of BQL data, creating the data frames `virload20` and`virload50` respectively.

Usage

```
virload
```

Format

This data frame contains the following columns:

ID an ordered factor with levels `1`, ..., `50` identifying the subject on whom the observation was made. The ordering is by Time at which the observation was made.

Time time since the beginning of the study (days).

Log_VL logarithm (base 10) of the viral load (copies/L).

cens indicator variable (cens=1 for censored data, cens=0 for observed data)

ipred individual predictions)

Source

Goujard, C., Barrail-Train, A., Duval, X., Nembot, G., Panhard, X., Savic, R., Descamps, D., Vrijens, B., Taburet, A., Mentre, F., and the ANRS 134 study group (2010). Virological response to atazanavir, ritonavir and tenofovir/emtricitabine: relation to individual pharmacokinetic parameters and adherence measured by medication events monitoring system (MEMS) in naive HIV-infected patients (ANRS134 trial). *International AIDS Society 2010*, Abstr WEPE0094.

Nguyen, T., Comets, E., Mentre, F. (2010). Prediction discrepancies (pd) for evaluation of models with data under limit of quantification. *20th meeting of the population approach group in Europe (PAGE), Athens, Greece*. Abstr 2182.

Examples

```
data(virload)
str(virload)
data(virload50)

#Plotting the data
plot(Log_VL~Time,data=virload,xlab="Time (d)",ylab="Viral loads, base 10 logarithmic scale  (cp/mL)")
plot(Log_VL~Time,data=virload50,xlab="Time (d)",ylab="Viral loads, base 10 logarithmic scale  (cp/mL)")
```

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