

Package ‘npde’

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

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npde-package	<i>Normalised prediction distribution errors for nonlinear mixed-effect models</i>
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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
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See the documentation for npde or autonpde for details

Author(s)

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References

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

Examples

```
data(theopp)
data(simtheopp)

# Calling autonpde with dataframes

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

# 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)
```

x\$npde

autonpde

*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 = 1, ix = 2, iy = 3, imdv = 0, namsav = "output",
boolsave = TRUE, type.graph = "eps", output = TRUE, verbose = FALSE,
calc.npde=TRUE, calc.pd=FALSE)
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	number of the column in the observed data containing the patient ID, defaults to 1 (will be ignored if the dataframe contains a column named id)
ix	number of the column in the observed data containing the independent variable (X), defaults to 2 (will be ignored if the dataframe contains a column named xobs)
iy	number of the column in the observed data containing the dependent variable (Y), defaults to 3 (will be ignored if the dataframe contains a column named yobs)
imdvs	number of the column containing information about missing data (MDV), defaults to 0 (column not present)
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)
boolsave	a boolean (T if graphs and results are to be saved to a file, F otherwise), defaults to T

<code>type.graph</code>	type of graph (one of "eps", "jpeg", "png", "pdf"), defaults to postscript ("eps")
<code>output</code>	a boolean (T if the function should return values, F otherwise), defaults to T
<code>verbose</code>	a boolean (T if messages are to be printed as each subject is processed, F otherwise), defaults to F
<code>calc.npde</code>	a boolean (T if npde are to be computed, F otherwise), defaults to T
<code>calc.pd</code>	a boolean (T if pd are to be computed, F otherwise), defaults to F

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.

Value

A list containing the following components:

<code>obsdat</code>	observed data, a dataframe containing 3 columns (<code>id</code> =patient ID, <code>xobs</code> =independent variable (X), <code>yobs</code> =dependent variable (Y))
<code>simdat</code>	simulated data, a dataframe containing 4 columns (<code>idsim</code> =patient ID, <code>irsim</code> =integer identifying the replicate; <code>xsim</code> =independent variable (X), <code>ysim</code> =dependent variable (Y))
<code>yobs</code>	the vector of observed dependent variable (Y), decorrelated
<code>ydsim</code>	the vector of simulated dependent variable (Y), decorrelated
<code>ypred</code>	a vector giving the mean of the predicted distribution for each observation
<code>xerr</code>	an integer code to keep track of errors during the computation; after a successful computation the value of <code>xerr</code> should be 0. A value of 1 or 2 signals errors during the computation.
<code>npde</code>	the vector of normalised prediction distribution errors, if <code>calc.npde</code> =T (NA otherwise)
<code>pd</code>	the vector of prediction discrepancies, if <code>calc.npd</code> =T (NA otherwise)

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 T, two files are created:

<code>results file</code>	the numerical results are saved in a file with extension <code>.npde</code> (the name of which is given by the user). The file contains the components <code>id</code> , <code>xobs</code> , <code>ypred</code> , <code>npde</code> , <code>pd</code> stored in columns
<code>graph file</code>	the graphs are saved to a file with the same name as the results file, and with extension depending on the format. See also graphnpde

Author(s)

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References

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

See Also

[graphnpde](#), [testnpde](#)

Examples

```
data(theopp)
data(simtheopp)

# Calling autonpde with dataframes

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

# 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)

x$npde
```

graphnpde

Save graphs of the normalised prediction distribution errors to a file

Description

Saves the graphs plotted by plotnpde to a file.

Usage

```
graphnpde(namegr, xobs, npde, ypred, type.graph)
```

Arguments

namegr	name of the file in which graphs are to be saved
xobs	the vector of observed independent variable (x)
npde	the vector of normalised prediction distribution errors (returned by the functions npde or autonpde with the option output=TRUE)
ypred	the vector giving the mean of the predicted distribution for each observation
type.graph	type of graph (one of "eps", "jpeg", "png", "pdf")

Details

See [plotnpde](#) for a description of the graphs plotted.

Value

None

Author(s)

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

References

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

See Also

[npde](#), [autonpde](#), [plotnpde](#)

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 .

Examples

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

pdemenu

Interactive query of the arguments needed for the computation of normalised prediction distribution errors

Description

This function can be used to set interactively the arguments needed to compute the normalised prediction distribution errors. It is called by npde.

Usage

```
pdemenu()
```

Details

This function is normally not called by the end-user.

Value

namobs	name of the file containing the observed data
namsim	name of the file containing the simulated data
iid	number of the column containing the patient ID
ix	number of the column containing the independent variable (X)
iy	number of the column containing the dependent variable (Y)
imdvs	number of the column containing information about missing data (MDV), 0 if this column is not present
boolsave	a boolean (T if results are to be saved to a file, F if not)
type.graph	type of graph (one of "eps", "jpeg", "png", "pdf")
namegr	name of the file in which graphs are to be saved
calc.npde	a boolean (T if npde are to be computed, F otherwise)
calc.npd	a boolean (T if npd are to be computed, F otherwise)

nameres	name of the file in which numerical results are to be saved
output	a boolean (T if the function should return values, F otherwise)
verbose	a boolean (T if messages are to be printed as each subject is processed, F otherwise)

Author(s)

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

References

K. Brendel, E. Comets, C. Laffont, C. Laveille, and F. Mentré. 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 (needs interactive input)
# x<-pdemenu()
```

plotnpde

Plots graphs of the normalised prediction distribution errors

Description

Plots 4 graphs to evaluate the shape of the distribution of the normalised prediction distribution errors (npde)

Usage

```
plotnpde(xobs, npde, ypred)
```

Arguments

xobs	the vector of the observed independent variable (X)
npde	the vector of normalised prediction distribution errors (returned by the functions npde or autonpde with the option output=TRUE)
ypred	a vector giving the mean of the predicted distribution for each observation

Value

Four graphs are produced:

a quantile-quantile plot

plot of the npde versus the corresponding quantiles of a normal distribution, with the line $y=x$ overlaid.

a histogram of the npde

the shape of the normal distribution is also shown

two scatterplots of the npde

a plot of the npde versus the independent variable X and a plot of the npde versus the empirical mean of the predicted distribution; for these last two graphs, we plot the lines corresponding to $y=0$ and to the 5 90

Author(s)

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

References

K. Brendel, E. Comets, C. Laffont, C. Laveille, and F. Mentré. 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

```
#Computing npde
data(theopp)
data(simtheopp)

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

#Using the npde in object x for the plot
plotnpde(x$obsdat$xobs,x$npde,x$ypred)
```

plotpd

Plots graphs of the normalised prediction distribution errors

Description

Plots 4 graphs to evaluate the shape of the distribution of prediction discrepancies

Usage

```
plotpd(xobs, pd, ypred)
```

Arguments

xobs	the vector of the observed independent variable (X)
pd	the vector of normalised prediction distribution errors (returned by the functions npde or autonpde with the option output=TRUE)
ypred	a vector giving the mean of the predicted distribution for each observation

Value

Four graphs are produced:

a quantile-quantile plot

plot of the pd versus the corresponding quantiles of a uniform distribution, with the line $y=x$ overlaid.

a histogram of the pd

the line corresponding to the uniform distribution is also shown

two scatterplots of the pd

a plot of the pd versus the independent variable X and a plot of the pd versus the empirical mean of the predicted distribution; for these last two graphs, we plot the lines corresponding to $y=0.5$, $y=0.05$ and $y=0.95$.

Author(s)

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

References

K. Brendel, E. Comets, C. Laffont, C. Laveille, and F. Mentré. 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

```
#Computing pd
data(theopp)
data(simtheopp)

x<-autonpde(theopp,simtheopp,1,3,4,boolsave=FALSE,calc.pd=TRUE,calc.npde=FALSE)
x$pd

#Using the npde in object x for the plot
plotpd(x$obsdat$xobs,x$pd,x$ypred)
```

simtheopp	<i>Simulated data for the computation of normalised prediction distribution errors</i>
-----------	--

Description

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

Usage

```
simtheopp
```

Format

This data frame contains the following columns:

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

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

ysim simulated theophylline concentration (mg/L).

Details

See [theopp](#) for a description of the original dataset.

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

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

Source

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

See Also

[theopp](#)

Examples

```

data(simtheopp)

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

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

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

```

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 .

Examples

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

testnpde

Tests for normalised prediction distribution errors

Description

Performs tests for the normalised prediction distribution errors returned by npde

Usage

```
testnpde(npde)
```

Arguments

npde the vector of prediction distribution errors (returned by the functions npde or autonpde with the option output=TRUE)

Details

Given a vector of normalised prediction distribution errors (npde) computed by npde or autonpde, this function compares the npde to the standardised normal distribution $N(0,1)$ using a Wilcoxon test of the mean, a Fisher test of the variance, and a Shapiro-Wilks test for normality. A global test is also reported.

Value

a list containing 4 components:

Wilcoxon test of mean=0

compares the mean of the npde to 0 using a Wilcoxon test

variance test compares the variance of the npde to 1 using a Fisher test

SW test of normality

compares the npde to the normal distribution using a Shapiro-Wilks test

global test an adjusted p-value corresponding to the minimum of the 3 previous p-values multiplied by the number of tests (3), or 1 if this p-value is larger than 1.

Author(s)

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

References

K. Brendel, E. Comets, C. Laffont, C. Laveille, and F. Mentré. 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

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

#Testing npde
y<-testnpde(x$npde)

# Not Run
# Assuming the results were saved to a file output.npde
# using the boolsave=T option and namsav="output" (default)
# dat<-read.table("output.npde",header=T)
# testnpde(dat$npde)
```

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. In the present package *npde*, we removed the data at time 0.

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

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

Source

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

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

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

Examples

```
data(theopp)
```

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

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