

# Package ‘drsmooth’

September 25, 2015

**Title** Dose-Response Modeling with Smoothing Splines

**Description** 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').

**Version** 1.9.0

**Date** 2015-09-20

**Maintainer** Anne Bichteler <abichteler@toxstrategies.com>

**Depends** R (>= 3.0.1)

**Imports** boot, car, mgcv, multcomp, DTK, segmented, lubridate, pgirmess, stats

**Suggests** testthat

**License** GPL (>= 3)

**LazyData** TRUE

**Collate** 'bartlett.r' 'chisquare.r' 'dosefactor.r' 'DIdata.R'  
'DRdata.R' 'dunnettst3.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.R'  
'dunnetts.format.r' 'dunns.R' 'dunns.format.r'  
'drsmooth.print.r' 'segment.plot.r' 'segment.print.r'  
'spline.plot.r' 'drsmooth.R' 'drsmooth-package.R'  
'dichot\_smooth.R' 'expand.R' 'fishers.exact.R' 'smooth.R'

**NeedsCompilation** no

**Author** Greg Hixon [aut],  
Chad Thompson [aut],  
Anne Bichteler [aut, cre],  
Liz Abraham [ctb]

**Repository** CRAN

**Date/Publication** 2015-09-25 00:01:50

## R topics documented:

drsmooth-package . . . . .	2
drsmooth . . . . .	3
expand . . . . .	5
lbcd . . . . .	6
nlaad . . . . .	7
nlbcd . . . . .	8
noel . . . . .	9
prelimstats . . . . .	10
segment . . . . .	12
smooth . . . . .	13
spline.plot . . . . .	13

<b>Index</b>	<b>15</b>
--------------	-----------

---

drsmooth-package	<i>drsmooth-package: Dose-response Modeling with Smoothing Splines</i>
------------------	--

---

### 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).

### Details

v.1.9.0 introduces spline-based dose-response modeling on dichotomous data, with examples using the included DIdata. See NEWS for details, as well as the help files for the exported functions itemized below.

### drsmooth functions

There are 8 user-initiated functions in this package; see the help pages for documentation of each.

prelimstats() executes up to 5 tests of homogeneity & normality.

noel() executes up to 5 tests to determine the no-observed-effect-level.

nlaad(), lbcd(), nlbcd() test linearity across all doses, linearity below a defined cut-off dose, and non-linearity below a defined cut-off dose, respectively.

spline.plot() only prints the smoothed dose-response curve.

segment() returns a two-segment linear dose-response model, by imposing a zero slope for the initial (left) segment and detecting one breakpoint where the dose-response relation changes to a positive slope (if such a breakpoint exists).

drsmooth() generates a spline model with the input dose and response, plots the spline-estimated dose-response function with its upper and lower 95 percent confidence bounds along with the actual data, and returns key metrics related to the dose-response function.

expand () expands summarized dichotomous data into the format expected by drsmooth(), if needed.

**See Also**

drsmooth

---

drsmooth*Dose-response Modeling with Smoothing Splines*

---

**Description**

Generates a spline model given dose and target response columns.

**Usage**

```
drsmooth(dosecolumn = "",
         targetcolumn = "",
         data_type = "",
         k = 4,
         return_predict = FALSE,
         write_predict = TRUE,
         STD_bias = TRUE,
         data = NA)
```

**Arguments**

dosecolumn	Name of dose column of interest in dataframe.
targetcolumn	Name of response column of interest in dataframe.
data_type	Allowed values "continuous" or "dichotomous".
k	Dimension of the basis used to represent the smooth term; see Details.
return_predict	If TRUE (default FALSE), returns dataframe of predicted values.
write_predict	If TRUE (the default), writes the dataframe of predicted values to a .csv file in the working directory.
STD_bias	If TRUE (the default), calculates the bias of the slope transition dose, a bootstrapped and resource-intensive computation.
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. Currently, the program will use the lowest dose group (whatever its value is) as the basis for iLOGEL and BMD estimates Normally we would assume that would be zero, but it is not forced to be.

Note that the confidence bounds depicted on the plot are for the dose-response function itself, and not for the raw data.

The parameter 'k', defaulted to 4, defines the dimensions allowed the smooth term in estimating the response relation. With 2 reserved for each end of the smooth, the default allows for 2 bends in this univariate smooth. In the case that this appears to overfit the data, the user may choose to override the default to 3, which would allow only one bend.

## 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

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: the difference between the point estimate and the mean of 1000 bootstrapped STDs.

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.

For data\_type = "continuous": BMD1sd and BMD10: Benchmark doses corresponding to a 1sd and 10 BMDL1sd and BMDL10: 90 percent (two-sided) lower bounds on the indicated BMDs.

For data\_type = "dichotomous": BMD1perc, BMD5perc, BMD10perc: Benchmark doses corresponding to a 1 BMDL1perc, BMDL5perc, BMDL10perc: 90 percent (two-sided) lower bounds on the indicated BMDs.

-2LL, the number of parameters associated with the spline model, and the AIC.

## Examples

```
# Produces and plots spline model with confidence bounds, and prints key metrics.
# For the plot only, see spline.plot
# The STD_bias is defaulted here to FALSE to speed run time.
# For continuous outcomes
data(DRdata)
drsmooth("dose", "MF_Log", data_type = "continuous", k = 4, return_predict = FALSE,
write_predict = FALSE, STD_bias = FALSE, data=DRdata)

# For dichotomous outcomes
data(DIdata)
# If necessary, convert summarized dataframe into 1 row per case dataframe (see drsmooth::expand)
DIdata_expanded <- expand(dosecolumn = "Dose", targetcolumn = "Tumor", ncolumn = "n", data = DIdata)

drsmooth("Dose", "Tumor", data_type = "dichotomous", return_predict = FALSE,
write_predict = FALSE, STD_bias = FALSE, data=DIdata_expanded)
```

---

expand

*Expand Summarized Dichotomous Data for drsmooth*

---

## Description

This function expands summarized dichotomous data for input into drsmooth.

## Usage

```
expand(dosecolumn = "",
       targetcolumn = "",
       ncolumn = "",
       data = NA,
       outputfilename = "")
```

## Arguments

dosecolumn      Character string, name of dose column to be tested.  
targetcolumn    Character string, name of response column to be tested.  
ncolumn         Character string, name of N column of total cases per dose.  
data            Input dataframe.  
outputfilename Character string, name of .csv file to be written out.

## Details

The input data frame to this function is expected to contain a numerical dose column, identified as 'dosecolumn,' a numerical outcome count column, identified as 'targetcolumn,' and a numerical N column with the total number of cases tested in the dose group, identified as 'ncolumn.' See drsmooth included data DIdata for an example. This function takes such a summarized dataframe and returns an expanded case-by-case replicate df, which is suitable as an input to the drsmooth function, with data\_type = "dichotomous". If an outputfilename is provided, the resulting df is also written to the working directory.

## Value

A dataframe is returned containing one row for each case in each dose. If an outputfilename is provided, the df is also written out in a .csv file. An expanded dataframe or file such as this one is appropriate as input to the drsmooth function when data\_type = "dichotomous".

## Examples

```
# Generates an expanded dataframe from the included data DIdata:
data(DIdata)
DIdata_expanded <- expand(dosecolumn = "Dose", targetcolumn = "Tumor", ncolumn = "n", data = DIdata)
```

---

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

---

**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.

The nlaad, nlbcd, and lbcd functions are currently only intended for use on continuous outcome data.

**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	<i>Non-linearity Across All Doses</i>
-------	---------------------------------------

---

## 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.

The nlaad, nlbcd, and lbcd functions are currently only intended for use on continuous outcome data.

## 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 *Non-linearity Below Cut-off Dose*


---

### 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.

The nlaad, nlbcd, and lbcd functions are currently only intended for use on continuous outcome data.

### 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>
------	---

---

### Description

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

### Usage

```
noel(dosecolumn = "",
     targetcolumn = "",
     data_type = "continuous",
     tests = c("all"),
     alternatives = c("greater", "two.sided"),
     alpha = .05,
     control = "",
     tot.obs = "",
     data = NA)
```

### Arguments

dosecolumn	Character string, name of dose column to be tested.
targetcolumn	Character string, name of response column to be tested.
data_type	Allowed values "continuous" (default) or "dichotomous".
tests	Available tests depend on data_type. See details.
alternatives	Character string(s) specifying the direction of the alternative hypothesis. Must be one or more of "greater", "two.sided", or "less".
alpha	Significance level (numeric) to be used.
control	Level of dose to be used as the control for dichotomous data.
tot.obs	Character string, column with number tested at each dose for dichotomous outcomes.
data	Input dataframe. See details for expected formats.

### Details

Dosecolumn should be assigned the name of the dose column in the input dataframe. Targetcolumn should be assigned the name of the response column in the input dataframe. Tests is defaulted to run all tests available, given the data\_type defined.

If the data\_type is defined as "continuous", Dunnett's, Dunn's, and Dunnett's T3 tests are available and are all executed (default), unless tests is defined as a subset of the list: c("dunnetts", "dunns", "dunnettst3"). The input data frame is expected to include a numeric column containing the dose and a numeric column containing a continuous response variable.

When `data_type` is defined as "dichotomous" for a dichotomous response variable, the Fisher's exact test is available and executed, with the `tests` parameter is either left at the `c("all")` default or specified as `c("fishers.exact")`. The control dose is defaulted to the lowest observed dose, unless a different control dose is provided as a string to the `control` parameter. The input data frame is expected to include summarized data of dichotomous outcome tests: one row for each dose, the total number tested at that dose, and the total number of events observed at that dose.

The `alternative` parameter specifies the direction(s) of the alternative hypothesis. All alternatives listed will be tested.

The alpha level determining significance can be specified.

### Value

Tables are printed 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:
data(DRdata)
noel("dose", "MF_Log", data=DRdata)

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

# Fisher's exact test for dichotomous outcome data:
data(DIdata)
noel(dosecolumn = "Dose",
     targetcolumn = "Tumor",
     data_type = "dichotomous",
     tot.obs = "n",
     data = DIdata)
```

---

```
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 `car::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.

All columns other than the one identified as the dosecolumn are subjected to these tests; therefore the input data frame should only contain the dosecolumn and response column(s). This function is currently only intended for use on continuous outcome data.

**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.

This function is currently only intended for use on continuous outcome data.

### 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	<i>Dose-response Modeling with Smoothing Splines</i>
--------	--

---

### Description

Replaced by drsmooth::drsmooth.

### 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

drsmooth::smooth has been replaced by drsmooth::drsmooth but a shell retained in v.1.9.0 to prompt the switch. v.2.0.0 will remove drsmooth::smooth altogether. Please see help for drsmooth, where additional detail on the new functionality is also available.

---

spline.plot	<i>Plot Spline</i>
-------------	--------------------

---

### 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 = "", k = 4, data_type = "", data = NA)
```

### Arguments

dosecolumn	Name of dose column.
targetcolumn	Name of response column.
k	Dimension of the basis used to represent the smooth term.
data_type	Allowed values "continuous" or "dichotomous".
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().
# For continuous outcomes:
data(DRdata)
spline.plot("dose", "MF_Log", k = 4, data_type = "continuous", data=DRdata)

# For dichotomous outcomes:
data(DIdata)
# If necessary, convert summarized dataframe into 1 row per case dataframe (see drsmooth::expand)
DIdata_expanded <- expand(dosecolumn = "Dose", targetcolumn = "Tumor", ncolumn = "n", data = DIdata)
spline.plot("Dose", "Tumor", k = 4, data_type = "dichotomous", data=DIdata_expanded)
```

# Index

drsmooth, 3  
drsmooth-package, 2

expand, 5

lbcd, 6

nlaad, 7

nlbcd, 8

noel, 9

prelimstats, 10

segment, 12

smooth, 13

spline.plot, 13