Package 'npde'

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Title Normalised Prediction Distribution Errors for Nonlinear
Mixed-Effect Models

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Description Provides 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.

License GPL (>= 2)

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LazyLoad yes

LazyData yes

Imports methods, scales, gridExtra, ggplot2, mclust, here, grid,
testthat

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Collate 'NpdeSimData.R' 'NpdeData.R' 'aaa_generics.R'
'NpdeData-methods.R' 'NpdeRes.R' 'NpdeRes-methods.R'
'NpdeObject.R' 'NpdeObject-methods.R' 'compute_distribution.R'
'compute_npde.R' 'compute_pd.R' 'compute_ploq.R' 'mainNpde.R'
'npde.R' 'npdeControl.R' 'plotNpde-meanProf.R'
'plotNpde-methods.R' 'plotNpde-plotFunctions.R'
'plotNpde-unitFunctionsAux.R' 'plotNpde-unitFunctionsPI.R'
'plotNpde-unitFunctionsRef.R'

NeedsCompilation no

R topics documented:

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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:	3.0
Date:	2017-01-02
License:	GPL version 2 or later

See the documentation for npde for details

Author(s)

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References

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

Examples

```
## Not run:
data(theopp)
data(simtheopp)

# Calling autonpde with dataframes

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

print(x)

## End(Not run)
```

---

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

Description

This function is used to build 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

```
## Not run:
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 simulated datasets)
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)

## End(Not run)
```

---

gof.test   *Goodness-of-fit tests for npde*

Description

Performs test on the selected variable (which=one of npde, pd or npd) or on a numeric vector

Usage

```
gof.test(object, parametric = TRUE, ...)

printgoftest(object, which = "npde", ...)
```

Arguments

object	an object (currently has methods for types numeric, NpdeRes and NpdeObject)
parametric	a boolean. If TRUE (default), parametric tests are performed
...	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.
which	character string giving (used by printgoftest)

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

```
## Not run:
data(theopp)

## End(Not run)
```

---

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:

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

$$3$$

Value

The kurtosis of x.

References

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

Examples

```
## Not run:
x <- rnorm(100)
kurtosis(x)
## End(Not run)
```

---

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, header=TRUE)

npde()
```

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
header	a boolean (TRUE if input files have headers, FALSE otherwise), defaults to TRUE

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

```
## Not run:
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"])

## End(Not run)
```

---

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

Several methods are available to handle censored data.

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.

More details can be found in the PDF documentation.

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   *Decorrelation methods in npde*

Description

Specifies the method used to decorrelate observed and simulated data

Arguments

x   a square matrix

    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

Details

More details can be found in the PDF documentation.

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

Usage

```
npde.graphs(object, ...)
```

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.plot.covariates   *Covariate plots for a NpdeObject object*

Description

Covariate plots for a NpdeObject object

Usage

```
npde.plot.covariates(npdeObject, which="x", ...)
```

Arguments

npdeObject	an object returned by a call to npde or autonpde
which	one of "x" (scatterplots of the metric versus X), "pred" (scatterplots of the metric versus predictions) or "ecdf" (empirical distribution function)
...	additional arguments to be passed on to the function, to control which metric (npde, pd, npd) is used or to override graphical parameters (see the PDF document for details, as well as set.plotoptions)

---

npde.plot.data   *Plot a NpdeData object*

Description

Produces a spaghetti plot of the data

Usage

```
npde.plot.data(npdeObject, ...)
```

Arguments

npdeObject   an object returned by a call to npde or autonpde

...   additional arguments to be passed on to the function, to control which metric
                (npde, pd, npd) is used or to override graphical parameters (see the PDF docu-
                ment for details, as well as set.plotoptions)

---

npde.plot.default   *Diagnostic plots*

Description

The default diagnostic plots produced after a call to npde or autonpde include a histogram of the
distribution, a QQ-plot compared to the theoretical distribution, and scatterplots versus the independ-
ent variable and versus the population predictions from the model

Usage

```
npde.plot.default(npdeObject, ...)
```

Arguments

npdeObject   an object returned by a call to npde or autonpde

...   additional arguments to be passed on to the function, to control which metric
                (npde, pd, npd) is used or to override graphical parameters (see the PDF docu-
                ment for details, as well as set.plotoptions)

| npde.plot.dist | *Plots of pd/npde versus their theoretical distribution* |

Description

Produces a plot of the corresponding metric versus their theoretical distribution as a histogram,a QQ-plot, or the empirical cdf

Usage

```
npde.plot.dist(npdeObject,which="npde",dist.type="qqplot",
covsplit=FALSE,...)
```

Arguments

npdeObject   an object returned by a call to npde or autonpde

which   a string determining which metric to plot, one of "npde", "pd" or "npd" (defaults to "npde")

dist.type   string, one of "ecdf" (empirical cumulative density function), "hist" (histogram) or "qqplot" (QQ-plot of the empirical distribution versus the theoretical quantiles) to determine which type of plot (default is "qqplot")

covsplit   boolean. If TRUE and covariates are present in the dataset, the plots will be stratified for each covariate

...   additional arguments to be passed on to the function, to control which metric (npde, pd, npd) is used or to override graphical parameters (see the PDF document for details, as well as set.plotoptions)

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, set.plotoptions

---

npde.plot.loq   *Plot of the probability that the observations are below the LOQ*

Description

Plots the probability that the observations are below the LOQ along with the model predicted interval

Usage

```
npde.plot.loq(npdeObject,xaxis="x",nsim=200,...)
```

Arguments

npdeObject	an object returned by a call to npde or autonpde
xaxis	a string character, one of "x" (to plot P(Y<LOQ) versus the value of the independent predictor) or "ypred" (versus the value of the population predictions). Defaults to "x"
nsim	number of simulations to be used for the computation of the prediction interval
...	additional arguments to be passed on to the function, to control which metric (npde, pd, npd) is used or to override graphical parameters (see the PDF document for details, as well as set.plotoptions)

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, set.plotoptions

---

npde.plot.npde   *Plots for pd and npde*

Description

Plots for pd and npde

Usage

```
npde.plot.pd(npdeObject, ...)

npde.plot.npde(npdeObject, ...)
```

Arguments

npdeObject   an object returned by a call to [npde](#) or [autonpde](#)

...   additional arguments to be passed on to the function, to control which metric
                (npde, pd, npd) is used or to override graphical parameters (see the PDF docu-
                ment for details, as well as [set.plotoptions](#))

---

npde.plot.select   *Select plot for a NpdeObject object*

Description

Select plot for a NpdeObject object

Usage

```
npde.plot.select(npdeObject,data=FALSE,ecdf=FALSE,qqplot=FALSE, histogram=FALSE,
x.scatter=FALSE,pred.scatter=FALSE,x.box=FALSE,pred.box=FALSE, cov.x.scatter=FALSE,
cov.pred.scatter=FALSE,cov.x.box=FALSE,cov.pred.box=FALSE, cov.ecdf=FALSE, vpc=FALSE,...)
```

Arguments

npdeObject   an object returned by a call to [npde](#) or [autonpde](#)

data   boolean, whether to produce a plot of the data

ecdf   boolean, whether to produce a distribution plot of the empirical distribution
                function

qqplot   boolean, whether to produce a QQ-plot of the empirical distribution function

histogram   boolean, whether to produce a histogram of the metric

x.scatter   boolean, whether to produce a scatterplot of the metric as a function of X

pred.scatter   boolean, whether to produce a scatterplot of the metric as a function of predic-
                tions

x.box	boolean, whether to produce whisker plots of the metric as a function of X
pred.box	boolean, whether to produce whisker plots of the metric as a function of predictions
cov.x.scatter	boolean, whether to produce a scatterplot of the metric as a function of X, split by covariate(s)
cov.pred.scatter	
	boolean, whether to produce a scatterplot of the metric as a function of predictions, split by covariate(s)
cov.x.box	boolean, whether to produce whisker plots of the metric as a function of X, split by covariate(s)
cov.pred.box	boolean, whether to produce whisker plots of the metric as a function of predictions, split by covariate(s)
cov.ecdf	boolean, whether to produce a distribution plot of the empirical distribution function, split by covariate(s)
vpc	boolean, whether to produce a VPC
...	additional arguments to be passed on to the function, to control which metric (npde, pd, npd) is used or to override graphical parameters (see the PDF document for details, as well as set.plotoptions)

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, set.plotoptions

---

npde.plot.vpc	*Visual Predictive Check (VPC)*

Description

Produces a VPC plot for the data using the simulated data provided. Note that non-stratified VPC are not suited to unbalanced designs when features such as dose or covariates enter the model. We suggest using reference profiles instead to retain a VPC-like profile while ensuring meaningful prediction intervals (Comets et al. 2013).

Usage

```
npde.plot.vpc(npdeObject, ...)
```

Arguments

npdeObject   an object returned by a call to npde or autonpde

...   additional arguments to be passed on to the function, to control which metric
                      (npde, pd, npd) is used or to override graphical parameters (see the PDF docu-
                      ment for details, as well as set.plotoptions)

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.

E. Comets, THT Nguyen, F. Mentré. Additional features and graphs in the new npde library for R.
22nd PAGE meeting, Glasgow, UK, 2013.

See Also

npde, autonpde, set.plotoptions

---

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

Description

Save the results to a table on disk

Usage

```
npde.save(object, ...)
```

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)

check.control.options(opt)

replace.control.options(opt,...)

replace.control.options(opt, ...)

check.control.options(opt)
```

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.npde	a boolean; TRUE to compute npde
calc.pd	a boolean; TRUE to compute pd
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

opt   a list of control options to be checked

...   named parameters to be changed. The names will be compared to the names of
                             the control variables and changed, with warnings issued for names that do not
                             match.

---

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

header   boolean indicating whether the file has a header (mandatory if detect is TRUE)

sep   field separator (for files on disk)

na.strings   strings to be considered as indicating NA

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 vari-
                     able Y (if missing and detect is TRUE, columns named yobs, response, resp,
                     conc, concentration (regardless of case) will be assumed to contain this infor-
                     mation)

name.covariates
                     name/number of the column(s) containing covariate information (optional)

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.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.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. Mentr\'e. 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

```
## Not run:
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)
## End(Not run)
```

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 a call to [npdeData](#) contain the following slots:

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

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

qqplot.npde(npde.data): QQ-plot for NpdeData object (TODO: change for NpdeObject in final package)

Examples

```
## Not run:
methods(class="NpdeData")

showClass("NpdeData")
## End(Not run)
```

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

results 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, 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

```
## Not run:
methods(class="NpdeObject")

showClass("NpdeObject")
## End(Not run)
```

---

npdeSimData   *Creates a NpdeSimData object*

Description

This function is used to create a NpdeSimData object containing the simulated data corresponding to an NpdeData object

Usage

```
npdeSimData(npde.data, name.simdata, header=TRUE, verbose=FALSE)
```

Arguments

npde.data   a NpdeData object

name.simdata   name of the file containing the simulated data, or a dataframe containing it

header   boolean indicating whether the file has a header (mandatory if detect is 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 NpdeSimData

Author(s)

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

See Also

[NpdeData](), [npde](), [autonpde]()

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.

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

```
## Not run:
showClass("NpdeSimData")

## End(Not run)
```

---

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

```
## Not run:
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)

## End(Not run)
```

---

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

```
## Not run:
data(theopp)
data(simtheopp)

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

## End(Not run)
```

| print.NpdeData | *Prints objects from the npde package* |

Description

prints objects of classes NpdeData, NpdeSimData, NpdeRes and NpdeObject

Usage

```
## S3 method for class 'NpdeData'
print(x, nlines = 10, ...)

## S3 method for class 'NpdeRes'
print(x, nlines = 10, ...)

## S3 method for class 'NpdeObject'
print(x, nlines = 10, ...)
```

Arguments

x	an object of class NpdeData, NpdeSimData, NpdeRes or NpdeObject
nlines	number of lines from the dataset to print
...	Additional arguments (ignored)

---

remifent   *Pharmacokinetics of Remifentanil*

Description

The `remifent` data frame has 1992 rows and 12 columns of data from an experiment on the pharmacokinetics of remifentanil in healthy volunteers.

Usage

    remifent

Format

This data frame contains the following columns:

ID a numeric vector identifying the subject on whom the observation was made. The ordering is by Time at which the observation was made.

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

Conc remifentanil concentration in the sample (ug/L).

Rate infusion rate (ug/min).

AMT total dose of remifentanil administered orally to the subject (ug).

Gender a factor with levels `Male` and `Female`.

Ht height of the subject (cm).

Wt weight of the subject (kg).

BSA body surface area (m2).

LBM lean body mass (kg).

age.grp an ordered factor dividing age in 3 age groups, young (`20-40`), middle-aged (`40-65`) and elderly (over `65`).

Details

This dataset is one of the datasets distributed in R in the nlme library. The original data was collected in a study by Minto et al, who studied the pharmacokinetics and pharmacodynamics of remifentanil in 65 healthy volunteers. Remifentanil is a synthetic opioid derivative, used as a major analgesic before surgery or in critical care. In the study, the subjects were given remifentanil as a continuous infusion over 4 to 20 min, and measurements were collected over a period of time varying from 45 to 230 min (mean 80 min), along with EEG measurements. The following covariates were recorded: gender, age, body weight, height, body surface area and lean body mass. The recruitment was specifically designed to investigate the effect of age, with recruitment over 3 age groups (young (20-40 yr), middle-aged (40-65 yr) and elderly (over 65 yr)).

This dataset is used to illustrate the new covariate graphs available in the npde library. It has been modified from the original Remifentanil dataset to include a Rate column and an age group column.

Source

Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL (1997). Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* 86(1):10-23.

Minto CF, Schnider TW, Shafer SL (1997). Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. *Anesthesiology* 86(1):24-33.

Pinheiro JC, Bates DM. (2000) *Mixed-effects Models in S and S-PLUS*, Springer (Appendix A.29)

Examples

```
data(remifent)
str(remifent)

#Plotting the remifentanil data
plot(Conc~Time,data=remifent,xlab="Time after dose (min)", ylab="Theophylline concentration (ug/L)")
```

---

set.plotoptions	*Set graphical preferences*

Description

This function is used to set options for graphs

Usage

```
set.plotoptions(object)

## S3 method for class 'NpdeData'
set.plotoptions(object)

## S3 method for class 'NpdeObject'
set.plotoptions(object)
```

Arguments

object   an object of class NpdeData or NpdeObject

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](#)

---

show   *Displays npde objects*

Description

Prints the structure of objects from the package

Usage

```
## S4 method for signature 'NpdeData'
show(object)

## S4 method for signature 'NpdeSimData'
show(object)

## S4 method for signature 'NpdeRes'
show(object)

## S4 method for signature 'NpdeObject'
show(object)
```

Arguments

object   an object from the npde package (NpdeData, NpdeRes, NpdeObject)

---

showall   *Contents of an object*

Description

Prints the contents of an object

Usage

```
showall(object)

## S3 method for class 'NpdeRes'
showall(object)

## S3 method for class 'NpdeObject'
showall(object)
```

Arguments

object   a NpdeData 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

A data frame with 132000 rows and 3 variables 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

```
## Not run:
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)

## End(Not run)
```

---

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

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

Value

The skewness of x.

References

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

Examples

```
## Not run:
x <- rnorm(100)
skewness(x)

## End(Not run)
```

---

subset.NpdeData   *Subsetting a NpdeData object*

Description

Return subset of data from a NpdeData object

Usage

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

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

Arguments

x	A NpdeData object
subset	logical expression indicating elements or rows to keep: missing values are taken as false.
...	Additional arguments (ignored)

---

summary.NpdeData   *Summary of a NpdeData object*

Description

Extracts elements from a NpdeData object

Usage

```
## S3 method for class 'NpdeData'
summary(object, print = TRUE, ...)

## S3 method for class 'NpdeRes'
summary(object, print = TRUE, ...)

## S3 method for class 'NpdeObject'
summary(object, ...)
```

Arguments

object	A NpdeData object
print	whether to print to data to stdev
...	Additional arguments (ignored)

---

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/kg).

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.

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

```
## Not run:
data(theopp)

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


## End(Not run)
```

---

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 log-scale (cp/mL)")
plot(Log_VL~Time,data=virload50,xlab="Time (d)",ylab="Viral loads, base 10 log-scale (cp/mL)")
```

`[,NpdeSimData-method`   *Get/set methods for NpdeData object*

Description

Access slots of a NpdeData using the object["slot"] format

Usage

```
## S4 method for signature 'NpdeSimData'
x[i, j, drop]

## S4 method for signature 'NpdeData'
x[i, j, drop]

## S4 replacement method for signature 'NpdeData'
x[i, j] <- value

## S4 method for signature 'NpdeRes'
x[i, j, drop]

## S4 method for signature 'NpdeObject'
x[i, j, drop]
```

Arguments

x	object from which to extract element(s) or in which to replace element(s)
i, j	indices specifying elements to extract or replace. Indices are numeric or character vectors or empty (missing) or NULL
drop	For matrices and arrays. If TRUE the result is coerced to the lowest possible dimension (see the examples). This only works for extracting elements, not for the replacement. See drop for further details
value	typically an array-like R object of a similar class as x

Index