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Type Package

Title Visualize Combined Action Response Surfaces and Report BRAID Analyses

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Description Provides functions to generate, format, and style surface plots for visualizing combined action data. Also provides functions for reporting on a BRAID analysis, including plotting curve-shifts, calculating IAE values, and producing full BRAID analysis reports.

License GPL (>= 3)

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Contents

braidReports-package	2
calculateIAE	3
es8analysis	4
formatResponseMap	5
makeBRAIDreport	6

potentiationPlot	9
responseMap	11
voronoi	13

Index	14
--------------	-----------

braidReports-package *Visualize Combined Action Response Surfaces and Report BRAID Analyses*

Description

Building on the ggplot2 plotting package, this package provides functions to generate, format, and style surface plots for visualizing combined action data without resorting to three-dimensional surface plots, which can be difficult to interpret. The package also provides functions for reporting on a BRAID analysis, including plotting curve-shifts, calculating IAE values, and producing full BRAID analysis reports.

Details

Package: braidReports
 Type: Package
 Version: 0.5.3
 Date: 2016-04-05
 License: GPL (>=3)

The heart of the package is the function `responseMap`, which produces a ggplot2 tile or surface plot from combined action data, consolidating many of the minutiae of plotting such surfaces into a single, easily used function. The functions `formatResponseMap` and `formatDifferenceMap` provide pre-built formatting and themes for quickly generating publishable or shareable activity plots and error plots. In addition, several functions provide additional analytical and reporting options for BRAID analyses (from the package `braidrm`). The function `calculateIAE` estimates the combined therapeutic window for a pair of active compounds; the function `potentiationPlot` produces fast and easy curve-shift plots to visualize the potentiation of one compound by the presence of another; and `makeBRAIDreport` serves as a (nearly) fully-functional apparatus for translating a BRAID analysis into a one-page comprehensive report.

Author(s)

Nathaniel R. Twarog <nathaniel.twarog@stjude.org>

References

Twarog, N.R., Stewart, E., Vowell Hamill, C., and Shelat, A. BRAID: A Unifying Paradigm for the Analysis of Combined Drug Action. *Scientific Reports* **In Press** (2016).

See Also[braidrm-package](#)

calculateIAE

*Calculate the Index of Achievable Efficacy***Description**

Calculates the index of achievable efficacy, or IAE, (a measure of a drug combination's efficacy relative to toxicological and pharmacological constraints) based on a response surface representation of a combination in the form of a full BRAID surface parameter vector.

Usage

```
calculateIAE(parv, lev, macs, same = FALSE)
```

Arguments

parv	a full 10-element BRAID surface parameter vector
lev	a single value or vector representing the effect level or levels at which the IAE should be calculated
macs	the maximum achievable concentrations of the two drugs whose effects are represented by the response surface. A single value may be given, which will be used for both drugs
same	a boolean variable representing whether the two drugs in the combination are believed to be the same drug (their dose-response parameters need not be identical). If TRUE, the values in macs must be identical

Details

The IAE is a measure of the aggregate ratio of achievable dose-pairs for a given combination and the minimum dose pairs required to achieve a given effect. Formally, it is defined as

$$IAE = \left(\frac{\int_{AC} dD_A dD_B}{\int_{AC} \left(1 - H \left(\frac{E_{AB}(D_A, D_B) - E}{E_f - E} \right) \right) dD_A dD_B} \right)^{1/2}$$

where AC is the space of all achievable dose pairs as determined by pharmacological or toxicological constraints. In this function, this space is represented either as a rectangular region in dose-pair-space bounded by the two values in the parameter macs (when same is FALSE) or the lower triangular region of dose-pair-space in which the sum of the two doses is less than the single value in macs (when same is TRUE).

Value

A single value or vector of values containing the estimated IAE for the response surface at the effect level or levels specified in lev.

Author(s)

Nathaniel R. Twarog

References

Twarog, N.R., Stewart, E., Vowell Hamill, C., and Shelat, A. BRAID: A Unifying Paradigm for the Analysis of Combined Drug Action. *Scientific Reports* **In Press** (2016).

See Also

[makeBRAIDreport](#)

Examples

```
data(es8analysis)
bfit <- es8analysis$braidFit
# Modelled effect is base-10 logarithm of cell survival relative to negative controls,
# so a level of -2 reflects 99% cell killing
calculateIAE(bfit$fullpar,c(-1,-2),c(1.015*10^-6,5*10^-5))
```

es8analysis

Analysis of a Ewings-Sarcoma Experiment

Description

This list is the results of full BRAID analysis run on the [es8olatmz](#) dataset from the `braidm` package. The list was output by the function [runBRAIDanalysis](#), and follows the format described therein.

Usage

```
data(es8analysis)
```

Format

A list of objects produced by the function [runBRAIDanalysis](#)

formatResponseMap *Format Response and Error Maps*

Description

Format response maps as activity maps using a multicolor gradient or error maps using a bidirectional gradient.

Usage

```
formatResponseMap(rmap, palette = NULL, cscale = NULL, x1 = expression(Conc[A]),
  y1 = expression(Conc[B]), z1 = "Activity")
formatDifferenceMap(rmap, zcenter = NULL, x1 = expression(Conc[A]),
  y1 = expression(Conc[B]), z1 = "Diff")
```

Arguments

rmap	a ggplot2 plot object depicting a response map, produced by the function responseMap
palette	a character vector or two or more colors defining the colorscale to be applied to the fill variable in the plot.
cscale	a value around which the colorscale applied to the fill variable will be centered. If NULL (the default), the colorscale will range from the minimum fill variable to the maximum.
x1	The character string or expression used to label the x-axis
y1	The character string or expression used to label the y-axis
z1	The character string or expression used to label the colorscale representing the response variable
zcenter	the value that forms the centerpoint (white) in the bidirectional color scale. If NULL (the default), the default setting for scale_fill_gradient2 is used.

Details

These functions are largely convenience functions, taking a response map produced by [responseMap](#) and formatting it with colorscales and axis labels. `formatResponseMap` with a multicolor gradient; by default it uses a modified 'jet' colormap, ranging from dark red to dark green, rather than the traditional dark blue. We find this function useful for visualizing response surfaces representing variables such as cytotoxicity, cell viability, enzyme activity, etc. The other formats the response map with a bidirectional color gradient (using the ggplot2 function `scale_fill_gradient2`; we find this format ideal for visualizing error maps.

Value

A ggplot2 plot object, with the appropriate scales and labels added.

Author(s)

Nathaniel R. Twarog

References

Twarog, N.R., Stewart, E., Vowell Hamill, C., and Shelat, A. BRAID: A Unifying Paradigm for the Analysis of Combined Drug Action. *Scientific Reports* **In Press** (2016).

See Also

[responseMap](#)

Examples

```
data(es8olatmz, package="braidrm")
rmap <- responseMap(act~conc1+conc2, es8olatmz)
formatResponseMap(rmap, x1="Olaparib", y1="TMZ", z1="Survival")
formatDifferenceMap(rmap, zcenter=-1)
```

makeBRAIDreport

Make a BRAID Report Page

Description

Produces a one page report depicting the results of a full BRAID analysis for a single combination.

Usage

```
makeBRAIDreport(brdAnalysis, compounds, iaelevs, macs, control = list())
```

Arguments

brdAnalysis	a list representing the results of a full BRAID analysis, produced by the braidrm function runBRAIDanalysis
compounds	A two element character vector containing the names of the two compounds tested. Should be the same string repeated if combination is self-vs.-self
iaelevs	one or two effect levels at which the IAE and potentiation will be estimated
macs	the maximum achievable concentrations for the two compounds tested for the calculation of the IAE. If one concentration is provided, it will be used for both compounds. If combination is self-vs.-self the two concentrations must be equal.
control	A list of optional control parameters adjusting the appearance of the report see Details for a full description

Details

This is, by design, a rather massive function that attempts, however foolhardily, to consolidate all the pieces necessary to produce a comprehensive visualization and report on the results of a BRAID analysis. By default, it produces a one page report containing four rows of three panels. The first row contains a plot of the measured data passed to the BRAID fit, plotted without interpolation; a table of the best fit BRAID parameters, with confidence intervals; and tables of one or more IAE values (with confidence intervals), as determined by the given maximum achievable concentrations and either a purely additive surface or the best fit BRAID surface. The second row contains the measured data plotted with interpolation to convey the shape of the measured response surface; a plot of the predicted response surface assuming the measured dose-response behavior and BRAID additivity; and a plot of the best fit BRAID response surface. The third row contains a uninterpolated plot of the error resulting from simple smoothing (to provide a reasonable upper bound on quality of fit); a plot of the error resulting from a predicted additive surface (with R-squared value); and a plot of the error resulting from the best fit BRAID surface (with R-squared value). The fourth and final row shows potentiation in the best fit surface, containing tables of EC values for a specified threshold for each drug in the presence of various levels of the other; a potentiation plot of the first drug potentiated by the second; and the corresponding plot with the two drugs reversed. The theme settings and sizes are intended for use on a portrait-oriented 8.5 by 11 inch page.

Many details of the plots and report are adjusted by the `control` parameter, which may contain any or all of the following elements:

- plot** a boolean determining whether the function arranges the constructed plots and tables and prints them to the existing graphics device. Doing so requires the package `gridExtra` (version 2.0.0 or greater); if this package is not included, a warning will be printed and this parameter will be reset to `FALSE`. Default value is `TRUE`
- return** a boolean determining whether the pieces generated for the report are returned as a result of the function. This option can be used if the user wishes to arrange the plot him or herself, rather than using the default layout approach. If `TRUE`, the function returns a list of fourteen objects; the nine `ggplot` plots described above, followed by the five tables assembled for the report. Note that the tables are returned as standard R arrays, not grid or graphics objects. Using this option with `plot` set to `FALSE` does not require the presence of `gridExtra`. Default value is `FALSE`
- actlabel** a string or R expression to be used as the label of the modeled effect in all plots. Default value is "Effect"
- abbs** in axis labels and tables, the two drugs being combined are represented by abbreviations. By default these abbreviations consist of the first three characters of each compound name, with non alphanumeric characters removed. However, the user may wish to use custom abbreviations (e.g. "TMZ" for "temozolomide"); they may do so by specifying two abbreviations as two strings in this optional parameter.
- levtext** an optional character vector the same length as `iaelevs`, determining how the corresponding levels will be displayed in tables. For example, if the modelled effect were proportional cell survival, the user might want to specify a label of "90" for a modelled effect of 0.1.
- irreg** a boolean variable, passed to `responseMap`, reflecting whether the dose pairs being plotted lie on a regularly spaced grid. Default value is `FALSE`
- clog** a boolean variable, reflecting whether the concentration variables are plotted on a logarithmic scale. This affects both the x- and y-axes in the seven surface plots, and the x-axis in the TWO potentiation plots. Default value is `TRUE`

- zlog** a boolean variable, reflecting whether the modeled effect is plotted on a logarithmic scale. This affects only the y-axis in the two potentiaton plots. Default value is FALSE
- xtrans** an optional function mapping the concentration of the first drug to the transformed value that the user wishes to plot. A simple example would be one in which the fit was performed on concentrations expressed in molar, but the user wishes to plot the concentrations in micromolar, in which case the value of 'xtrans' might be `function(x) x*10^6`.
- ytrans** an optional function mapping the concentration of the second drug to the transformed value that the user wishes to plot
- xunit** a string or R expression (e.g. `expression(mu*M)`) specifying how the units of the first drug should be displayed in axis labels and tables. If not specified, units will be omitted.
- yunit** a string or R expression (e.g. `expression(mu*M)`) specifying how the units of the second drug should be displayed in axis labels and tables. If not specified, units will be omitted.
- ztrans** an optional function mapping the modelled effect to the transformed value that the user wishes to plot. An example might be a case in which the modelled effect variable is a logarithmic transform of a real-world measurement, and the user wishes to plot the measured value, in which case the value of 'ztrans' might be `function(z) 10^z`.
- palette** a vector of two or more strings representing R colors, which will be passed to the ggplot2 function `scale_fill_gradientn` to specify the colormap for the plotted response surfaces. If left unspecified, a modified version of the classic "jet" colorscale (with dark green substituted for dark blue) will be used. Alternatively, if the user sets this parameter to the string "gjet" or "revgjet", the plots will use the modified "jet" colormap or its reverse.
- ptsize** an optional size parameter passed to `geom_point` to control the size of plotted points
- lnsize** an optional size parameter passed to `geom_line` to control the size of plotted lines.

Value

If the control parameter return is set TRUE, a list of ggplot2 plots and tables as described in the Description section above. If return is set to FALSE or omitted, the function returns NULL.

Author(s)

Nathaniel R. Twarog

References

Twarog, N.R., Stewart, E., Vowell Hamill, C., and Shelat, A. BRAID: A Unifying Paradigm for the Analysis of Combined Drug Action. *Scientific Reports* **In Press** (2016).

See Also

[runBRAIDanalysis](#), [responseMap](#), [potentiationPlot](#)

Examples

```
data(es8analysis)
pcont<-list(xtrans=function(x) x*10^6,ytrans=function(y) y*10^6,ztrans=function(z) 10^z,
           xunit=expression(mu*M),yunit=expression(mu*M),zlog=TRUE,abbs=c("01a", "TMZ"),
```



```

    levtext=c("90", "99"), palette="revgjet", plot=FALSE, return=TRUE)
brep <- makeBRAIDreport(es8analysis, c("Olaparib", "Temozolomide"),
  c(-1, -2), c(10^-6, 5*10^-5), pcont)
brep[[1]]
brep[[10]]

```

 potentiationPlot

Plot Potentiation in a BRAID Fitted Combination

Description

Generates a ggplot2 plot object depicting the potentiation or curve-shift of one compound by the presence of another, based on BRAID surface fit generated by the 'braidrm' package.

Usage

```
potentiationPlot(bfit, levs, dnum = 1, concs = NULL, control = list())
```

Arguments

bfit	an object of class 'braidrm' representing a BRAID surface fit
levs	a vector of levels of the "potentiating" drug to be plotted
dnum	index of the drug to be plotted on the x-axis (the "potentiated" drug). Default value 1
concs	an optional parameter specifying the concentrations of the "potentiated" drug to be plotted. If NULL (the default), a length-100 vector of evenly spaced concentrations will be plotted covering the range of concentrations in all combinations in which both drugs are non-zero.
control	A list of optional control parameters adjusting the appearance of the plot. See Details for a full description

Details

This function is less basic than the response mapping function [responseMap](#), and is intended as a convenience for those who wish to visualize potentiation in a BRAID-fit surface. Many details of the plot are adjusted by the control parameter, which may contain any or all of the following elements:

xlog a boolean variable reflecting whether the concentration plotted on the x-axis (the "potentiated" drug) should be plotted on a logarithmic scale. Default value is TRUE

ylog a boolean variable reflecting whether the concentration plotted on the x-axis (the modelled effect) should be plotted on a logarithmic scale. Default value is FALSE

addscales a boolean that controls whether logarithmic scales will be explicitly added to the resulting plot. ggplot2 prefers that only one scale be added to a given aesthetic, and throws a warning otherwise, so those who wish to plot the x- or y-variables logarithmically, but wish to add their own ggplot2 scales (to control axis limits, labels, etc.) should set this parameter to FALSE. Default value is TRUE

- xtrans** an optional function mapping the concentration of the potentiated drug to the transformed value that the user wishes to plot. A simple example would be one in which the fit was performed on concentrations expressed in molar, but the user wishes to plot the concentrations in micromolar, in which case the value of 'xtrans' might be `function(x) x*10^6`.
- ytrans** an optional function mapping the modelled effect to the transformed value that the user wishes to plot. An example might be a case in which the modelled effect variable is a logarithmic transform of a real-world measurement, and the user wishes to plot the measured value, in which case the value of 'ytrans' might be `function(y) 10^y`.
- thresh** an optional value (or vector of values) of the modeled effect that will be plotted as a dotted horizontal line. Used to visualize where the shifted dose-response curves cross a desired threshold or thresholds. Note that if ytrans is specified, the values in thresh should be desired thresholds *prior* to transformation.
- ciplot** a boolean variable reflecting whether 95% confidence intervals will be plotted around the potentiated DR curves. If the 'braidrm' object `bf.it` does not possess valid confidence intervals, then this parameter automatically is set to FALSE; if it has been explicitly set to TRUE, a warning will be printed indicating that confidence intervals cannot be plotted. Default value is TRUE
- cialpha** a boolean variable controlling how the confidence intervals are plotted. By default, confidence intervals are plotted as filled ribbons (using `geom_ribbon`) with an alpha (opacity) value of 0.3. This allows the confidence ranges to overlap, and use the same color scale as the plotted curves while remaining visually distinguishable. Unfortunately, some graphics outputs (including EPS) do not support transparency. Setting this parameter to FALSE will plot the confidence intervals with full opacity; the user may distinguish them from the DR curves by using a different color scale for the 'colour' and 'fill' aesthetics. Default value is TRUE
- pts** a boolean variable determining whether points are plotted along the potentiated DR curves. If true, each DR curve will have points plotted at all unique concentrations of the potentiated drug (in the plotted range) which appeared in any combination in the fitted data in which both drugs had non-zero concentrations. Note, however, that this does not plot actual measured effect, as there no guarantee that the levels of the potentating drug which are plotted were tested in the original experiment. Plotting these points simply offers a way to visualize which concentrations of the potentiated drug were actually measured experimentally. Default value is FALSE
- ptsize** an optional size parameter passed to `geom_point` to control the size of plotted points. If pts is omitted or set to FALSE this parameter is ignored.
- pconcs** if desired, the user may set this control parameter to explicitly determine which concentrations of the potentiated drug will be plotted as points. This is used in `makeBRAIDreport` when concentration corrections have altered the concentrations fed into the BRAID fitting model.
- lnsize** an optional size parameter passed to `geom_line` and, if thresh is included, `geom_hline` to control the size of plotted lines.

Though this function is intended to much of the heavy lifting in plotting potentiation (especially as applied to confidence intervals), many choices are left to the user. Axis labels are not applied, and scales are not applied to the 'colour' or 'fill' aesthetics. Users may also, of use any `ggplot2` theme functions to further adjust the appearance of the plot.

Value

A ggplot2 plot object, depicting the dose-response curves of the potentiated drug in the presence of various levels of the potentiating drug.

Author(s)

Nathaniel R. Twarog

References

Twarog, N.R., Stewart, E., Vowell Hamill, C., and Shelat, A. BRAID: A Unifying Paradigm for the Analysis of Combined Drug Action. *Scientific Reports In Press* (2016).

See Also

[makeBRAIDreport](#)

Examples

```
data(es8analysis)
bfit <- es8analysis$braidFit
pcont <- list(xtrans=function(x) x*10^6,ytrans=function(y) 10^y,ylog=TRUE,thresh=-1)
potentiationPlot(bfit,c(0,10^-6,10^-5,10^-4),control=pcont)
```

responseMap

Visualizing Combination Response Maps

Description

Produces a ggplot2 plot depicting some response variable as a function of two input variables; generally this will be some biological effect as a function of two compound concentrations.

Usage

```
## Default S3 method:
responseMap(model,data,irreg=FALSE,interpolate=TRUE,margins=TRUE,
  logscale=TRUE,zlims=NULL,raster=TRUE)
## S3 method for class 'formula'
responseMap(model,data,...)
```

Arguments

model	a two-column array containing the values of input 1 and input 2 in each data point, or a symbolic formula (e.g. $act \sim conc1+conc2$) specifying which variables are to be visualized
data	if model is an array, a vector of values in response to inputs 1 and 2; if model is a formula, a data frame containing the columns specified in formula

irreg	reflects whether or not data points lie in a regularly-spaced grid in the space of data points to be plotted
interpolate	determines whether the plot will produce a smoothed response surface using Gaussian interpolation, or if the space will be visualized as a set of discrete measurements using nearest neighbor segmentation
margins	determines whether input pairs in which one of the two inputs is zero will be plotted; applies only to logarithmically scaled plots
logscale	determines whether the input variables will be plotted on a logarithmic scale, or a standard linear scale. Because this function is intended primarily for visualizing combined action dose-response, a logarithmic dose-pair space is the default.
zlims	an optional parameter specifying lower and upper bounds on the response variable. If present, all effect values outside the given range will be clipped to the minimum and maximum values
raster	by default, interpolated response surfaces will be rendered using the ggplot2 function <code>geom_raster</code> , a faster and optimized raster image version of <code>geom_tile</code> . In certain settings, however, <code>geom_raster</code> can produce unusual appearance. Setting this parameter to <code>FALSE</code> will force the plot to be rendered using <code>geom_tile</code>
...	not used

Details

This function produces and returns a ggplot2 plot, but does not draw it to a graphics device. As the strength of ggplot2 is in the ability to annotate, build on, and style plots using additional layers and themes, this function adds no theme information, and very little scale information. To produce a more aesthetic plot, it is recommended that plot be given a custom color scale, axis labels, and theme by using the appropriate ggplot2 functions. For convenience, the functions [formatResponseMap](#) and [formatDifferenceMap](#) format and add labels to plots produced by responseMap, but any ggplot2 changes that are desired can be made. If you wish to add additional layers (such as contour curves), the data variables available for mapping aesthetics are x, y, and z.

Value

A ggplot2 plot object, depicting the response variable (represented by the plot's `'fill'` variable) as a function of two inputs (the x- and y-dimensions).

Author(s)

Nathaniel R. Twarog

References

Twarog, N.R., Stewart, E., Vowell Hamill, C., and Shelat, A. BRAID: A Unifying Paradigm for the Analysis of Combined Drug Action. *Scientific Reports* **In Press** (2016).

See Also

[formatResponseMap](#), [formatDifferenceMap](#), [voronoi](#)

Examples

```
data(es80latmz, package="braidrm")
rmap <- responseMap(act~conc1+conc2, es80latmz)
formatResponseMap(rmap, x1="Olaparib", y1="TMZ", z1="Survival")
rmap <- responseMap(act~conc1+conc2, es80latmz, interpolate=FALSE, margins=FALSE)
formatDifferenceMap(rmap, zcenter=-1, x1="Olaparib", y1="TMZ", z1="Survival")
```

voronoi	<i>Voronoi segmentation</i>
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Description

Calculates the Voronoi (nearest-neighbor) segmentation of a two-dimensional rectangular region based on a set of points.

Usage

```
voronoi(pts, bbox = NULL)
```

Arguments

pts	a two column array of points around which to calculate Voronoi cells
bbox	the rectangular bounding box the Voronoi cells must fill, represented by a length 4 vector of the form <code>c(xmin, xmax, ymin, ymax)</code> . If <code>NULL</code> , a bounding box will be constructed containing all points with padding on each side

Details

Though this function is not strictly necessary to the use of other functions in this package, we found the construction of a Voronoi segmentation to be a rather tedious task, and felt that making the function available to those who want a simple segmentation function was a reasonable choice.

Value

A data frame intended for use in the `ggplot2` function [geom_polygon](#). The data frame describes one polygon for each given input point, with the 'x' and 'y' columns specifying the x- and y-coordinates of the vertices of the polygon, and the column 'poly' specifying the index of the point (in the input array `pts`) around which the polygon sits.

Author(s)

Nathaniel R. Twarog

See Also

[responseMap](#)

Index

- * **aplot**
 - formatResponseMap, 5
- * **datasets**
 - es8analysis, 4
- * **dplot**
 - voronoi, 13
- * **hplot**
 - makeBRAIDreport, 6
 - potentiationPlot, 9
 - responseMap, 11
- * **misc**
 - calculateIAE, 3
- * **package**
 - braidReports-package, 2

braidReports (braidReports-package), 2
braidReports-package, 2

calculateIAE, 2, 3

es8analysis, 4
es8olatmz, 4

formatDifferenceMap, 2, 12
formatDifferenceMap
(formatResponseMap), 5
formatResponseMap, 2, 5, 12

geom_hline, 10
geom_line, 8, 10
geom_point, 8, 10
geom_polygon, 13
geom_ribbon, 10

makeBRAIDreport, 2, 4, 6, 10, 11

potentiationPlot, 2, 8, 9

responseMap, 2, 5–9, 11, 13
runBRAIDanalysis, 4, 6, 8

scale_fill_gradientn, 8

voronoi, 12, 13