Package ‘BIGL’

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Description Response surface methods for drug synergy analysis. Available methods include generalized and classical Loewe formulations as well as Highest Single Agent methodology. Response surfaces can be plotted in an interactive 3-D plot and formal statistical tests for presence of synergistic effects are available. Implemented methods and tests are described in the article "BIGL: Biochemically Intuitive Generalized Loewe null model for prediction of the expected combined effect compatible with partial agonism and antagonism" by Koen Van der Borght, Annelies Tourny, Rytis Bagdziunas, Olivier Thas, Maxim Nazarov, Heather Turner, Bie Verbist & Hugo Ceulemans (2017) <doi:10.1038/s41598-017-18068-5>.
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addResids

Add residuals by adding to mean effects

Description

Add residuals by adding to mean effects

Usage

addResids(means, ...)

Arguments

means a vector of means

... passed on to predictVar
**backscaleResids** | **Backscale residuals**

**Description**

Backscale residuals

**Usage**

`backscaleResids(scaledResids, ...)`

**Arguments**

- `scaledResids`: scaled residuals
- `...`: passed on to `predictVar`

---

**Blissindependence** | **Bliss Independence Model**

**Description**

This function returns fractional response levels for when these are based on Bliss Independence Model.

**Usage**

`Blissindependence(doseInput, parmInput, ...)`

**Arguments**

- `doseInput`: Dose-response dataframe containing "d1" and "d2" columns
- `parmInput`: Numeric vector or list with appropriately named parameter inputs. Typically, it will be coefficients from a `MarginalFit` object.
- `...`: Further arguments that are currently unused
bootConfInt

**Obtain confidence intervals for the raw effect sizes on every off-axis point and overall**

**Description**

Obtain confidence intervals for the raw effect sizes on every off-axis point and overall

**Usage**

```r
bootConfInt(
  Total,  
  idUnique,  
  bootStraps,  
  transforms,  
  respS,  
  B.B,  
  method,  
  CP,  
  reps,  
  nl,  
  cutoff,  
  R,  
  fitResult,  
  bootRS,  
  data_off,  
  posEffect = all(Total$effect >= 0),  
  transFun,  
  invTransFun,  
  model,  
  rescaleResids,  
  ...  
)
```

**Arguments**

- `Total`: data frame with all effects and mean effects
- `idUnique`: unique combinations of on-axis points, a character vector
- `bootStraps`: precomputed bootstrap objects
- `transforms`: Transformation functions. If non-null, `transforms` is a list containing 5 elements, namely biological and power transformations along with their inverse functions and `compositeArgs` which is a list with argument values shared across the 4 functions. See vignette for more information.
- `respS`: the observed response surface
- `B.B`: Number of iterations to use in bootstrapping null distribution for either meanR or maxR statistics.
method  What assumption should be used for the variance of on- and off-axis points. This argument can take one of the values from c("equal","model","unequal"). With the value "equal" as the default. "equal" assumes that both on- and off-axis points have the same variance, "unequal" estimates a different parameter for on- and off-axis points and "model" predicts variance based on the average effect of an off-axis point. If no transformations are used the "model" method is recommended. If transformations are used, only the "equal" method can be chosen.

CP  Prediction covariance matrix. If not specified, it will be estimated by bootstrap using B.CP iterations.

reps  Numeric vector containing number of replicates for each off-axis dose combination. If missing, it will be calculated automatically from output of predictOffAxis function.

n1  the number of off-axis points

cutoff  Cut-off to use in maxR procedure for declaring non-additivity (default is 0.95).

R  Numeric vector containing mean deviation of predicted response surface from the observed one at each of the off-axis points. If missing, it will be calculated automatically from output of predictOffAxis function.

fitResult  Monotherapy (on-axis) model fit, e.g. produced by fitMarginals. It has to be a "MarginalFit" object or a list containing df, sigma, coef, shared_asymptote and method elements for, respectively, marginal model degrees of freedom, residual standard deviation, named vector of coefficient estimates, logical value of whether shared asymptote is imposed and method for estimating marginal models during bootstrapping (see fitMarginals). If biological and power transformations were used in marginal model estimation, fitResult should contain transforms elements with these transformations. Alternatively, these can also be specified via transforms argument.

bootRS  a boolean, should bootstrapped response surfaces be used in the calculation of the confidence intervals?

data_off  data frame with off-axis information

posEffect  a boolean, are effects restricted to be positive

transFun  the transformation and inverse transformation functions for the variance

invTransFun  the transformation and inverse transformation functions for the variance

model  The mean-variance model

rescaleResids  a boolean indicating whether to rescale residuals, or else normality of the residuals is assumed.

...  Further arguments that will be later passed to generateData function during bootstrapping

Value

A list with components

offAxis  The off-axis bootstrapped confidence intervals

single  A mean effect and percentile and studentized bootstrap intervals
boxcox.transformation  

**Description**

Apply two-parameter Box-Cox transformation

**Usage**

```r
two_param_transform <- boxcox.transformation(y, lambda, alpha = 0)
```

**Arguments**

- `y`: Numeric vector
- `lambda`: Power parameter in power transform
- `alpha`: Shift parameter in 2-parameter power transform. Defaults to 0 which implies a 1-parameter Box-Cox transform.

**Value**

Power-transformed data

---

coef.MarginalFit  

**Description**

Coefficients from marginal model estimation

**Usage**

```r
coef(object, ...)
```

**Arguments**

- `object`: Output of `fitMarginals` function
- `...`: Further arguments
constructFormula

Construct a model formula from parameter constraint matrix

Description

For parameter names defined in naming vector, formula is constructed so that consMatrix %*% naming = consVector is satisfied. Constraint coefficients are normalized and convert into fractions.

Usage

constructFormula(
  consMatrix = NULL, 
  consVector = NULL, 
  naming = c("h1", "h2", "b", "m1", "m2", "e1", "e2"), 
  extraVars = c("d1", "d2"), 
  formulaArgs = c("effect", "fn")
)

Arguments

consMatrix Constraint matrix
consVector Constraint vector
naming Parameter names
extraVars Non-parameter variables used in the formula and function evaluation. These will be appended to the formula.
formulaArgs Character vector of length two. First element indicates name for the response variable. Second element indicates name of the function.

Value

This function returns a model construct appropriate for fitMarginals function. It also separates variables into those that are free and those which are constrained.

Examples

constM <- rbind(c(0, 0, 1, 0, 0, 0), 
    c(0, 0, 0, -1, 1, 0))
constV <- c(0, 9)
constructFormula(constM, constV)
**contour.ResponseSurface**

*Method for plotting of contours based on maxR statistics*

---

**Description**

Method for plotting of contours based on maxR statistics

**Usage**

```r
## S3 method for class 'ResponseSurface'
contour(x, ...)
```

**Arguments**

- `x`  
  Output of `fitSurface`
- `...`  
  Further parameters passed to `plot.maxR`

---

**df.residual.MarginalFit**

*Residual degrees of freedom in marginal model estimation*

---

**Description**

Residual degrees of freedom in marginal model estimation

**Usage**

```r
## S3 method for class 'MarginalFit'
df.residual(object, ...)
```

**Arguments**

- `object`  
  Output of `fitMarginals` function
- `...`  
  Further arguments


**directAntivirals_ALL**

**Partial data with combination experiments of direct-acting antivirals**

**Description**

A dataset containing 11 combination experiments of direct-acting antivirals.

**Format**

A data frame with 3520 rows and 6 variables:

- experiment: ID of experiment (1-11)
- cpd1: name of the first compound (4 different compounds)
- cpd2: name of the second compound (11 different compounds)
- effect: observed effect (cell count)
- d1: dose of the first compound
- d2: dose of the second compound

**directAntivirals_ALL**

**Full data with combination experiments of direct-acting antivirals**

**Description**

A dataset containing 11 combination experiments of direct-acting antivirals. This dataset is larger than `directAntivirals` dataset as it includes concentrations at levels of 1e6 which can render plots visually unappealing.

**Format**

A data frame with 4224 rows and 6 variables:

- experiment: ID of experiment (1-11)
- cpd1: name of the first compound (4 different compounds)
- cpd2: name of the second compound (11 different compounds)
- effect: observed effect (cell count)
- d1: dose of the first compound
- d2: dose of the second compound
**fitMarginals**

*Fit two 4-parameter log-logistic functions for a synergy experiment*

**Description**

This function uses dose-response data for two compounds and estimates coefficients for monotherapy models of both of these compounds such that they share a common baseline. Currently, these coefficients are estimated by default using a non-linear least squares approximation. Although entire dose-response data can be provided, estimation will subset the part of data where at least one of the compounds is dosed at zero, i.e. on-axis data.

**Usage**

```r
fitMarginals(
  data,
  transforms = NULL,
  start = NULL,
  constraints = NULL,
  fixed = NULL,
  method = c("nlslm", "nls", "optim"),
  names = NULL,
  ...
)
```

**Arguments**

- `data` Dose-response dataframe. Marginal data will be extracted from it automatically.
- `transforms` Transformation functions. If non-null, `transforms` is a list containing 5 elements, namely biological and power transformations along with their inverse functions and `compositeArgs` which is a list with argument values shared across the 4 functions. See vignette for more information.
- `start` Starting parameter values. If not specified, they will be obtained from `initialMarginal`.
- `constraints` List of constraint matrix and vector which will be passed to `constructFormula`. If `constraints = NULL`, no constraints on parameter estimation will be imposed.
- `fixed` This arguments provides a user-friendly alternative to impose a fixed value for marginal parameters. It must be a named vector with names contained in `c("h1","h2","b","m1","m2","e1","e2")`. For example, `fixed = c("m1" = 1, "h1" = 1)` will automatically generate appropriate constraint matrix and vector to set the maximal response and the Hill coefficient of the first compound to 1. If both constraints and fixed arguments are passed, then only fixed will be used.
- `method` Which estimation method should be used to obtain the estimates. If `method = "nls"`, simple non-linear least squares `nls` will be used. If `method = "nlslm"` Levenberg-Marquardt non-linear least squares `nlsLM` is used instead (default). If `method = "optim"`, residual sum of squares will be minimized using general purpose optimization based on Nelder-Mean algorithm in `optim`. This method can be noticeably slower than the non-linear least squares methods.
names

Compound names to be used on the plot labels.

... Further arguments that are passed to the optimizer function, such as lower or upper (for the "nlslm" method), or control.

Details

Model formula is specified as \( \text{effect} \sim \text{fn}(h1, h2, \ldots) \) where \( \text{fn} \) is a hard-coded function which fits two 4-parameter log-logistic functions simultaneously so that the baseline can be shared. If transformation functions are provided, \( \text{fn} \) is consequently adjusted to account for them.

Value

This function returns a \texttt{MarginalFit} object with monotherapy coefficient estimates and diverse information regarding monotherapy estimation. \texttt{MarginalFit} object is essentially a list with appropriately named elements.

Among these list elements, "\texttt{coef}" is a named vector with parameter estimates. \( h1 \) and \( h2 \) are Hill's slope coefficients for each of the compounds, \( m1 \) and \( m2 \) are their maximal response levels whereas \( b \) is the shared baseline. Lastly, \( e1 \) and \( e2 \) are log-transformed EC50 values.

"\texttt{sigma}" is standard deviation of residuals for the estimated monotherapy model and "\texttt{df}" is the degrees of freedom for the residuals. "\texttt{vcov}" is the variance-covariance matrix of the estimated parameters.

Return object also contains information regarding data, biological and power transformations used in this estimation as well as model construct and method of estimation.

Examples

```r
  data <- subset(directAntivirals, experiment == 1)
  ## Data must contain d1, d2 and effect columns
  transforms <- getTransformations(data)
  fitMarginals(data, transforms)
```

---

\texttt{fitSurface}

Fit response surface model and compute meanR and maxR statistics

Description

This function computes predictions for off-axis dose combinations according to the BIGL or HSA null model and, if required, computes appropriate meanR and maxR statistics. Function requires as input dose-response dataframe and output of \texttt{fitMarginals} containing estimates for the monotherapy model. If transformation functions were used in monotherapy estimation, these should also be provided.
Usage

```r
fitSurface(
  data,
  fitResult,
  transforms = fitResult$transforms,
  null_model = c("loewe", "hsa", "bliss", "loewe2"),
  effect = "effect",
  d1 = "d1",
  d2 = "d2",
  statistic = c("none", "meanR", "maxR", "both"),
  CP = NULL,
  B.CP = 50,
  B.B = NULL,
  nested_bootstrap = FALSE,
  error = 4,
  sampling_errors = NULL,
  wild_bootstrap = FALSE,
  cutoff = 0.95,
  parallel = FALSE,
  progressBar = TRUE,
  method = c("equal", "model", "unequal"),
  confInt = TRUE,
  bootRS = TRUE,
  trans = "identity",
  rescaleResids = FALSE,
  invtrans = switch(trans, identity = "identity", log = "exp"),
  newtonRaphson = FALSE,
  asymptotes = 2,
  bootmethod = method
)
```

Arguments

data  Dose-response dataframe.

fitResult  Monotherapy (on-axis) model fit, e.g. produced by `fitMarginals`. It has to be a "MarginalFit" object or a list containing df, sigma, coef, shared_asymptote and method elements for, respectively, marginal model degrees of freedom, residual standard deviation, named vector of coefficient estimates, logical value of whether shared asymptote is imposed and method for estimating marginal models during bootstrapping (see `fitMarginals`). If biological and power transformations were used in marginal model estimation, `fitResult` should contain transforms elements with these transformations. Alternatively, these can also be specified via `transforms` argument.

transforms  Transformation functions. If non-null, `transforms` is a list containing 5 elements, namely biological and power transformations along with their inverse functions and `compositeArgs` which is a list with argument values shared across the 4 functions. See vignette for more information.
null_model  Specified null model for the expected response surface. Currently, allowed options are "loewe" for generalized Loewe model, "hsa" for Highest Single Agent model, "bliss" for Bliss additivity, and "loewe2" for the alternative Loewe generalization.

effect  Name of the response column in the data ("effect")

d1  Name of the column with doses of the first compound ("d1")

d2  Name of the column with doses of the second compound ("d2")

statistic  Which statistics should be computed. This argument can take one of the values from c("none", "meanR", "maxR", "both").

CP  Prediction covariance matrix. If not specified, it will be estimated by bootstrap using B.CP iterations.

B.CP  Number of bootstrap iterations to use for CP matrix estimation

B.B  Number of iterations to use in bootstrapping null distribution for either meanR or maxR statistics.

nested_bootstrap  When statistics are calculated, if nested_bootstrap = TRUE, CP matrix is recalculated at each bootstrap iteration of B.B using B.CP iterations. Using such nested bootstrap may however significantly increase computational time. If nested_bootstrap = FALSE, CP bootstrapped data reuses CP matrix calculated from the original data.

error  Type of error for resampling in the bootstrapping procedure. This argument will be passed to generateData. If error = 4 (default), the error terms for generating distribution of the null will be resampled from the vector specified in sampling_errors. If error = 1, normal errors are added. If error = 2, errors are sampled from a mixture of two normal distributions. If error = 3, errors are generated from a rescaled chi-square distribution.

sampling_errors  Sampling vector to resample errors from. Used only if error is 4 and is passed as argument to generateData. If sampling_errors = NULL (default), mean residuals at off-axis points between observed and predicted response are taken.

wild_bootstrap  Whether special bootstrap to correct for heteroskedasticity should be used. If wild_bootstrap = TRUE, errors are generated from sampling_errors multiplied by a random variable following Rademacher distribution. Argument is used only if error = 4.

cutoff  Cut-off to use in maxR procedure for declaring non-additivity (default is 0.95).

parallel  Whether parallel computing should be used for bootstrap. This parameter can take either integer value to specify the number of threads to be used or logical TRUE/FALSE. If parallel = TRUE, then max(1, detectCores() - 1) is set to be the number of threads. If parallel = FALSE, then a single thread is used and cluster object is not created.

progressBar  A boolean, should progress of bootstraps be shown?

method  What assumption should be used for the variance of on- and off-axis points. This argument can take one of the values from c("equal", "model", "unequal"). With the value "equal" as the default. "equal" assumes that both on- and off-axis points have the same variance, "unequal" estimates a different parameter
for on- and off-axis points and "model" predicts variance based on the average effect of an off-axis point. If no transformations are used the "model" method is recommended. If transformations are used, only the "equal" method can be chosen.

confInt a boolean, should confidence intervals be returned?

bootRS a boolean, should bootstrapped response surfaces be used in the calculation of the confidence intervals?

trans, invtrans the transformation function for the variance and its inverse, possibly as strings

rescaleResids a boolean indicating whether to rescale residuals, or else normality of the residuals is assumed.

newtonRaphson A boolean, should Newton-Raphson be used to find Loewe response surfaces? May be faster but also less stable to switch on

asymptotes Number of asymptotes. It can be either 1 as in standard Loewe model or 2 as in generalized Loewe model.

bootmethod The resampling method to be used in the bootstraps. Defaults to the same as method

Details

Please see the example vignette vignette("analysis",package = "BIGL") and the report "Lack of fit test for detecting synergy" included in the papers folder for further details on the test statistics used: system.file("papers","newStatistics.pdf",package = "BIGL")

Value

This function returns a ResponseSurface object with estimates of the predicted surface. ResponseSurface object is essentially a list with appropriately named elements.

Elements of the list include input data, monotherapy model coefficients and transformation functions, null model used to construct the surface as well as estimated CP matrix, occupancy level at each dose combination according to the generalized Loewe model and "offAxisTable" element which contains observed and predicted effects as well as estimated z-scores for each dose combination.

If statistical testing was done, returned object contains "meanR" and "maxR" elements with output from meanR and maxR respectively.

Examples

```r
## Not run:
data <- subset(directAntivirals, experiment == 4)
## Data should contain d1, d2 and effect columns
transforms <- list("PowerT" = function(x, args) with(args, log(x)),
                 "InvPowerT" = function(y, args) with(args, exp(y)),
                 "BiolT" = function(x, args) with(args, N0 * exp(x * time.hours)),
                 "InvBiolT" = function(y, args) with(args, 1/time.hours * log(y/N0)),
                 "compositeArgs" = list(N0 = 1, time.hours = 72))
fitResult <- fitMarginals(data, transforms)
```
surf <- fitSurface(data, fitResult, statistic = "meanR")
summary(surf)
## End(Not run)

fitted.MarginalFit  
*Compute fitted values from monotherapy estimation*

**Description**

Compute fitted values from monotherapy estimation

**Usage**

```r
## S3 method for class 'MarginalFit'
fitted(object, ...)
```

**Arguments**

- `object`  
  Output of `fitMarginals` function
- `...`  
  Further arguments

---

fitted.ResponseSurface  
*Predicted values of the response surface according to the given null model*

**Description**

Predicted values of the response surface according to the given null model

**Usage**

```r
## S3 method for class 'ResponseSurface'
fitted(object, ...)
```

**Arguments**

- `object`  
  Output of `fitSurface`
- `...`  
  Further parameters
**generalizedLoewe**

Compute combined predicted response from drug doses according to standard or generalized Loewe model.

**Description**

Compute combined predicted response from drug doses according to standard or generalized Loewe model.

**Usage**

```r
generalizedLoewe(
  doseInput,
  parmInput,
  asymptotes = 2,
  startvalues = NULL,
  newtonRaphson = FALSE,
  ...
)
```

**Arguments**

- `doseInput`: Dose-response dataframe containing "d1" and "d2" columns
- `parmInput`: Numeric vector or list with appropriately named parameter inputs. Typically, it will be coefficients from a MarginalFit object.
- `asymptotes`: Number of asymptotes. It can be either 1 as in standard Loewe model or 2 as in generalized Loewe model.
- `startvalues`: Starting values for the non-linear equation, from the observed data
- `newtonRaphson`: a boolean, is Newton raphson used for finding the response surface? May be faster but also less stable
- `...`: Further arguments that are currently unused

**generateData**

Generate data from parameters of marginal monotherapy model

**Description**

This function is used to generate data for bootstrapping of the null distribution for various estimates. Optional arguments such as specific choice of sampling vector or corrections for heteroskedasticity can be specified in the function arguments.
generateData(  
pars,  
sigma,  
data = NULL,  
transforms = NULL,  
null_model = c("loewe", "hsa", "bliss", "loewe2"),  
error = 1,  
sampling_errors = NULL,  
means = NULL,  
model = NULL,  
method = "equal",  
wild_bootstrap = FALSE,  
rescaleResids,  
invTransFun,  
newtonRaphson = FALSE,  
bootmethod = method,  
...  
)

Arguments

pars  Coefficients of the marginal model along with their appropriate naming scheme. These will typically be estimated using fitMarginals. Furthermore, pars can simply be a MarginalFit object and transforms object will be automatically extracted.

sigma  Standard deviation to use for randomly generated error terms. This argument is unused if error = 4 so that sampling error vector is provided.

data  Data frame with dose columns ("d1", "d2") to generate the effect for. Only "d1" and "d2" columns of the dose-response dataframe should be passed to this argument. "effect" column should not be passed and if it is, the column will be replaced by simulated data.

transforms  Transformation functions. If non-null, transforms is a list containing 5 elements, namely biological and power transformations along with their inverse functions and compositeArgs which is a list with argument values shared across the 4 functions. See vignette for more information.

null_model  Specified null model for the expected response surface. Currently, allowed options are "loewe" for generalized Loewe model, "hsa" for Highest Single Agent model, "bliss" for Bliss additivity, and "loewe2" for the alternative Loewe generalization.

error  Type of error for resampling. error = 1 (Default) adds normal errors to the simulated effects, error = 2 adds errors sampled from a mixture of two normal distributions, error = 3 generates errors from a rescaled chi-square distribution. error = 4 will use bootstrap. Choosing this option, the error terms will be resampled from the vector specified in sampling_errors.

sampling_errors  Sampling vector to resample errors from. Used only if error = 4.
get.abs_tval

**means**

The vector of mean values of the response surface, for variance modelling

**model**

The mean-variance model

**method**

What assumption should be used for the variance of on- and off-axis points. This argument can take one of the values from `c("equal", "model", "unequal")`. With the value "equal" as the default. "equal" assumes that both on- and off-axis points have the same variance, "unequal" estimates a different parameter for on- and off-axis points and "model" predicts variance based on the average effect of an off-axis point. If no transformations are used the "model" method is recommended. If transformations are used, only the "equal" method can be chosen.

**wild_bootstrap**

Whether special bootstrap to correct for heteroskedasticity should be used. If `wild_bootstrap = TRUE`, errors are generated from `sampling_errors` multiplied by a random variable following Rademacher distribution. Argument is used only if `error = 4`.

**rescaleResids**

a boolean indicating whether to rescale residuals, or else normality of the residuals is assumed.

**invTransFun**

the inverse transformation function, back to the variance domain

**newtonRaphson**

A boolean, should Newton-Raphson be used to find Loewe response surfaces? May be faster but also less stable to switch on

**bootmethod**

The resampling method to be used in the bootstraps. Defaults to the same as method

... Further arguments

**Value**

Dose-response dataframe with generated data including "effect" as well as "d1" and "d2" columns.

**Examples**

```r
coefs <- c("h1" = 1, "h2" = 1.5, "b" = 0,
          "m1" = 1, "m2" = 2, "e1" = 0.5, "e2" = 0.1)

## Dose levels are set to be integers from 0 to 10
generateData(coefs, sigma = 1)

## Dose levels are taken from existing dataset with d1 and d2 columns
data <- subset(directAntivirals, experiment == 1)
generateData(data = data[, c("d1", "d2")], pars = coefs, sigma = 1)
```

---

**get.abs_tval**

Return absolute t-value, used in optimization call in `optim.boxcox`

**Description**

Return absolute t-value, used in optimization call in `optim.boxcox`
Usage

get.abs_tval(value, fac, lambda, zero.add2 = 0)

Arguments

- value: data
- fac: factor
- lambda: box-cox parameter
- zero.add2: 2nd box-cox parameter

Description

Summarize data by factor

Usage

get.summ.data(value, fac)

Arguments

- value: data to summarize
- fac: factor to summarize by

Description

Estimate CP matrix from bootstraps

Usage

getCP(bootStraps, null_model, transforms, sigma0, doseGrid)
getd1d2

Arguments

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>bootStraps</td>
<td>the bootstraps carried out already</td>
</tr>
<tr>
<td>null_model</td>
<td>Specified null model for the expected response surface. Currently, allowed options are &quot;loewe&quot; for generalized Loewe model, &quot;hsa&quot; for Highest Single Agent model, &quot;bliss&quot; for Bliss additivity, and &quot;loewe2&quot; for the alternative Loewe generalization.</td>
</tr>
<tr>
<td>transforms</td>
<td>Transformation functions. If non-null, transforms is a list containing 5 elements, namely biological and power transformations along with their inverse functions and compositeArgs which is a list with argument values shared across the 4 functions. See vignette for more information.</td>
</tr>
<tr>
<td>sigma0</td>
<td>standard deviation of the null model on the real data</td>
</tr>
<tr>
<td>doseGrid</td>
<td>a grid of dose combinations</td>
</tr>
</tbody>
</table>

Value

Estimated CP matrix

getd1d2 A function to get the d1d2 identifier

Description

A function to get the d1d2 identifier

Usage

getd1d2(dat)

Arguments

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>dat</td>
<td>the data frame containing d1 and d2 entries</td>
</tr>
</tbody>
</table>

Value

a vector of d1d2 identifiers
getR

Helper functions for the test statistics

Description
Helper functions for the test statistics

Usage
getR(data, idUnique, transforms, respS)

Arguments
- data: the datasets
- idUnique: id of unique off axis points
- transforms: Transformation functions. If non-null, transforms is a list containing 5 elements, namely biological and power transformations along with their inverse functions and compositeArgs which is a list with argument values shared across the 4 functions. See vignette for more information.
- respS: the evaluated response surface

GetStartGuess
Estimate initial values for dose-response curve fit

Description
Estimate initial values for dose-response curve fit

Usage
GetStartGuess(df, transforms = NULL)

Arguments
- df: Dose-response dataframe containing "dose" and "effect" columns
- transforms: Transformation functions. If non-null, transforms is a list containing 5 elements, namely biological and power transformations along with their inverse functions and compositeArgs which is a list with argument values shared across the 4 functions. See vignette for more information.
getTransformations

Description

This function takes in response data from a dose-response model and attempts to find an optimal Box-Cox power transform based on optim.boxcox function. It then returns a list of transformation functions which contains this power transform and its inverse which can be subsequently used in fitMarginals and fitSurface.

Usage

getTransformations(data, shift = FALSE, args = list(N0 = 1, time.hours = 1))

Arguments

data
Dose-response dataframe.

shift
If TRUE or is a numeric value, then a two-parameter Box-Cox transformation is assumed. This parameter will be passed on to optim.boxcox function.

args
List with elements that are added to the list of transformation function and which can be used by these functions. In particular, this list should be of type args = list("N0" = 1,"time.hours" = 1) where N0 and time.hours are arguments used for the biological transform.

Details

Additionally, returned list contains biological transform and its inverse based on a simple exponential growth model, especially useful when response data is provided in cell counts. User can additionally provide arguments for these biological transforms where N0 stands for initial cell count and time.hours indicates number in hours after which response data was measured.

getTransformations relies on optim.boxcox to obtain the optimal Box-Cox transformation parameters. However, optim.boxcox optimizes for the power parameter only within the interval (0.1, 0.9). Hence, if obtained power parameter is close to 0.1, then a logarithmic transformation is applied instead.

Value

This function returns a list with transformation functions. These include power transformation ("PowerT") and its inverse ("InvPowerT") as well as biological transformation ("BiolT") and its inverse ("InvBiolT").

Power transformation is a 1-parameter Box-Cox transformation. If shift = TRUE, then power transformation is a 2-parameter Box-Cox transformation. Optimal values for power and shift operators are selected by means of optim.boxcox function.

Biological transformation y = N0 * exp(x * t) where N0 is the initial cell count and t is the incubation time. If response/effect variable (y) is given in terms of cell counts, biological transformation ensures that modelisation is done for the growth rate instead (x).
Returned list also contains "compositeArgs" elements shared by all the transformation functions. These arguments include initial cell count ("N0") and incubation time ("time.hours").

**Examples**

```r
data <- subset(directAntivirals, experiment == 1)
## Data must contain d1, d2 and effect columns
getTransformations(data)
```

---

**harbronLoewe**  
*Alternative Loewe generalization*

**Description**

Alternative Loewe generalization

**Usage**

```r
harbronLoewe(
  doseInput,
  parmInput,
  asymptotes = 2,
  startvalues = NULL,
  newtonRaphson = FALSE,
  ...
)
```

**Arguments**

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><code>doseInput</code></td>
<td>Dose-response dataframe containing &quot;d1&quot; and &quot;d2&quot; columns</td>
</tr>
<tr>
<td><code>parmInput</code></td>
<td>Numeric vector or list with appropriately named parameter inputs. Typically, it will be coefficients from a <code>MarginalFit</code> object.</td>
</tr>
<tr>
<td><code>asymptotes</code></td>
<td>Number of asymptotes. It can be either 1 as in standard Loewe model or 2 as in generalized Loewe model.</td>
</tr>
<tr>
<td><code>startvalues</code></td>
<td>Starting values for the non-linear equation, from the observed data</td>
</tr>
<tr>
<td><code>newtonRaphson</code></td>
<td>a boolean, is Newton raphson used for finding the response surface? May be faster but also less stable</td>
</tr>
<tr>
<td>...</td>
<td>Further arguments that are currently unused</td>
</tr>
</tbody>
</table>
**hsa**

Highest Single Agent model

**Description**

This function returns response levels for when these are based on Highest Single Agent (HSA) model.

**Usage**

hsa(doseInput, parmInput, ...)

**Arguments**

- **doseInput** Dose-response dataframe containing "d1" and "d2" columns
- **parmInput** Numeric vector or list with appropriately named parameter inputs. Typically, it will be coefficients from a MarginalFit object.
- **...** Further arguments that are currently unused

**initialMarginal**

Estimate initial values for fitting marginal dose-response curves

**Description**

This is a wrapper function which, when a dose-response dataframe is provided, returns start value estimates for both compounds that could be supplied to fitMarginals function. This function is also used by fitMarginals if no initials values were supplied.

**Usage**

initialMarginal(data, transforms = NULL, ...)

**Arguments**

- **data** Dose-response dataframe. Marginal data will be extracted from it automatically.
- **transforms** Transformation functions. If non-null, transforms is a list containing 5 elements, namely biological and power transformations along with their inverse functions and compositeArgs which is a list with argument values shared across the 4 functions. See vignette for more information.
- **...** Further parameters that are currently not used

**Details**

Note that this function returns e1 and e2 which are log-transformed inflection points for respective compounds.
Value

Named vector with parameter estimates. Parameter names are consistent with parameter names
in `fitMarginals`. h1 and h2 are Hill’s slope coefficients for each of the compounds, m1 and m2
are their maximal response levels whereas b is the shared baseline. Lastly, e1 and e2 are log-
transformed EC50 values.

Note

Returns starting value for e = log(EC50).

Examples

```r
data <- subset(directAntivirals, experiment == 1)
## Data must contain d1, d2 and effect columns
transforms <- getTransformations(data)
initialMarginal(data, transforms)
```

---

isobologram

*Isobologram of the response surface predicted by the null model*

Description

If transformation functions are used, then the isobologram response levels will be plotted on the
transformed scale.

Usage

```r
isobologram(x, grid.len = 100, logScale = TRUE, ...)
```

Arguments

- `x` Output of `fitSurface`
- `grid.len` Number of concentrations to plot for each compound in the contour plot. An
evenly spaced grid of doses will be generated for each compound given its re-
spective observed minimum and maximum doses. Note that `grid.len^2` com-
putations will be needed later so this number should stay reasonably low.
- `logScale` If `logScale = TRUE`, then grid of doses is evenly spaced in the logarithmic scale.
- `...` Further parameters that are not used at this moment.
4-parameter logistic dose-response function

Description

4-parameter logistic dose-response function

Usage

L4(dose, b, L, U, logEC50)

Arguments

dose Dose level
b Hill’s coefficient (slope of the curve)
L Baseline effect (at zero dose)
U Asymptote effect (at infinite dose)
logEC50 Point of inflection (in logarithmic terms)

marginalNLS Fit two 4-parameter log-logistic functions with non-linear least squares

Description

This function does not automatically extract marginal data and requires model input obtained from constructFormula.

Usage

marginalNLS(data, transforms = NULL, start, model, nlsfn = nls, ...)

Arguments

data Dose-response dataframe. Marginal data will be extracted from it automatically.
transforms Transformation functions. If non-null, transforms is a list containing 5 elements, namely biological and power transformations along with their inverse functions and compositeArgs which is a list with argument values shared across the 4 functions. See vignette for more information.
start Starting parameter values. If not specified, they will be obtained from initialMarginal.
model List with model parameters. Typically, this is an output from constructFormula.
nlsfn Non-linear least-squares optimizer function
... Further arguments that are passed to the optimizer function, such as lower or upper (for the "nlslm" method), or control.
marginalOptim  

*Fit two 4-parameter log-logistic functions with common baseline*

**Description**

This function is an alternative to non-linear least squares and provides optimization framework with `optim` function. It is however noticeably slower than NLS methods and can be especially time consuming in large datasets, in particular if bootstrap statistics are calculated.

**Usage**

```r
marginalOptim(data, transforms = NULL, start, model, ...)
```

**Arguments**

- **data**  Dose-response dataframe. Marginal data will be extracted from it automatically.
- **transforms**  Transformation functions. If non-null, `transforms` is a list containing 5 elements, namely biological and power transformations along with their inverse functions and `compositeArgs` which is a list with argument values shared across the 4 functions. See vignette for more information.
- **start**  Starting parameter values. If not specified, they will be obtained from `initialMarginal`.
- **model**  List with model parameters. Typically, this is an output from `constructFormula`.
- **...**  Further parameters passed to `optim` function

**Value**

Variance-covariance matrix which is returned by `optim` is based on the fact that minimization of sum-of-squared residuals leads essentially to a maximum likelihood estimator and so variance-covariance matrix can be estimated using inverse Hessian evaluated at the optimal parameters. In some cases, so obtained variance-covariance matrix might not be positive-definite which probably means that estimates are unstable because of either a poor choice of initial values or poor properties of the data itself.

maxR  

*Compute maxR statistic for each off-axis dose combination*

**Description**

`maxR` computes maxR statistics for each off-axis dose combination given the data provided. It provides a summary with results indicating whether a given point is estimated to be synergetic or antagonistic. These can be based either on normal approximation or a fully bootstrapped distribution of the statistics.
Usage

```r
maxR(
  data_off,
  fitResult,
  transforms = fitResult$transforms,
  null_model = c("loewe", "hsa", "bliss", "loewe2"),
  R,
  CP,
  reps,
  nested_bootstrap = FALSE,
  B.B = NULL,
  cutoff = 0.95,
  cl = NULL,
  B.CP = NULL,
  method = c("equal", "model", "unequal"),
  bootStraps,
  idUnique,
  n1,
  doseGridOff,
  transFun,
  invTransFun,
  ...
)
```

Arguments

data_off data frame with off-axis information

fitResult Monotherapy (on-axis) model fit, e.g. produced by `fitMarginals`. It has to be a "MarginalFit" object or a list containing `df`, `sigma`, `coef`, `shared_asymptote` and `method` elements for, respectively, marginal model degrees of freedom, residual standard deviation, named vector of coefficient estimates, logical value of whether shared asymptote is imposed and method for estimating marginal models during bootstrapping (see `fitMarginals`). If biological and power transformations were used in marginal model estimation, `fitResult` should contain `transforms` elements with these transformations. Alternatively, these can also be specified via `transforms` argument.

transforms Transformation functions. If non-null, `transforms` is a list containing 5 elements, namely biological and power transformations along with their inverse functions and `compositeArgs` which is a list with argument values shared across the 4 functions. See vignette for more information.

null_model Specified null model for the expected response surface. Currently, allowed options are "loewe" for generalized Loewe model, "hsa" for Highest Single Agent model, "bliss" for Bliss additivity, and "loewe2" for the alternative Loewe generalization.

R Numeric vector containing mean deviation of predicted response surface from the observed one at each of the off-axis points. If missing, it will be calculated automatically from output of `predictOffAxis` function.
maxR

CP Prediction covariance matrix. If not specified, it will be estimated by bootstrap using B.CP iterations.

reps Numeric vector containing number of replicates for each off-axis dose combination. If missing, it will be calculated automatically from output of predictOffAxis function.

nested_bootstrap When statistics are calculated, if nested_bootstrap = TRUE, CP matrix is recalculated at each bootstrap iteration of B.B using B.CP iterations. Using such nested bootstrap may however significantly increase computational time. If nested_bootstrap = FALSE, CP bootstrapped data reuses CP matrix calculated from the original data.

B.B Number of iterations to use in bootstrapping null distribution for either meanR or maxR statistics.

cutoff Cut-off to use in maxR procedure for declaring non-additivity (default is 0.95).

c1 If parallel computations are desired, c1 should be a cluster object created by makeCluster. If parallel computing is active, progress reporting messages are not necessarily ordered as it should be expected.

B.CP Number of bootstrap iterations to use for CP matrix estimation

method What assumption should be used for the variance of on- and off-axis points. This argument can take one of the values from c("equal", "model", "unequal"). With the value "equal" as the default. "equal" assumes that both on- and off-axis points have the same variance, "unequal" estimates a different parameter for on- and off-axis points and "model" predicts variance based on the average effect of an off-axis point. If no transformations are used the "model" method is recommended. If transformations are used, only the "equal" method can be chosen.

bootStraps precomputed bootstrap objects

idUnique unique combinations of on-axis points, a character vector

n1 the number of off-axis points

doseGridOff dose grid for off-axis points

transFun the transformation and inverse transformation functions for the variance

invTransFun the transformation and inverse transformation functions for the variance

... Further arguments that will be later passed to generateData function during bootstrapping

Value

This function returns a maxR object with estimates for the maxR statistical test. maxR object is essentially a list with appropriately named elements.

In particular, maxR object contains "Ymean" element which is a summary table of maxR test results for each dose combination. This table contains mean deviation from the predicted surface, normalized deviation ("absR") as well as a statistical call whether this deviation is significant. Distributional information on which these calls are made can be retrieved from the attributes of the "Ymean" dataframe.
Also, maxR object contains "Call" element which indicates the general direction of the deviation of the observed surface from the null. This call is based on the strongest local deviation in the "Ymean" table. 4 values are available here: "Syn", "Ant", "None", "Undefined". If one compound acts as an agonist while another one is an antagonist, then a deviation from the null is classified as "Undefined". If both compounds act in the same direction, then a stronger than individual effect is classified as synergy while a weaker effect would be classified as antagonism.

### meanR

**Description**

`meanR` computes the meanR statistic for the provided model and returns the computed F-statistic and the estimated p-value. P-value can be calculated either by assuming an exact distribution or using bootstrapping procedure. In the latter case, null distribution of bootstrapped F-statistics is also returned.

**Usage**

```r
meanR(data_off, fitResult, transforms = fitResult$transforms, null_model = c("loewe", "hsa", "bliss", "loewe2"), R, CP, reps, nested_bootstrap = FALSE, B.B = NULL, B.CP = NULL, cl = NULL, method = c("equal", "model", "unequal"), bootStraps, paramsBootstrap, idUnique, n1, transFun, invTransFun, ...)
```

**Arguments**

- `data_off`: data frame with off-axis information
- `fitResult`: Monotherapy (on-axis) model fit, e.g. produced by `fitMarginals`. It has to be a "MarginalFit" object or a list containing df, sigma, coef, shared_asymptote and method elements for, respectively, marginal model degrees of freedom,
residual standard deviation, named vector of coefficient estimates, logical value of whether shared asymptote is imposed and method for estimating marginal models during bootstrapping (see `fitMarginals`). If biological and power transformations were used in marginal model estimation, `fitResult` should contain `transforms` elements with these transformations. Alternatively, these can also be specified via `transforms` argument.

### transforms
Transformation functions. If non-null, `transforms` is a list containing 5 elements, namely biological and power transformations along with their inverse functions and `compositeArgs` which is a list with argument values shared across the 4 functions. See vignette for more information.

### null_model
Specified null model for the expected response surface. Currently, allowed options are "loewe" for generalized Loewe model, "hsa" for Highest Single Agent model, "bliss" for Bliss additivity, and "loewe2" for the alternative Loewe generalization.

### R
Numeric vector containing mean deviation of predicted response surface from the observed one at each of the off-axis points. If missing, it will be calculated automatically from output of `predictOffAxis` function.

### CP
Matrix which is part of covariance matrix for the `R` argument

### reps
Numeric vector containing number of replicates for each off-axis dose combination. If missing, it will be calculated automatically from output of `predictOffAxis` function.

### nested_bootstrap
When statistics are calculated, if `nested_bootstrap` = TRUE, CP matrix is recalculated at each bootstrap iteration of B.B using B.CP iterations. Using such nested bootstrap may however significantly increase computational time. If `nested_bootstrap` = FALSE, CP bootstrapped data reuses CP matrix calculated from the original data.

### B.B
Number of iterations to use in bootstrapping null distribution for either meanR or maxR statistics.

### B.CP
Number of bootstrap iterations to use for CP matrix estimation

### c1
If parallel computations are desired, c1 should be a cluster object created by `makeCluster`. If parallel computing is active, progress reporting messages are not necessarily ordered as it should be expected.

### method
What assumption should be used for the variance of on- and off-axis points. This argument can take one of the values from c("equal","model","unequal"). With the value "equal" as the default. "equal" assumes that both on- and off-axis points have the same variance, "unequal" estimates a different parameter for on- and off-axis points and "model" predicts variance based on the average effect of an off-axis point. If no transformations are used the "model" method is recommended. If transformations are used, only the "equal" method can be chosen.

### bootStraps
precomputed bootstrap objects

### paramsBootstrap
parameters for the nested bootstrap

### idUnique
unique combinations of on-axis points, a character vector
modelVar

\[ n_1 \] the number of off-axis points

transFun, invTransFun

the transformation and inverse transformation functions for the variance

... Further arguments that will be later passed to \texttt{generateData} function during bootstrapping

Value

This function returns a \texttt{meanR} object with estimates for the \texttt{meanR} statistical test. \texttt{meanR} object is essentially a list with appropriately named elements.

\texttt{meanR} object list includes notably the calculated F-statistic, p-value and degrees of freedom ("n1" and "df0" respectively) used to find the critical value of the F-distribution under the null.

If \texttt{meanR} test is run with bootstrapping, then p-value estimate is based on bootstrapped null distribution of test statistic and an additional element "FDist" (of class "ecdf") is returned.

\begin{verbatim}
modelVar

Calculate model variance, assuming variance increases linearly with mean

Description

Calculate model variance, assuming variance increases linearly with mean

Usage

\texttt{modelVar(dat_off, transFun, invTransFun)}

Arguments

\begin{verbatim}
dat_off off-axis points data
transFun, invTransFun

the transformation and inverse transformation functions for the variance
\end{verbatim}

Value

the predicted model variance
**optim.boxcox**

*Find optimal Box-Cox transformation parameters*

**Description**

Find optimal Box-Cox transformation parameters

**Usage**

`optim.boxcox(value, fac, shift = FALSE)`

**Arguments**

- `value`: Response variable in the data, e.g. "effect" column
- `fac`: Factor indicating groups of replicates, e.g. `interaction(d1, d2)`
- `shift`: Whether to use 2-parameter Box-Cox transformation. Input may be TRUE/FALSE or a numeric value indicating the shift parameter to use. If FALSE, shift parameter is set to zero.

**Value**

Numeric vector with power and shift parameter in that order.

**Examples**

```r
data <- subset(directAntivirals, experiment == 1)
optim.boxcox(data$effect, interaction(data$d1, data$d2))
```

---

**outsidePoints**

*List non-additive points*

**Description**

List all points with corresponding p-values declared non-additive by the maxR statistical test.

**Usage**

`outsidePoints(maxR, B = 10000)`

**Arguments**

- `maxR`: maxR statistics table returned by Ymean component from the output of `maxR` function. This can also be "maxR" element in the output of `fitSurface` function.
- `B`: Iterations to use for the distribution of the maxR statistic. This is only used if Ymean dataframe does not have a "distr" attribute attached as is normally done when using `fitSurface` or `maxR` function.
Value

Returns a dataframe listing only dose combinations that exhibit significant deviations from the expected response surface.

Examples

data <- subset(directAntivirals, experiment == 2)
## Data must contain d1, d2 and effect columns
fitResult <- fitMarginals(data)
surf <- fitSurface(data, fitResult, statistic = "maxR")
outsidePoints(surf$maxR$Ymean)

plot.BIGLconfInt

Plot confidence intervals in a contour plot

Description

Plot confidence intervals in a contour plot

Usage

## S3 method for class 'BIGLconfInt'
plot(x, color = "effect-size", showAll = TRUE, ...)

Arguments

x         off axis confidence intervals, a data frame
color     analysis with which to colour cells, either effect-size or maxR
showAll   show all intervals in the plot or only significant ones, logical defaulting to TRUE
...       additional arguments, currently ignored

Note

written after the contour() function in the drugCombo package
plot.MarginalFit  

Plot monotherapy curve estimates

Description

Plot monotherapy curve estimates

Usage

## S3 method for class 'MarginalFit'
plot(x, ncol = 2, logScale = TRUE, smooth = TRUE, dataScale = FALSE, ...)

Arguments

- `x`  
  Output of `fitMarginals` function or a "MarginalFit" object
- `ncol`  
  Number of plots per row
- `logScale`  
  Whether x-axis should be plotted on a logarithmic scale
- `smooth`  
  Whether to draw a smooth fitted curve (default), or line segments connecting predicted points only
- `dataScale`  
  Whether to draw plot on original data scale in case when transformations were used for fitting. Default (FALSE) is to plot on the `coef(x)` scale
- `...`  
  Further arguments

Value

Returns a ggplot object. It can be consequently modified by using standard operations on ggplot objects (if ggplot2 package is loaded).

plot.maxR  

Plot of maxR object

Description

Plot of maxR object

Usage

## S3 method for class 'maxR'
plot(  
  x,  
  main = "Contour plot for maxR",  
  xlab = "Dose (Compound 1)",  
  ylab = "Dose (Compound 2)",  
  colorPalette = c("blue", "white", "red"),  
...  
)
Arguments

x Output of `maxR`. This can also be "maxR" element in the output of `fitSurface`.
main Fixed non-moving title for the 3D plot
xlab X axis label using font, size and color `par(c("font.lab","cex.lab","col.lab"))`.
ylab Y axis label, same font attributes as xlab.
colorPalette Vector of color names for surface
logScale Draw doses on log-scale (setting zeroes to be finite constant)
zTransform Optional transformation function for z-axis. By default, identity function is used.
plevels Probability levels used to generate a color scale
cutoff Probability cutoff to use for range of colors
maxshow Forced value for range of colors
... Further arguments that are passed to `format` function for formatting of axis labels

plot.meanR

Plot bootstrapped cumulative distribution function of meanR null distribution

Description

Plot bootstrapped cumulative distribution function of meanR null distribution

Usage

```r
## S3 method for class 'meanR'
plot(x, ...)
```

Arguments

x Output from `meanR`
... Further arguments
plot.ResponseSurface  Method for plotting response surface objects

Description
Method for plotting response surface objects

Usage
## S3 method for class 'ResponseSurface'
plot(x, color = c("z-score", "maxR", "occupancy", "confInt"), ...)

Arguments
x       Output of fitSurface
color   Character indicating on what values surface coloring will be based.
        If color = "z-score", surface coloring will be based on median of standartized
        off-axis Z-scores. Median function can be replaced by other function using an
        optional colorfun argument which will be passed to plotResponseSurface.
        Color breaks are determined here by standard deviation of off-axis Z-scores.
        For color = "maxR", coloring will be based on values of maxR statistic and
        the quantile of its distribution (bootstrapped or not). If color = "occupancy",
        coloring will be based on calculated occupancy rate for the respective dose com-
        bination.
...     Further parameters passed to plotResponseSurface. colorBy argument in this
        method is computed automatically and thus cannot be passed to plotResponseSurface.

plotConfInt  Plot confidence intervals from BIGL object in a contour plot

Description
Plot confidence intervals from BIGL object in a contour plot

Usage
plotConfInt(BIGLobj, ...)

Arguments
BIGLobj   Output from fitSurface
...       passed on to plot.BIGLconfInt
plotMeanVarFit

Make a mean-variance plot

Description

Make a mean-variance plot

Usage

plotMeanVarFit(
  data,
  trans = "identity",
  invtrans = switch(trans, identity = "identity", log = "exp"),
  main = paste(switch(trans, identity = "No", log = "log", "transformation"),
    log = switch(trans, identity = "", log = "y", ""),
    ...)
)

Arguments

data a dataset or matrix with d1, d2 and effect column
trans, invtrans the transformation function for the variance and its inverse, possibly as strings
main the title of the plot
log log-transform of the axes, as in plot()
... passed on to plot()

Details

This is a crucial graphical check for deciding on the

Value

Plots the mean-variance trend

plotResponseSurface

Plot response surface

Description

Plot the 3-dimensional response surface predicted by one of the null models. This plot allows for a visual comparison between the null model prediction and observed points. This function is mainly used as the workhorse of plot.ResponseSurface method.
Usage

plotResponseSurface(
  data,
  fitResult = NULL,
  transforms = fitResult$transforms,
  predSurface = NULL,
  null_model = c("loewe", "hsa", "bliss", "loewe2"),
  colorPalette = c("blue", "grey70", "red"),
  colorBy = "none",
  colorPoints = c("black", "sandybrown", "brown", "white"),
  breaks = c(-Inf, 0, Inf),
  radius = NULL,
  logScale = TRUE,
  colorfun = median,
  zTransform = function(x) x,
  add = FALSE,
  main = "",
  legend = TRUE,
  xat = "actual",
  yat = "actual",
  plotfun = NULL,
  ...
)

Arguments

data Dose-response dataframe.

fitResult Monotherapy (on-axis) model fit, e.g. produced by fitMarginals. It has to be a
"MarginalFit" object or a list containing df, sigma, coef, shared_asymptote
and method elements for, respectively, marginal model degrees of freedom,
residual standard deviation, named vector of coefficient estimates, logical value
of whether shared asymptote is imposed and method for estimating marginal
models during bootstrapping (see fitMarginals). If biological and power trans-
formations were used in marginal model estimation, fitResult should contain
transforms elements with these transformations. Alternatively, these can also
be specified via transforms argument.

transforms Transformation functions. If non-null, transforms is a list containing 5 el-
ements, namely biological and power transformations along with their inverse
functions and compositeArgs which is a list with argument values shared across
the 4 functions. See vignette for more information.

predSurface Vector of all predicted responses based on expand.grid(uniqueDoses). If not
supplied, it will be computed with predictOffAxis function.

null_model If predSurface is not supplied, it is computed using one of the available null
models, i.e. "loewe", "hsa", "bliss" and "loewe2". See also fitSurface.

colorPalette Vector of color names for surface
colorBy

This parameter determines values on which coloring is based for the 3-dimensional surface. If matrix or a data frame with d1 and d2 columns is supplied, dose combinations from colorBy will be matched automatically to the appropriate dose combinations in data. Unmatched dose combinations will be set to 0. This is especially useful for plotting results for off-axis estimates only, e.g. off-axis Z-scores or maxR test statistics. If colorBy = "colors", surface will be colored using colors in colorPalette argument.

colorPoints

Colors for off-axis and on-axis points. Character vector of length four with colors for 1) off-axis points; 2) on-axis points of the first drug (i.e. second drug is dosed at zero); 3) on-axis points of the second drug; 4) on-axis points where both drugs are dosed at zero.

breaks

Numeric vector with numerical breaks. To be used in conjunction with colorPalette argument.

radius

Radius of spheres. If missing, an educated guess based on number of digits in average effect will be made.

logScale

Draw doses on log-scale (setting zeroes to be finite constant)

colorfun

If replicates in colorBy variable are present, these will be aggregated using colorfun function. This can also be a custom function returning a scalar.

zTransform

Optional transformation function for z-axis. By default, identity function is used.

add

Add the predicted response surface to an existing plot. Will not draw any points, just the surface. Must be called after another call to plotResponseSurface.

main

Fixed non-moving title for the 3D plot

legend

Whether legend should be added

xat

x-axis ticks: "pretty", "actual" or a numeric vector

yat

y-axis ticks: "pretty", "actual" or a numeric vector

plotfun

If replicates for dose combinations in data are available, points can be aggregated using plotfun function. Typically, it will be mean, median, min or max but a custom-defined function returning a scalar from a vector is also possible.

...

Further arguments to format axis labels

Details

Title for the plot and legend are drawn as bitmaps and do not rotate with the rest of the plot. Since they are bitmaps, they do not scale properly, hence resizing window will result in unappealing visuals. For them to look properly, it suffices to set the appropriate RGL window size and rerun the plotting command.

Value

Plot is shown on a rgl device.
Examples

```r
## Not run:
data <- subset(directAntivirals, experiment == 1)
## Data must contain d1, d2 and effect columns
fitResult <- fitMarginals(data)
data_mean <- aggregate(effect ~ d1 + d2, data = data[, c("d1", "d2", "effect")],
                      FUN = mean)

## Construct the surface from marginal fit estimates based on HSA
## model and color it by mean effect level
plotResponseSurface(data, fitResult, null_model = "hsa",
                     colorBy = data_mean, breaks = 10^c(0, 3, 4, 6),
                     colorPalette = c("grey", "blue", "green"))

## Response surface based on Loewe additivity model and colored with
## rainbow colors. Legend will not be displayed in any case.
plotResponseSurface(data, fitResult, null_model = "loewe",
                     colorBy = "colors", colorPalette = rainbow(6))

## End(Not run)
```

---

**predict.MarginalFit**  
*Predict values on the dose-response curve*

**Description**

Predict values on the dose-response curve

**Usage**

```r
## S3 method for class 'MarginalFit'
predict(object, newdata, ...)
```

**Arguments**

- `object`  
  Output of `fitMarginals` function

- `newdata`  
  An optional data frame in which to look for \texttt{d1} and \texttt{d2} variables with which to predict. If omitted, the fitted values are used. Doses that are passed to this function must correspond to marginal data, i.e. at least one of the doses must be zero.

- `...`  
  Further arguments
**predictOffAxis**

**Compute off-axis predictions**

**Description**

Given a dataframe with dose-response data, this function uses coefficient estimates from the marginal (on-axis) monotherapy model to compute the expected values of response at off-axis dose combinations using a provided null model.

**Usage**

```r
predictOffAxis(
  doseGrid,
  fitResult,
  transforms = fitResult$transforms,
  null_model = c("loewe", "hsa", "bliss", "loewe2"),
  fit = NULL,
  ...
)
```

**Arguments**

- `doseGrid`: A dose grid with unique combination of doses
- `fitResult`: Monotherapy (on-axis) model fit, e.g. produced by `fitMarginals`. It has to be a "MarginalFit" object or a list containing `df`, `sigma`, `coef`, `shared_asymptote` and `method` elements for, respectively, marginal model degrees of freedom, residual standard deviation, named vector of coefficient estimates, logical value of whether shared asymptote is imposed and method for estimating marginal models during bootstrapping (see `fitMarginals`). If biological and power transformations were used in marginal model estimation, `fitResult` should contain `transforms` elements with these transformations. Alternatively, these can also be specified via `transforms` argument.
- `transforms`: Transformation functions. If non-null, `transforms` is a list containing 5 elements, namely biological and power transformations along with their inverse functions and `compositeArgs` which is a list with argument values shared across the 4 functions. See vignette for more information.
- `null_model`: Specified null model for the expected response surface. Currently, allowed options are "loewe" for generalized Loewe model, "hsa" for Highest Single Agent model, "bliss" for Bliss additivity, and "loewe2" for the alternative Loewe generalization.
- `fit`: a pre-calculated off-axis fit
- `...`: Further arguments passed on to the Loewe fitters

**Value**

This function returns a named vector with predicted off-axis points.
Examples

data <- subset(directAntivirals, experiment == 1)
## Data must contain d1, d2 and effect columns
transforms <- getTransformations(data)
fitResult <- fitMarginals(data, transforms)
uniqueDoses <- with(data, list("d1" = sort(unique(data$d1)),
   "d2" = sort(unique(data$d2))))
doseGrid <- expand.grid(uniqueDoses)
predictOffAxis(fitResult, null_model = "hsa", doseGrid = doseGrid)

predictResponseSurface

Predict the entire response surface, so including on-axis points, and return the result as a matrix. For plotting purposes.

Description

Predict the entire response surface, so including on-axis points, and return the result as a matrix. For plotting purposes.

Usage

predictResponseSurface(
   doseGrid, fitResult, null_model, transforms = fitResult$transforms
)

Arguments

doseGrid A dose grid with unique combination of doses

fitResult Monotherapy (on-axis) model fit, e.g. produced by fitMarginals. It has to be a "MarginalFit" object or a list containing df, sigma, coef, shared_asymptote and method elements for, respectively, marginal model degrees of freedom, residual standard deviation, named vector of coefficient estimates, logical value of whether shared asymptote is imposed and method for estimating marginal models during bootstrapping (see fitMarginals). If biological and power transformations were used in marginal model estimation, fitResult should contain transforms elements with these transformations. Alternatively, these can also be specified via transforms argument.

null_model Specified null model for the expected response surface. Currently, allowed options are "loewe" for generalized Loewe model, "hsa" for Highest Single Agent model, "bliss" for Bliss additivity, and "loewe2" for the alternative Loewe generalization.
**predictVar**

Transformation functions. If non-null, `transforms` is a list containing 5 elements, namely biological and power transformations along with their inverse functions and `compositeArgs` which is a list with argument values shared across the 4 functions. See vignette for more information.

**predictVar**  
Predict variance

**Description**

Predict variance

**Usage**

```r
predictVar(means, model, invTransFun)
```

**Arguments**

- `means`  
a vector of means
- `model`  
The mean-variance model
- `invTransFun`  
the inverse transformation function, back to the variance domain

**print.summary.BIGLconfInt**

*Print summary of BIGLconfInt object*

**Description**

Print summary of BIGLconfInt object

**Usage**

```r
## S3 method for class 'summary.BIGLconfInt'
ping(x, ...)
```

**Arguments**

- `x`  
Summary of BIGLconfInt object
- `...`  
Further arguments
print.summary.MarginalFit

Print method for summary of MarginalFit object

Description

Print method for summary of MarginalFit object

Usage

## S3 method for class 'summary.MarginalFit'
print(x, ...)

Arguments

x     Summary of MarginalFit object
...
     Further arguments

print.summary.maxR

Print summary of maxR object

Description

Print summary of maxR object

Usage

## S3 method for class 'summary.maxR'
print(x, ...)

Arguments

x     Summary of "maxR" object
...
     Further arguments
print.summary.meanR  

Print summary of meanR object

Description

Print summary of meanR object

Usage

## S3 method for class 'summary.meanR'
print(x, ...)

Arguments

x  Summary of meanR object
...
Further arguments

print.summary.ResponseSurface  

Print method for the summary function of ResponseSurface object

Description

Print method for the summary function of ResponseSurface object

Usage

## S3 method for class 'summary.ResponseSurface'
print(x, ...)

Arguments

x  Summary of ResponseSurface object
...
Further parameters
residuals.MarginalFit  Residuals from marginal model estimation

Description

Residuals from marginal model estimation

Usage

## S3 method for class 'MarginalFit'
residuals(object, ...)

Arguments

object  Output of fitMarginals function
...
  Further arguments

runBIGL  Run the BIGL application for demonstrating response surfaces

Description

Run the BIGL application for demonstrating response surfaces

Usage

runBIGL(...)  

Arguments

...
  Pass parameters to runApp

Examples

## Not run:
runBIGL()

## End(Not run)
sampleResids

Sample residuals according to a new model

Description

Sample residuals according to a new model

Usage

```
sampleResids(means, sampling_errors, method, rescaleResids, ...)
```

Arguments

- `means`: a vector of means
- `sampling_errors`: Sampling vector to resample errors from. Used only if `error` is 4 and is passed as argument to `generateData`. If `sampling_errors = NULL` (default), mean residuals at off-axis points between observed and predicted response are taken.
- `method`: What assumption should be used for the variance of on- and off-axis points. This argument can take one of the values from `c("equal","model","unequal")`. With the value "equal" as the default. "equal" assumes that both on- and off-axis points have the same variance, "unequal" estimates a different parameter for on- and off-axis points and "model" predicts variance based on the average effect of an off-axis point. If no transformations are used the "model" method is recommended. If transformations are used, only the "equal" method can be chosen.
- `rescaleResids`: a boolean indicating whether to rescale residuals, or else normality of the residuals is assumed.
- `...`: passed on to `predictVar`

Value

sampled residuals

scaleResids

Functions for scaling, and rescaling residuals. May lead to unstable behaviour in practice

Description

Functions for scaling, and rescaling residuals. May lead to unstable behaviour in practice

Usage

```
scaleResids(sampling_errors, ...)
```
simulateNull

Arguments

  sampling_errors
  A vector of raw residuals
  ...
  passed on to predictVar

Details

Residuals are calculated with respect to the average observation on the off-axis point, so replicates are required!

simulateNull

Simulate data from a given null model and monotherapy coefficients

Description

Simulate data from a given null model and monotherapy coefficients

Usage

simulateNull(
  data,
  fitResult,
  doseGrid,
  transforms = fitResult$transforms,
  startvalues,
  null_model = c("loewe", "hsa", "bliss", "loewe2"),
  ...
)

Arguments

data
  Dose-response dataframe.

fitResult
  Monotherapy (on-axis) model fit, e.g. produced by fitMarginals. It has to be a "MarginalFit" object or a list containing df, sigma, coef, shared_asymptote and method elements for, respectively, marginal model degrees of freedom, residual standard deviation, named vector of coefficient estimates, logical value of whether shared asymptote is imposed and method for estimating marginal models during bootstrapping (see fitMarginals). If biological and power transformations were used in marginal model estimation, fitResult should contain transforms elements with these transformations. Alternatively, these can also be specified via transforms argument.

doseGrid
  A grid of dose combinations

transforms
  Transformation functions. If non-null, transforms is a list containing 5 elements, namely biological and power transformations along with their inverse functions and compositeArgs which is a list with argument values shared across the 4 functions. See vignette for more information.
startvalues  Starting values for the non-linear equation, from the observed data
null_model  Specified null model for the expected response surface. Currently, allowed options are "loewe" for generalized Loewe model, "hsa" for Highest Single Agent model, "bliss" for Bliss additivity, and "loewe2" for the alternative Loewe generalization.
...
Further parameters that will be passed to `generateData`

Value

List with data element containing simulated data and fitResult element containing marginal fit on the simulated data.

Examples

data <- subset(directAntivirals, experiment == 1)
## Data must contain d1, d2 and effect columns
fitResult <- fitMarginals(data)
simDat <- simulateNull(data, fitResult, expand.grid(d1 = data$d1, d2 = data$d2),
null_model = "hsa")
Description

Summary of MarginalFit object

Usage

```r
## S3 method for class 'MarginalFit'
summary(object, ...)
```

Arguments

- `object` Output of `fitMarginals` function
- `...` Further arguments

Description

Summary of maxR object

Usage

```r
## S3 method for class 'maxR'
summary(object, ...)
```

Arguments

- `object` Object of "maxR" class
- `...` Further arguments
**summary.meanR**

*Summary of meanR object*

---

**Description**

Summary of meanR object

**Usage**

```r
## S3 method for class 'meanR'
summary(object, ...)
```

**Arguments**

- `object`: Output from `meanR`  
- `...`: Further arguments

---

**summary.ResponseSurface**

*Summary of ResponseSurface object*

---

**Description**

Summary of ResponseSurface object

**Usage**

```r
## S3 method for class 'ResponseSurface'
summary(object, ...)
```

**Arguments**

- `object`: Output of `fitSurface`  
- `...`: Further parameters
vcov.MarginalFit

Estimate of coefficient variance-covariance matrix

Description

Estimate of coefficient variance-covariance matrix

Usage

```r
## S3 method for class 'MarginalFit'
vcov(object, ...)
```

Arguments

- `object` Output of `fitMarginals` function
- `...` Further arguments
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