

Package ‘drsmooth’

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Title Dose-Response Modeling with Smoothing Splines

Description Drsmooth provides tools for assessing the shape of a dose-response curve by testing linearity and non-linearity at user-defined cut-offs. It also provides two methods of estimating a threshold dose, or the dose at which the dose-response function transitions to significantly increasing: bi-linear (based on pkg:segmented) and smoothed with splines (based on pkg:mgcv).

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Collate 'bartlett.r' 'chisquare.r' 'dosefactor.r' 'DRdata.R'
'dunnetts1.r' 'dunnetts2.r' 'dunnettst3.r' 'dunns1.r' 'dunns2.r' 'jonckheere.r' 'lbcd.r' 'nlaad.r' 'nlbcd.r'
'outlier.r' 'pkg_prep.r' 'prelimstats.r' 'segment.r' 'shapiro.r' 'firstDeriv.r' 'noel.r' 'dunnetts.format.r'
'dunns.format.r' 'drsmooth.print.r' 'segment.plot.r'
'segment.print.r' 'spline.plot.r' 'drsmooth-package.R' 'smooth.r'

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lbcd	<i>Linearity Below Cut-off Dose</i>
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Description

This function tests linearity below a specified dose.

Usage

```
lbcd(dosecolumn = "", targetcolumn = "", cutoffdose = 0,
     data = NA)
```

Arguments

dosecolumn	Name of dose column in input dataframe.
targetcolumn	Name of response column in input dataframe.
cutoffdose	Cut-off dose (numeric).
data	Input dataframe.

Details

The user may provide a limit below which the linearity of the dose-response relationship is tested. A significant result indicates that the slope is non-zero below the user-specified cutoff dose.

Value

A summary table showing the intercept and slope coefficients for the linear function below the user-specified dose, along with standard errors and significance tests.

Examples

```
# Conducts a linear regression for all doses below 1.5
# (i.e., all dose levels up to and including 1.4929).
# The significance test on the dose coefficient is the test of non-zero linear slope:
lbcd("dose", "MF_Log", cutoffdose=1.5, data=DRdata)

# This produces an error, as no cutoffdose was specified:
## Not run:
lbcd("dose", "MF_Log", data=DRdata)

## End(Not run)
```

nlaad

Non-linearity Across All Doses

Description

This function determines whether a non-linear spline model of the dose-response relationship differs significantly from a linear model across all doses.

Usage

```
nlaad(dosecolumn = "", targetcolumn = "", data = NA)
```

Arguments

dosecolumn	Name of dose column in dataframe.
targetcolumn	Name of response column in dataframe.
data	Input dataframe.

Details

The non-linear spline model (output "Model 2") is compared to the linear model (output "Model 1") using an anova F-test. If the spline model fits the data significantly better, the F will be large and the associated p value will be significant.

Value

The analysis of variance table comparing the non-linear spline model with the linear model to assess non-linearity across all doses.

Examples

```
# Prints the F test of the difference between the spline model (output "Model 2")
# and the linear model (output "Model 1") as a test of nonlinearity
# across all doses:
nlaad("dose", "MF_Log", data=DRdata)
```

nlbcd	<i>Non-linearity Below Cut-off Dose</i>
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Description

This function tests non-linearity below a specified dose.

Usage

```
nlbcd (dosecolumn = "", targetcolumn = "", cutoffdose =  
0, data = NA)
```

Arguments

dosecolumn	Name of dose column in input dataframe.
targetcolumn	Name of response column in input dataframe.
cutoffdose	Numeric tested cut-off dose.
data	Input dataframe.

Details

The user may provide a limit below which the non-linearity of the dose-response relationship is tested. A significant result indicates that the dose-response relationship exhibits non-linearity below the user-specified cutoff dose. NOTE: The dose-response relationship estimated by this function is not necessarily the same as that estimated by the nlaad function, as the nlbcd only uses doses below the cutoff and nlaad uses all doses. The user should keep this in mind in interpreting the outputs of these functions.

Value

The analysis of variance table comparing the non-linear spline model with the linear model to assess non-linearity across doses below the user-specified cutoff.

Examples

```
# Prints the F test of the difference between the spline model (output "Model 2")  
# and the linear model (output "Model 1") as a test of nonlinearity  
# for doses below 1.5 (i.e., all dose levels up to and including 1.49):  
nlbcd("dose", "MF_Log", cutoffdose=1.5, data=DRdata)  
  
# This produces an error, as no cutoffdose was specified:  
## Not run:  
nlbcd("dose", "MF_Log", data=DRdata)  
  
## End(Not run)
```

noel	<i>No/Lowest Observed Effect Levels</i>
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Description

This function calculates and displays the results of the requested no/lowest observed effect level tests.

Usage

```
noel(dosecolumn = "", targetcolumn = "", tests =
     c("dunnetts1", "dunnetts2", "dunns1", "dunns2",
       "dunnettst3"), direction = "greater", alpha = .05, data
     = NA)
```

Arguments

dosecolumn	Character string, name of dose column to be tested
targetcolumn	Character string, name of response column to be tested
tests	List of tests to run. Specify a subset by omitting any tests not desired: c("dunnetts1", "dunnetts2", "dunns1", "dunns2", "dunnettst3")
direction	Direction of the anticipated difference
alpha	Significance level (numeric) to be used
data	Input dataframe.

Details

Dunnett's one-tailed, Dunnett's two-tailed, Dunn's one-tailed, Dunn's two-tailed, and Dunnett's T3 tests are all executed, unless a subset of these tests is specified by replacing the default list with a subset of the available tests. Dosecolumn should be assigned the name of the dose column in the input dataframe, e.g. "dose". Targetcolumn should be assigned the name of the response column in the input dataframe, e.g. "resp". If the direction of the dose-response relation is expected to be negative, direction can be specified as "less". The alpha level determining significance can be specified. Data must be assigned the input dataframe.

Value

Shown are tables giving the comparisons of the active dose levels to the zero dose control along with indications of significance specific to each type of test.

Examples

```
# Prints all available tests of no/lowest observed effect levels
# at default alpha=.05:
noel("dose", "MF_Log", data=DRdata)
```

```
# Prints only Dunnett's one-tailed and Dunn's 2-tailed tests at default alpha=.05:
noel("dose", "MF_Log", tests=c("dunnettst1", "dunns2"), data=DRdata)

# Shows Dunnett's T3 tests at user-specified alpha of .01
noel("dose", "MF_Log", tests=c("dunnettst3"), alpha=.01, data=DRdata)
```

```
prelimstats
```

```
Preliminary Statistics
```

Description

This function calculates and displays the p values for the requested distribution tests.

Usage

```
prelimstats(dosecolumn="", tests=c("outlier", "bartlett",
  "shapiro", "chisquare", "jonckheere"), data=NA)
```

Arguments

dosecolumn	Name of column containing dose in input data frame, e.g. "dose"
tests	List of tests to run. May specify a subset by omitting any of the default tests = c("outlier", "bartlett", "shapiro", "chisquare", "jonckheere").
data	Input dataframe.

Details

Outlier (Bonferroni Outlier Test), homogeneity (Bartlett's), normality (Shapiro-Wilk), composite homogeneity/normality (Fisher chi-square combining Bartlett's and Shapiro-Wilk), and Jonckheere's (monotone trend) tests are available. All tests are executed unless a smaller set is specified using the 'tests' parameter.

Outlier test. Calls outlierTest – there is at least one Bonferroni-adjusted outlier if the p value is less than the targeted alpha level.

Bartlett's. Variances are non-homogeneous if the p value is less than the targeted alpha level.

Shapiro-Wilk. The variable is non-normally distributed if the p-value is less than the targeted alpha level.

Chisquare. Fisher's combined p value for Bartlett's and Shapiro-Wilk tests. This indexes the conformance of the outcome and its transformations to both normality and variance homogeneity. Generally, the response transformation associated with the least-significant (highest p-value) is the most desirable transformation.

Jonckheere. There is evidence of a monotonic trend if the p-value is lower than the targeted alpha.

Value

Shown are p values for the homogeneity, normality, and trend tests, and the Bonferroni-adjusted p value for the most outlierly case.

Examples

```
# Prints all available preliminary tests:
prelimstats("dose", data=DRdata)

# Prints only the outlier test:
prelimstats("dose", tests="outlier", data=DRdata)

# Prints only the homogeneity and normality tests:
prelimstats("dose", tests=c("bartlett", "shapiro"), data=DRdata)
```

segment

Segmented Hockey Stick Test

Description

This function returns a two-segment linear dose-response model, by imposing a zero slope for the initial (left) segment, detecting one breakpoint where the dose-response relation changes to a positive slope (if such a breakpoint exists), then reporting the breakpoint dose, its standard error and p-value, and plotting the model.

Usage

```
segment(dosecolumn = "", targetcolumn = "", data = NA)
```

Arguments

dosecolumn	Name of dose column of interest in dataframe.
targetcolumn	Name of response column of interest in dataframe.
data	Input dataframe.

Details

This function:

- 1) Attempts to identify one breakpoint using the 'segmented' function, starting the search at the median of the input dose variable, and imposing a zero-slope left-hand segment before any identified breakpoint.
- 2) If a breakpoint has been identified using this iterative approach, the p-value is returned and model plotted; otherwise the function returns no breakpoint.

Value

Returns the estimated breakpoint, standard error, and 90 percent confidence limits on the breakpoint, as well as a plot of the estimated two-segment dose-response relationship.

Examples

```
# Prints the breakpoint, its standard error, and 95% confidence limits
# along with a plot of the estimated two-segment linear relationship:
segment("dose", "MF_Log", data=DRdata)
```

smooth

*Dose-response Modeling with Smoothing Splines***Description**

Generates a spline model given dose and target response columns.

Usage

```
smooth(dosecolumn = "", targetcolumn = "", data = NA)
```

Arguments

dosecolumn	Name of dose column of interest in dataframe.
targetcolumn	Name of response column of interest in dataframe.
data	Input dataframe.

Details

This function generates a spline model with the input dose and target response columns, plots the spline-estimated dose-response function with its upper and lower 95 percent confidence bounds in green and red respectively along with the actual data, and returns key metrics related to the dose-response function. Note that the confidence bounds depicted on the plot are for the dose-response function itself, and not for the raw data.

Value

A plot of the spline-estimated dose-response function along with the actual data. Also, several key metrics are reported:

STD (slope transition dose): The lowest dose at which the slope of the dose-response function is significantly (90 two-sided) positive.

STD_l and STD_u: The 90 percent lower and upper confidence bounds on the STD.

STD_bias (experimental): An estimate of the bias associated with the STD.

iLOGEL (experimental: interpolated lowest observed effect level) The lowest dose at which the predicted response exceeds the 90 percent upper confidence bound of the response at zero dose. This value can be anywhere within the dose range – hence "interpolated."

iLOGEL_l and iLOGEL_u: The 90 percent lower and upper confidence bounds on the iLOGEL.

Examples

```
# Produces and plots spline model with confidence bounds, and prints key metrics.  
# For the plot only, see spline.plot  
# Due to run-time, this example is documented as "don't run."  
## Not run:  
smooth("dose", "MF_Log", data=DRdata)  
  
## End(Not run)
```

spline.plot

Plot Spline

Description

This function generates a spline model with the input dose and target response columns, and plots the spline-estimated dose-response function with its upper and lower 95 percent confidence bounds in green and red respectively along with the actual data. Note that the confidence bounds depicted on the plot are for the dose-response function itself, and not for the raw data.

Usage

```
spline.plot(dosecolumn = "", targetcolumn = "", data =  
            NA)
```

Arguments

dosecolumn	Name of dose column.
targetcolumn	Name of response column.
data	Input dataframe.

Value

A plot of the spline-estimated dose-response function along with the actual data.

Examples

```
# Produces and plots the spline model with confidence bounds.  
#For the same plot with key metrics, see drsmooth().  
spline.plot("dose", "MF_Log", data=DRdata)
```

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