

Package ‘drugCombo’

November 13, 2018

Type Package

Title Drug Interaction Modeling Based on Loewe Additivity Following Harbron's Approach

Version 1.0.3

Date 2018-11-09

Author Maxim Nazarov, Nele Goeyvaerts, Chris Harbron (original article and code)

Maintainer Maxim Nazarov <maxim.nazarov@openanalytics.eu>

Description Perform assessment of synergy/antagonism for drug combinations based on the Loewe additivity model, following Harbron's approach (Statistics in Medicine, 2010, <doi:10.1002/sim.3916>). The package allows flexible modeling of the drug interaction index and supports “2-stage” estimation in addition to “1-stage” estimation, including bootstrap-based confidence intervals. The method requires data on the monotherapy responses and the package accommodates both checkerboard and ray designs. Functions are available for graphical exploration of model goodness-of-fit and diagnostics, as well as for synergy/antagonism assessment in 2D and 3D.

License GPL-3

RoxygenNote 6.0.1

Depends R (>= 2.10)

Imports ggplot2, minpack.lm, BIGL (>= 0.9), rgl, nlme, Deriv, methods, stats

Suggests knitr, rmarkdown, testthat, Cairo

VignetteBuilder knitr, rmarkdown

LazyData true

Encoding UTF-8

NeedsCompilation no

Repository CRAN

Date/Publication 2018-11-13 14:10:03 UTC

R topics documented:

bootstrapCoefs	2
checkerboardData	3
contour.tauSurface	3
fitModel	4
fitPlot2d	6
fitPlot3d	6
getBootTaus	7
getTauSurface	8
invL4	9
plot.HarbronFit	9
plot.tauSurface	10
print.tauSurface	11
rayData	12
tauPlot2d	12
tauPlot3d	14
unique.tauSurface	15
Index	16

bootstrapCoefs	<i>Show estimated model parameters from all bootstrap iterations</i>
----------------	--

Description

Show estimated model parameters from all bootstrap iterations

Usage

```
bootstrapCoefs(tauSurface)
```

Arguments

tauSurface A tauSurface object returned by [getTauSurface](#).

Value

matrix of parameter estimates from the bootstrap iterations as returned by [getBootTaus](#)

Author(s)

Maxim Nazarov

checkerboardData	<i>Example checkerboard design drug combination data</i>
------------------	--

Description

A dataset containing data from 10 different in-vitro drug combination experiments for an antiviral treatment (compound 1) using a checkerboard design. The variables are as follows:

Format

A data frame with 9360 observations of 5 variables:

- d1: dose of the first compound
- d2: dose of the second compound
- effect: observed effect (normalized cell counts)
- plate: plate ID (1 to 3 within experiment)
- exp: experiment ID (1 to 10)

contour.tauSurface	<i>Contour-plot method for "tauSurface" objects</i>
--------------------	---

Description

Contour-plot method for "tauSurface" objects

Usage

```
## S3 method for class 'tauSurface'  
contour(x, digits = 4, ...)
```

Arguments

x	A tauSurface object returned by getTauSurface .
digits	Number of digits used in format for the dose labels.
...	Further parameters, currently not used.

Details

The function returns a heatmap-like plot displaying the interaction index (tau) estimates and point-wise confidence intervals numerically. Blue and red colours are used to indicate areas of synergy (if confidence interval lies entirely below 1) or antagonism (if confidence interval lies entirely above 1). Note that color intensity is determined by the absolute values of the interaction indices.

Value

a ggplot2 object

Author(s)

Maxim Nazarov

fitModel

Fit drug interaction index model according to Harbron's framework

Description

This is the main function to fit an interaction index model to drug combination data based on the Loewe additivity model. The interaction index can be specified in a flexible way as a function of doses and other variables.

Usage

```
fitModel(data, mono = NULL, model = NULL, tauFormula = NULL,
         tauLog = FALSE, tauStart = 1 * (!tauLog), stage = 1, fixed = NULL,
         inactiveIn = 0, verbose = FALSE, ...)
```

Arguments

data	A (long) data frame to fit the model to. Required columns are "d1", "d2" and "effect". Other variables are allowed and can be used in tauFormula.
mono	An optional "MarginalFit" object, obtained from fitMarginals .
model	A pre-defined model to use for the interaction index tau. One of "additive", "uniform", "linear1", "separate1", "linear2", "separate2", "separate12" or "zhao". See details.
tauFormula	A formula to define the interaction index tau, using either 'literal' (as in nls) or 'symbolic' (as in lm) specification.
tauLog	Whether to fit the model using log-transformed tau parameters. This is mostly useful for "separate"-type tau models for better convergence. Note that if TRUE, tau cannot be negative, which may be not appropriate for some models, such as "linear1" and "linear2". Note that this affects the coefficient names in the result ("logtau1", "logtau2", ... instead of "tau1", "tau2", ...), so if fixed argument is used, this should be taken into account.
tauStart	Vector of starting values for tau parameters, either of length 1 or of the same length as the total number of tau parameters.
stage	Whether to run a 1-stage or 2-stage estimation.
fixed	Constraints on monotherapy and/or tau parameters as a vector of the form 'name = value', if NULL (default), taken from mono. Note that the tau parameters should be named "tau1", "tau2", ... if tauLog = FALSE (default), or "logtau1", "logtau2", ... if tauLog = TRUE.

inactiveIn	which compound is inactive (1 or 2), or 0 (default) when both compounds are active.
verbose	Whether to show extra information useful for debugging.
...	Further arguments passed to the <code>nlsLM</code> call. For example, <code>trace = TRUE</code> is useful to see the trace of the fitting process and may help identify issues with convergence.

Details

There are different ways to specify a model for the interaction index tau:

- Using one of the pre-defined models as specified in the `model` argument:
 - "additive", for additivity model,
 - "uniform", one overall value for tau,
 - "linear1", linear dependency on log10 dose of the first compound,
 - "linear2", linear dependency on log10 dose of the second compound,
 - "separate1", different tau for each dose of the first compound,
 - "separate2", different tau for each dose of the second compound,
 - "separate12", different tau for each combination of doses of the two compounds,
 - "zhao", quadratic response surface model following Zhao et al 2012.
- Using a literal or symbolic formula. Note that for the monotherapies, tau is assumed to be equal to 1. Therefore, continuous models may entail discontinuities in the interaction index when d_1 and d_2 approach 0.

Value

Fitted object of class "HarbronFit" which is an `nls`-like object with extra elements.

Author(s)

Maxim Nazarov

Examples

```
data("checkerboardData", package = "drugCombo")
data1 <- checkerboardData[checkerboardData$exp == 1, ]
mono1 <- fitMarginals(data1, fixed = c(b = 1))
# all three ways below are equivalent
fitLin1 <- fitModel(data = data1, mono = mono1, model = "linear1")
fitLin1b <- fitModel(data1, mono1, tauFormula = ~ log10(d1))
fitLin1c <- fitModel(data1, mono1, tauFormula = ~ tau1+tau2*log10(d1))
```

fitPlot2d

Plot 2d surface (slices) of observations and model fit

Description

Plot 2d surface (slices) of observations and model fit

Usage

```
fitPlot2d(fit, fit2 = NULL, side = c("d1", "d2", "total"),
  useFineGrid = TRUE, modelNames = NULL)
```

Arguments

fit	A HarbronFit object returned by fitModel .
fit2	An optional HarbronFit object returned by fitModel . If provided, a 2d-plot comparing two model fits is produced. Note that the two models should have been fitted on the same data. Note that this argument can also be used as side.
side	Which side ("d1", "d2" or "total" for the sum of d1 and d2) to use as x-axis.
useFineGrid	Whether to use fine grid for plotting fitted curves (default), or calculate predictions only at the observed data points.
modelNames	Model names to use for the plot legend in the case of model comparison (i.e. when fit2 is provided).

Value

ggplot2 object

Author(s)

Maxim Nazarov

fitPlot3d

Plot 3d surface of observations and model fit

Description

Plot 3d surface of observations and model fit

Usage

```
fitPlot3d(fit, logScale = TRUE, useFineGrid = TRUE, showMesh = TRUE,
  widget = FALSE)
```

Arguments

fit	A HarbronFit object returned by fitModel .
logScale	Whether to use log-scale for x and y axes.
useFineGrid	Whether to use fine grid for plotting the fitted surface (default), or calculate predictions only at the observed data points.
showMesh	Whether to show 'mesh' on the plot. Note: currently doesn't play nicely with the useFineGrid argument, so the latter is ignored.
widget	Whether to return a "htmlwidget" object instead of plotting on a 3d device.

Value

A 3d plot is shown or an object of class "htmlwidget" as returned by [rglwidget](#).

Author(s)

Maxim Nazarov

getBootTaus

Run nonparametric bootstrap on the interaction index model

Description

Function to run nonparametric bootstrap on the interaction index model. It is usually called from [getTauSurface](#).

Usage

```
getBootTaus(fit, niter = 100, resample = c("all", "mono", "stratified"),
  seed = NULL, verbose = FALSE, ...)
```

Arguments

fit	A HarbronFit object returned by fitModel .
niter	Number of bootstrap samples to use.
resample	Resampling method for bootstrap. Either "all" (default) for resampling from all data, "mono" for separately resampling monotherapy and combination data, or "stratified" for resampling at each dose combination separately. Note that the latter method is not meaningful if there are no replicates in the data.
seed	Random seed to use for bootstrap
verbose	Whether to show progress information.
...	Further arguments passed to the fitModel calls.

Value

A matrix of interaction index estimates based on the bootstrap samples.

Author(s)

Maxim Nazarov

getTauSurface	<i>Compute interaction index surface and confidence intervals</i>
---------------	---

Description

Computes estimates and confidence intervals for the interaction surface for all dose combinations.

Usage

```
getTauSurface(fit, data = NULL, addCI = TRUE, method = c("default",
  "boot"), level = 0.95, niter = 100, resample = c("all", "mono",
  "stratified"), seed = NULL, ...)
```

Arguments

<code>fit</code>	A HarbronFit object returned by fitModel .
<code>data</code>	Dose combinations to compute interaction index for. If NULL (default), taken from the <code>fit</code> object.
<code>addCI</code>	Whether confidence intervals need to be computed.
<code>method</code>	Which method to use to calculate confidence intervals: "default" for Wald-type or "boot" for nonparametric bootstrap.
<code>level</code>	The confidence level required for the confidence intervals (default is 0.95).
<code>niter</code>	Number of bootstrap samples to use.
<code>resample</code>	Resampling method for bootstrap. Either "all" (default) for resampling from all data, "mono" for separately resampling monotherapy and combination data, or "stratified" for resampling at each dose combination separately. Note that the latter method is not meaningful if there are no replicates in the data.
<code>seed</code>	Random seed to use for bootstrap
<code>...</code>	Further parameters that are passed to getBootTaus .

Value

An object of class "tauSurface" which is essentially a list with the following components: data frame with interaction index (τ) estimates, standard errors and pointwise confidence intervals, formulas for computing tau at any given dose (only for models with continuous functions used to define tau), and details on the tau specification from the `fit`. In addition, if the "boot" method was used, all the bootstrap estimates are returned and can be accessed with [bootstrapCoefs](#).

Author(s)

Maxim Nazarov

See Also

[plot.tauSurface](#), [contour.tauSurface](#) for visual representation of the tau surface.

 invL4

Inverse 4-parameter log-logistic (response-dose) function

Description

Inverse 4-parameter log-logistic (response-dose) function

Usage

```
invL4(y, h, b, m, logEC50)
```

Arguments

y	Response.
h	Hill's coefficient (slope of the curve).
b	Baseline effect (at zero dose).
m	Maximal/asymptote effect (at infinite dose).
logEC50	Point of inflection (in logarithmic terms).

Value

Dose level.

 plot.HarbronFit

Plot method for HarbronFit objects

Description

Diagnostic and goodness-of-fit plots (in 2D and 3D).

Usage

```
## S3 method for class 'HarbronFit'
plot(x, y = NULL, which = c("nls", "2d", "3d"), ...)
```

Arguments

x	A HarbronFit object returned by <code>fitModel</code> .
y	A (optional) second HarbronFit object returned by <code>fitModel</code> . If provided, which argument is ignored and a 2d-plot comparing two model fits is produced. Note that the two models should have been fitted on the same data. Note that this argument can also be used as which. See examples.
which	Whether to show default <code>plot.nls</code> ("nls"), a 'slice' plot with fitted curves overlaid on top of the observed data ("2d") or a 3d-plot with fitted surface overlaid on top of the observed data ("3d").
...	Further arguments passed to <code>plot.nls</code> , <code>fitPlot2d</code> or <code>fitPlot3d</code> depending on which.

Value

Output from `plot.nls`, a ggplot2 object if which = "2d", or a 3d rgl plot if which = "3d".

Author(s)

Maxim Nazarov

Examples

```
data("checkerboardData", package = "drugCombo")
data1 <- checkerboardData[checkerboardData$exp == 1, ]
fitUniform <- fitModel(data1, model = "uniform")
fitLinear <- fitModel(data1, model = "linear1")
plot(fitUniform, fitLinear)
plot(fitLinear, "2d") # here 2nd argument is interpreted as `which`
```

plot.tauSurface *Plot method for "tauSurface" objects*

Description

2D slice and 3D surface plots for the interaction index surface.

Usage

```
## S3 method for class 'tauSurface'
plot(x, y = NULL, which = c("2d", "3d"), ...)
```

Arguments

x	A tauSurface object returned by getTauSurface .
y	An optional second tauSurface object returned by getTauSurface . If provided, which argument is ignored and a 2d-plot comparing two tau surfaces is produced. Note that the two estimates should have been calculated on the same HarbronFit object. Note that this argument can also be used as which. See examples.
which	Whether to show a 3d plot (surface plot) or a 2d plot (slice plot). Correspondingly tauPlot3d or tauPlot2d is called.
...	Further arguments passed to tauPlot3d or tauPlot2d .

See Also

[tauPlot3d](#), [tauPlot2d](#) for the underlying functions and their arguments. [contour.tauSurface](#) for another visual representation of the estimated interaction indices.

Examples

```
data("checkerboardData", package = "drugCombo")
data1 <- checkerboardData[checkerboardData$exp == 1, ]
fitUniform <- fitModel(data1, model = "uniform")
tauUniform <- getTauSurface(fitUniform)
fitLinear <- fitModel(data1, model = "linear1")
tauLinear <- getTauSurface(fitLinear)
plot(tauUniform)
plot(tauLinear, which = "2d", side = "d2", facetBy = "d1")
plot(tauLinear, which = "3d")
plot(tauUniform, tauLinear, tauNames = c("uniform", "linear"))
plot(tauUniform, tauLinear, continuous2 = FALSE)
```

print.tauSurface *Print method for "tauSurface" objects*

Description

Print method for "tauSurface" objects

Usage

```
## S3 method for class 'tauSurface'
print(x, ...)
```

Arguments

x	Output of getTauSurface .
...	Further arguments, currently not used.

rayData	<i>Example ray design drug combination data</i>
---------	---

Description

A dataset containing data from an in-vitro drug combination experiment in oncology using a ray design. The variables are as follows:

Format

A data frame with 378 observations of 4 variables:

- d1: dose of the first compound
- d2: dose of the second compound
- effect: observed effect (radioactivity level)
- ray: a character vector with values 0, 0.2, 0.35, 0.5, 0.65, 0.8 and 1, corresponding to the mixture factors. Each ray has 9 dose combinations with 6 replicates.

tauPlot2d	<i>Plot estimated interaction index surface slice along one of the doses</i>
-----------	--

Description

Plot estimated interaction index surface slice along one of the doses

Usage

```
tauPlot2d(tauSurface, tauSurface2 = NULL, side = "d1", groupBy = NULL,
  colorBy = groupBy, facetBy = "auto", continuous = FALSE,
  continuous2 = FALSE, addLine = continuous || continuous2, funs = NULL,
  funs2 = NULL, title = NULL, tauNames = NULL, digits = 4)
```

Arguments

tauSurface	A tauSurface object returned by getTauSurface .
tauSurface2	An optional second tauSurface object returned by getTauSurface . If provided, a 2d-plot comparing the two tau surfaces is produced. Note that the estimates should have been calculated on the same HarbronFit object.
side	Data column to use as x-axis: "d1", "d2", "total" or another variable from the data in the tauSurface object.
groupBy	Data column to use as grouping. Note that if comparison of two surfaces is performed, this will be ignored.
colorBy	Data column to use for coloring.

facetBy	Whether to facet plots by extra variables used in the tau formula ("auto") or manually provided data column(s) to facet by.
continuous	Whether continuous type of plot is requested (for tauSurface1). This is automatically detected if used via <code>plot.tauSurface</code> , but can be overwritten.
continuous2	Whether continuous type of plot is requested (for tauSurface2). This is automatically detected if used via <code>plot.tauSurface</code> , but can be overwritten.
addLine	Whether to connect tau estimates for subsequent doses.
funs	A list with functions to compute tau surface and confidence bands (for tauSurface1). These are returned by the <code>getTauSurface</code> and are automatically used when the <code>plot.tauSurface</code> is called.
funs2	A list with functions to compute tau surface and confidence bands (for tauSurface2). These are returned by the <code>getTauSurface</code> and are automatically used when the <code>plot.tauSurface</code> is called.
title	Plot title.
tauNames	Tau surface names to use for the plot legend in the case of comparison of estimates (i.e. when tauSurface2 is provided).
digits	Number of digits used in <code>format</code> for the dose labels.

Details

The function returns a 2d plot for the interaction index (tau) estimates as a function of one of the two doses in a checkerboard design, or rays in a ray design. Pointwise confidence intervals are displayed as error bars. In addition to plotting tau estimates from one `tauSurface` object, the function can be used to compare two `tauSurface` objects. This can be used, for example, to see the difference between Wald-type and bootstrap-based confidence intervals for tau. Although the function can be used 'manually', typically one calls the `plot.tauSurface` method, which then calls this function when `which = "2d"`.

Value

A `ggplot2` object.

Author(s)

Maxim Nazarov

See Also

`plot.tauSurface`, `tauPlot3d`

tauPlot3d	<i>Plot 3d surface of interaction index estimates</i>
-----------	---

Description

Plot 3d surface of interaction index estimates

Usage

```
tauPlot3d(tauSurface, logScale = TRUE, continuous = FALSE, funs = NULL,
          addPlane = continuous, colorPoints = TRUE, widget = FALSE)
```

Arguments

tauSurface	A tauSurface object returned by getTauSurface .
logScale	Whether to use log-scale for x and y axes.
continuous	Whether continuous type of plot is requested. This is automatically detected if used via plot.tauSurface , but can be overwritten.
funs	A list with functions to compute tau surface and confidence bands. These are returned by the getTauSurface and are automatically used when the plot.tauSurface is called.
addPlane	Whether to add estimated tau plane.
colorPoints	Whether to color points by synergy/antagonism. Blue color is used for points deemed synergistic (if the confidence interval lies entirely below 1), red for points deemed antagonistic (if the confidence interval lies entirely above 1). Other points are colored white.
widget	Whether to return a "htmlwidget" object instead of plotting on 3d device.

Details

The function returns a 3d plot for the interaction index (tau) estimates as a function of the doses of the two drugs. Pointwise confidence intervals are displayed as error bars. Although the function can be used 'manually', typically one calls the [plot.tauSurface](#) method, which then calls this function when `which = "3d"`.

Value

A 3d plot is shown or an object of the class "htmlwidget" as returned by [rglwidget](#).

Author(s)

Maxim Nazarov

See Also

[plot.tauSurface](#), [tauPlot2d](#)

`unique.tauSurface` *Unique method for "tauSurface" objects*

Description

"unique" method to extract unique interaction index estimates from a "tauSurface" object in a tabular format.

Usage

```
## S3 method for class 'tauSurface'  
unique(x, ...)
```

Arguments

<code>x</code>	Output of getTauSurface .
<code>...</code>	Further arguments, currently not used.

Index

bootstrapCoefs, [2](#), [8](#)

checkerboardData, [3](#)

contour.tauSurface, [3](#), [9](#), [11](#)

fitMarginals, [4](#)

fitModel, [4](#), [6–8](#), [10](#)

fitPlot2d, [6](#), [10](#)

fitPlot3d, [6](#), [10](#)

format, [3](#), [13](#)

getBootTaus, [2](#), [7](#), [8](#)

getTauSurface, [2](#), [3](#), [7](#), [8](#), [11–15](#)

invL4, [9](#)

nlsLM, [5](#)

plot.HarbronFit, [9](#)

plot.nls, [10](#)

plot.tauSurface, [9](#), [10](#), [13](#), [14](#)

print.tauSurface, [11](#)

rayData, [12](#)

rglwidget, [7](#), [14](#)

tauPlot2d, [11](#), [12](#), [14](#)

tauPlot3d, [11](#), [13](#), [14](#)

unique.tauSurface, [15](#)