# Package 'npde'

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**Title** Normalised Prediction Distribution Errors for Nonlinear Mixed-Effect Models

**Version** 3.2

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

**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)

**Encoding** UTF-8

**LazyLoad** yes

**LazyData** yes

**Imports** methods, scales, ggplot2, mclust, grid, gridExtra, testthat, rlang

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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-auxDistPlot.R' 'plotNpde-auxScatter.R' 'plotNpde-auxScatterPlot.R' 'plotNpde-binningPI.R' 'plotNpde-covplot.R' 'plotNpde-distributionPlot.R' 'plotNpde-methods.R' 'plotNpde-plotFunctions.R' 'plotNpde-scatterplot.R'

**NeedsCompilation** no

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# R topics documented:

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

## Description

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

## Author(s)

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

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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.

PDF documentation for npde 3.0: https://github.com/ecomets/npde30/blob/main/userguide_npde_3.0.pdf

## Examples

```
data(theopp)
data(simtheopp)

# Calling autonpde with dataframes

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

autonpde *Compute normalised prediction distribution errors*

## Description

These functions compute normalised prediction distribution errors (npde) and 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.npd=TRUE, decorr.method = "cholesky",
 cens.method = "cdf", units = list(x="",y=""), detect=FALSE, ties=TRUE, header=TRUE)

npde()

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) |
| 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") |
| verbose | a boolean (TRUE if messages are to be printed as each subject is processed, FALSE otherwise), defaults to FALSE |
| calc.npde | a boolean (TRUE if npde are to be computed, FALSE otherwise), defaults to TRUE |

| | |
|---|---|
| calc.npd | a boolean (TRUE if npd are to be computed, FALSE otherwise), defaults to TRUE |
| 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 |
| cens.method | a character string indicating the method used to handle censored data (see npde.cens.method) defaults to cdf |
| 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 |
| 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 |
| 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.

Diagnostic graphs are produced for npd, and npde are used in the tests as their distribution takes into account the correlation between repeated observations.

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.

PDF documentation for npde 3.0: https://github.com/ecomets/npde30/blob/main/userguide_npde_3.0.pdf

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

plot(x)
```

---

# 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.npd 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.npd/calc.npde are set), 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 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)
```

---

# 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 (Shapiro-test for normality (npd, npde)/Kolmogorove-Smirnov test for uniformity)

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

The p-values are adjusted using a Bonferroni correction: the raw p-values of the 3 individual tests are multiplied by 3, and the p-value for the global test is equal to the minimum of the adjusted p-values.

## 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)
data(simtheopp)
#' # Calling autonpde with dataframes
x<-autonpde(theopp,simtheopp,1,3,4,boolsave=FALSE)
gof.test(x)
```

---

# 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:

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

$$3$$

## Value

The kurtosis of x.

## References

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

## Examples

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

---

# 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.

## Value

This is not a function and does not have a return value, this is a statistical method.

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.

## Examples

```
# You need to have gridExtra installed to successfully run this example
if(requireNamespace("gridExtra", quietly=TRUE)) {
  data(warfarin)
  data(simwarfarinCov)
  wcov<-autonpde(namobs=warfarin,namsim=simwarfarinCov, iid=1,ix=2,iy=4,icov=c(3,6:8),
  namsav="warfCov", units=list(x="hr",y="mg/L", covariates=c("mg","kg","-","yr")))

  # Diagnostic plots for warfarin with a covariate model
  plot(wcov)

  # Covariate plots
  xwt.scatt<-plot(wcov, plot.type="x.scatter", covsplit=TRUE, which.cov="wt")
  xwt.qqplot<-plot(wcov, plot.type="qqplot", covsplit=TRUE, which.cov="wt")
  xwt.box<-plot(wcov, plot.type="covariates", which.cov="wt")
  xsex.scatt<-plot(wcov, plot.type="x.scatter", covsplit=TRUE, which.cov="sex")
  xsex.qqplot<-plot(wcov, plot.type="qqplot", covsplit=TRUE, which.cov="sex")
  xsex.box<-plot(wcov, plot.type="covariates", which.cov="sex")

  # Transforming the reference profile for npd, compared to a VPC plot
  plot.tnpd<-plot(wcov, plot.type="x.scatter", ref.prof=list(id=2),
  main="tnpd with reference profile ID=2")
  plot.vpc<-plot(wcov, plot.type="vpc", main="VPC")
  gridExtra::grid.arrange(grobs=list(plot.tnpd, plot.vpc), nrow=1, ncol=2)
  }
```

---

`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 |
| | @return This is not a function and does not have a return value, this is a statistical method. |

## 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")

## Value

No return value, called for side effects

## 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.covariate` *Covariate diagnostic plots*

## Description

Boxplot of the selected variable versus categories of covariates

## Usage

```
npde.plot.covariate(npdeObject, which.y="npd", ...)
```

## Arguments

| | |
|---|---|
| `npdeObject` | an object returned by a call to `npde` or `autonpde` |
| `which.y` | a string specifying the variable on the Y-axis (one of "yobs", "npde", "pd", "npd") |
| `...` | 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` and `npdeControl`) |

## Details

For a categorical covariate, boxplots are produced for each category. Continous covariates are split into quantile (by default, first quartile (<Q1), interquartile range (Q1-Q3) and upper quartile (>Q3), but the number of categories can be set by using the ncat argument).

For each category, the median according to simulations under the model is shown (it can be suppressed by using the argument bands=FALSE)..

## Value

a ggplot object or a list of ggplot objects (grobs)

## Author(s)

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

## References

K. Brendel, E. Comets, C. Laffont, F. Mentre F. 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

`npde`, `autonpde`, `set.plotoptions`, `npdeControl`

## 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 document for details, as well as set.plotoptions) |

### Value

a ggplot object or a list of ggplot objects (grobs)

## 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 independent 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 document for details, as well as set.plotoptions) |

### Details

By default, npd are used for the diagnostic plots. If an unknown argument to which (eg which="XXX") is given, this is changed to npd (with a warning message if verbose=TRUE or the verbose option in the option slot of the npdeObject is TRUE).

## Value

a ggplot object or a list of ggplot objects (grobs)

---

`npde.plot.dist` *Distribution plots of pd/npde*

---

## Description

Produces a plot of the cdistribution of a metric compared to their theoretical distribution. Three types of distribution plots are available: a histogram, a QQ-plot, or the empirical cdf.

## Usage

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

## 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 "npd" |
| `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") |
| `...` | 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`) |

## Value

a ggplot object or a list of ggplot objects (grobs)

## 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`) |

## Value

a ggplot object or a list of ggplot objects (grobs)

## 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, ...)

npde.plot.npd(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 document for details, as well as set.plotoptions) |

### Value

a ggplot object or a list of ggplot objects (grobs)

## npde.plot.scatterplot *Scatterplots and VPC*

### Description

Produces a scatterplot. Different types of scatterplots can be produced, with associated prediction bands (see details).

### Usage

```
npde.plot.scatterplot(npdeObject, which.x="x", which.y="npd", ref.prof=NULL, ...)
```

### Arguments

| | |
|---|---|
| npdeObject | an object returned by a call to npde or autonpde |
| which.x | a string specifying the variable on the X-axis (one of "x", "pred", "cov") |
| which.y | a string specifying the variable on the Y-axis (one of "yobs", "npde", "pd", "npd"), defaults to "npd" |

| | |
|---|---|
| ref.prof | either a character string (one of "covariate" or "all"), or a named list specifying the characteristics of the reference profile (see details) |
| ... | 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 and npdeControl) |

## Details

VPC: obtained using which.x="x", which.y="yobs"

Scatterplots of npde/pd/npd can be obtained versus "x" (independent variable) or "pred" (population predictions from the model)

Scatterplots of npde/pd/npd/observations can be obtained versus covariates by setting the which.x argument to "cov" and selecting the appropriate which.y. The function will use the covariates in the which.cov element of the prefs slot. This can be overriden to cycle over all the covariates in the dataset by supplying the argument which.cov="all" in the call to the function.

Reference profile: a reference profile can be added to scatterplots of npd and npde versus the independent variable (see Comets et al. 2013)

If ref.prof="all" (and covsplit is FALSE), the reference plot will be computed over all subjects using the mean and SD of all simulated data in each bin (see documentation).

If ref.prof="covariate" and an additional argument covsplit is given (covsplit=TRUE), the reference plot will be adjusted for each covariate category over all the covariates in the which.cov element of the prefs slot (see npdeControl for details on the prefs slot of the npdeObject).

If ref.prof is given as a named list (eg list(ID=c(1,5)) or list(sex=0, dose=c(50,100)), where names should refer to columns in the data file (eg ID should be a column in the data)), the reference profile will be obtained by combining (in the first example above, the reference profile will be obtained using the simulated data for subjects 1 and 5, while in the second example it will be computed using the subjects with sex=0 given doses 50 or 100).

## Value

a ggplot object or a list of ggplot objects (grobs)

## 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, T.H.T. Nguyen, and F. Mentré F. Additional features and graphs in the new npde library for R. *22th meeting of the Population Approach Group in Europe*, Glasgow, United Kingdom, 2013.

## See Also

npde, autonpde, set.plotoptions, npdeControl

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.scatter=FALSE,
cov.x.scatter=FALSE, cov.pred.scatter=FALSE,cov.x.box=FALSE,cov.pred.box=FALSE,
cov.ecdf=FALSE, cov.hist=FALSE, cov.qqplot=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 predictions |
| 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.scatter | boolean, whether to produce a scatterplot of the metric as a function of covariate(s) |
| 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) |
| cov.hist | boolean, whether to produce a distribution plot of the empirical distribution function, split by covariate(s) |

| | |
|---|---|
| cov.qqplot | 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) |

## Value

a ggplot object or a list of ggplot objects (grobs)

## 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.splitcov *Plots split by covariate for a NpdeObject object*

---

## Description

Plots split by covariate for a NpdeObject object (equivalent to using covsplit=TRUE with the appropriate plot.type)

## Usage

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

## Arguments

| | |
|---|---|
| npdeObject | an object returned by a call to npde or autonpde |
| which.plot | one of "x" (scatterplots of the metric versus X), "pred" (scatterplots of the metric versus predictions), "ecdf" (empirical distribution function), "hist" (histogram), "qqplot" |
| ... | 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) |

## Value

a ggplot object or a list of ggplot objects (grobs)

---

`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)

## Value

No return value, called for side effects

## 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.npd = 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.npd | a boolean; TRUE to compute npd |
| 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. |

### Value

A list of settings for the computation of pd/npde

---

`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 (a header is 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 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.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

```
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)
```

---

# 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

```
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

**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

```
methods(class="NpdeObject")

showClass("NpdeObject")
```

---

## 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, sep="", na.strings=c("NA","."),
detect=FALSE, 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 (a header is mandatory if detect is TRUE) |
| sep | field separator (for files on disk) |
| na.strings | strings to be considered as indicating NA |
| detect | a boolean controlling whether automatic recognition of columns in the dataset is on, defaults to FALSE if FALSE, the first 3 columns of the simulated data file will will be used as simulated id, predictor and response respectively if TRUE, the function will look for columns named respectively idsim, xsim and ysim (it will fail with an error message if these columns are not present in the simulated data) |
| 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

```
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.

### Value

currently does not return anything, use plot(x, plot.type="data") on the npdeObject x (TODO; a ggplot object)

### 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 plots are represented as a 2x2 array with distribution plots on the top row (histogram and QQ-plot), and scatterplots of npde versus independent variable and population predictions on the bottom row. The graph is plotted in a graphic device window, unless the result is stored in an object (eg myplot<-plot(x)) which can then be printed (eg using print(myplot)).

@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.

## Value

a ggplot object or a list of ggplot objects (grobs)

## See Also

set.plotoptions

## Examples

```
data(theopp)
data(simtheopp)

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

---

# 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) |

## Value

None

`set.plotoptions` *Set graphical preferences*

## Description

This function is used to set options for graphs

## Usage

```
set.plotoptions(object)

## Default S3 method:
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 |

## Value

No return value, shows the object

---

`simtheopp` *Simulated data for the computation of normalised prediction distribution errors in the theophylline dataset*

---

## 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.

## References

PDF documentation for npde 3.0: https://github.com/ecomets/npde30/blob/main/userguide_npde_3.0.pdf

## 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)
```

---

# 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)
```

---

## 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) |

### Value

a NpdeData object with a subset of the original data

## 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) |

### Value

A list with elements N (nb of subjects), data (dataframe containing the data), ntot.obs (total nb of observations), nind.obs (nb of observations per subject)

## 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)

## References

PDF documentation for npde 3.0: https://github.com/ecomets/npde30/blob/main/userguide_npde_3.0.pdf

## Examples

```
data(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).

## 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

## Details

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

The file simvirload contains 500 simulations under the same model. A full version of the simulated data with 1000 simulations can be downloaded from the github for npde3.0: https://github.com/ecomets/npde30/blob/main/keep/data/simvirload.tab

## 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.

## References

PDF documentation for npde 3.0: https://github.com/ecomets/npde30/blob/main/userguide_npde_3.0.pdf

## 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)")
```

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`warfarin` *Pharmacokinetics of warfarin*

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## Description

The `warfarin` data frame has 251 rows and 8 columns of data containing data on the pharmacokinetics of warfarin, an anticoagulant drug used in the prevention of thrombosis and thromboembolism.

## Usage

```
warfarin
```

## Format

This data frame contains the following columns:

**id** an integer identifying the subject on whom the observation was made

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

**amt** total dose received by the subject (mg)

**dv** warfarin concentration in the sample (mg/L)

**dvid** observation type (1 for all observations)

**wt** weight of the subject (kg)

**sex** subject gender (0=female, 1=male)

**age** age of the subject (yr)

## Details

The dataset is the PK part of a larger dataset including both warfarin concentrations and prothrombin complex activity (PCA), which measures the decreased coagulation activity resulting from the inhibition of vitamin K recycling, the mechanism of action of warfarin. It contains the concentrations measured in 32 healthy subjects after a single oral dose of warfarin sodium (1.5 mg/kg of body weight). The subjects in the study were sampled at different times over a period of up to 120 hours.

The data is distributed with the Monolix software as a demo for PK/PD modelling. The data has been slightly reformated for R, removing the line at time=0 and filling the amt column with the dose for each subject, following the output of simulx which was used to simulate data from two alternative models to fit this dataset.

Two datasets containing simulated data are associated with the `warfarin` data. For each dataset, 1000 simulations of the original data were performed for the computation of npde. The package contains only the simulated data simwarfarinCov because of size constraints. simwarfarinBase can be downloaded from the github for npde3.0: https://github.com/ecomets/npde30/blob/main/keep/data/simwarfarinBase.tab

**simwarfarinBase** the data in this dataset was simulated according to a base model without covariates: the PK model was a two-compartment model, with first-order absorption and a time-delay. Interindividual variability was modelled as log-normal distributions for parameters Tlag, ka, Cl and V1, and the error model was a combined error model. The parameters were estimated by Monolix.

**simwarfarinCov** the data in this dataset was simulated according to a model including several covariates: an age (centered on 30 yr) effect on Cl, a weight (centered on 70 kg) effect on Cl and V1, and a gender effect on V1. The covariate model was built in Monolix.

## Source

O'Reilly (1968). Studies on coumarin anticoagulant drugs. Initiation of warfarin therapy without a loading dose. Circulation 1968, 38:169-177.

## References

PDF documentation for npde 3.0: https://github.com/ecomets/npde30/blob/main/userguide_npde_3.0.pdf

## Examples

```
data(warfarin)

#Plotting the warfarin PK data
plot(dv~time,data=warfarin,xlab="Time after dose (hr)",
ylab="Warfarin concentration (mg/L)")
```

`[,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 |

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