Package 'synergyfinder'

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Type Package

Title Calculate and Visualize Synergy Scores for Drug Combinations

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Description Efficient implementations for analyzing pre-clinical multiple drug combination datasets. 1. Synergy scores valuculation via all the popular models, including HSA, Loewe, Bliss and ZIP; 2. Drug Sensitivity Score (CSS) and Relitave Inhibition (RI) for drug sensitivity evaluation; 3. Visualization for drug combination matrices and scores. Based on this package, we also provide a web application (http://synergyfinder.org/) for users who prefer more friendly user interface.

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Encoding UTF-8

URL http://synergyfinder.org/

RoxygenNote 7.1.1

Suggests knitr, rmarkdown

VignetteBuilder knitr

biocViews Software, StatisticalMethod

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R topics documented:

`.AdjustColumnName` *Adjust Column Names of Input Data Table*

Description

This function changes the column names in other format into the style: block_id, drug1, drug2, conc1, conc2, response, conc_unit1, conc_unit2.

Usage

```
.AdjustColumnName(data)
```

Arguments

`data`	A data frame. It is the input data for function ReshapeData

Value

The data frame with the changed column names.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

`.Bootstrapping` *Bootstraping Sample from Replicates in Response Data*

Description

Bootstraping Sample from Replicates in Response Data

Usage

```
.Bootstrapping(response)
```

Arguments

`response`	A data frame. It contains the dose response information about one drug combination block with replicates. It must contain the columns "conc1", "conc2", ... for concentrations of drugs tested and the "response" column for observed % inhibition if cell growth.

Value

A data frame. It contains a full drug combination matrix whose data points are randomly selected from replicates.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

.Distance *Calculate Distance from a Point to a Plane*

Description

This function is used to calculate the distance from a point to a plane. It could also be used in high dimension spaces. The formula comes from https://en.wikipedia.org/wiki/Distance_from_a_point_to_a_plane For two dimension point, the distance to the line w1*x+w2*y+b = 0 For three dimension point, the distance to the plan w1*x+w2*y+w3*z+b = 0

Usage

```
.Distance(w, b, point)
```

Arguments

w	A numeric vector. It contains the parameters for all the coordinates in the spaces to define the "plan".
b	A numeric value. It is the constant values in the formula which defines the "plan".
point	A numeric vector. It contains the coordinates in the spaces to define the "point".

Value

A numeric value. It is the distance from point defined by x0 to the "plane" defined by w and b

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

.ExtendedScores *Make a Smooth Surface for Scores*

Description

Make a Smooth Surface for Scores

Usage

```
.ExtendedScores(scores_mat, len)
```

Arguments

scores_mat	a matrix contains scores which will be visualized
len	length of the interval between plotted data points.

Value

a matrix which which contains interpolated points for input scores_mat.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

.Extract2DrugPlotData *Extract Data for 2 Drug Combination Plots*

Description

Extract Data for 2 Drug Combination Plots

Usage

```
.Extract2DrugPlotData(
  data,
  plot_block = 1,
  drugs = c(1, 2),
  plot_value = "response",
  statistic = NULL
)
```

Arguments

data	A list object generated by function ReshapeData.
plot_block	A character/integer. It indicates the block ID for the block to visualize.
drugs	A vector of characters or integers with length of 2. It contains the index for two drugs to plot. For example, c(1,2) indicates to plot "drug1" and "drug2" in the input data.
plot_value	A character value. It indicates the value to be visualized. If the data is the direct output from ReshapeData, the values for this parameter are: • **response_origin** The original response value in input data. It might be % inhibition or % viability. • **response** The % inhibition after preprocess by function ReshapeData If the data is the output from CalculateSynergy, following values are also available: • **ZIP_ref, Bliss_ref, HSA_ref, Loewe_ref** The reference additive effects predicted by ZIP, Bliss, HSA or Loewe model, respectively. • **ZIP_synergy, Bliss_synergy, HSA_synergy, Loewe_synergy** The synergy score calculated by ZIP, Bliss, HSA or Loewe model, respectively.

- **ZIP_fit** The response fitted by ZIP model.

`statistic` A character or NULL. It indicates the statistics printed in the plot while there are replicates in input data. Available values are:

- **sem** Standard error of mean;
- **ci** 95% confidence interval.

If it is `NULL`, no statistics will be printed.

Value

A data frame. It contains the concentrations for selected drugs, the selected values for plotting, and the text for printing on the heatmap.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

.ExtractMultiDrugPlotData

Extract Data Table and Annotation Information for Multi-drug Plotting

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Description

This function extracts the information for Multi-drug plotting from input list `data`. It is an auxiliary function for PlotMultiDrugSurface and PlotMultiDrugBar.

Usage

```
.ExtractMultiDrugPlotData(
  data,
  plot_block = 1,
  plot_value = "response",
  statistic = NULL,
  titles = TRUE
)
```

Arguments

`data` A list object generated by function `ReshapeData`.

`plot_block` A character/integer. It indicates the block ID for the block to visualize.

`plot_value` A vector of characters. It contains the name of one or more metrics to be visualized. If the `data` is the direct output from ReshapeData, the values for this parameter are:

- **response_origin** The original response value in input data. It might be % inhibition or % viability.
- **response** The % inhibition after preprocess by function ReshapeData

If the `data` is the output from CalculateSynergy, following values are also available:

- **ZIP_ref, Bliss_ref, HSA_ref, Loewe_ref** The reference additive effects predicted by ZIP, Bliss, HSA or Loewe model, respectively.
- **ZIP_synergy, Bliss_synergy, HSA_synergy, Loewe_synergy** The synergy score calculated by ZIP, Bliss, HSA or Loewe model, respectively.
- **ZIP_fit** The response fitted by ZIP model.

`statistic` A character or NULL. It indicates the statistics printed in the plot while there are replicates in input data. Available values are:

- **sem** Standard error of mean;
- **ci** 95

If it is `NULL`, no statistics will be printed.

`titles` A logical value. If it is `TRUE`, the plot tile, subtilte, and title for z axis will be extracted and output.

Value

A list. It contains the elements:

- **plot_table** A data frame contains concentrations for all drugs, the values for `plot_value`.
- **drug_pair** A data frame contains the drug names and concentration unites, whither the block is replicate or not.
- **plot_title** A string for plot title.
- **z_axis_subtitle** A string for plot z-axis title.

Author(s)

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.own_log *CSS Facilitate Function - Log Calculation (nature based) LL.4 Model*

Description

#' This function calculates ln(1+10^(b*(c-x))) to be used in `.ScoreCurve` function

Usage

```
.own_log(b, c, x)
```

Arguments

`b` A numeric value. It is the fitted parameter b from `L.4` model.

`c` A numeric value. It is the fitted parameter c from `L.4` model.

`x` A numeric value. It is the relative IC50 for the curve. log10(e), where e is the fitted parameter e from `L.4` model.

Value

ln(1+10^(b*(c-x)))

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

.own_log2 *CSS Facilitate Function - Log (nature based) Calculation L.4 Model*

Description

This function calculates ln(1+exp(x)) to be used in .ScoreCurve_L4 function

Usage

```
.own_log2(x)
```

Arguments

x	A numeric value. It is relative IC50 for the curve. The fitted parameter e from L.4 model.

Value

A numeric value. It is ln(1+exp(x))

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

.Pt2mm *Convert Font Size from pt to mm*

Description

This function converts font sizes from "pt" unite to "mm" unite.

Usage

```
.Pt2mm(x)
```

Arguments

x	A numerical value. It is the font size in "pt" unite.

Value

A numerical value in "mm" unite

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

.RoundValues *Round the Numbers for Plotting*

Description

This function will round the input numbers by 2 digits, if the absolute of number is larger than or equal to 1. It will take 2 significant digits, if the absolute of number is smaller than 1.

Usage

```
.RoundValues(numbers)
```

Arguments

numbers	A vector of numeric values. It contains the numbers need to be rounded.

Value

A vector of rounded numbers.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

.ScoreCurve *CSS Facilitate Function - .ScoreCurve for Curves Fitted by LL.4 Model*

Description

New function used to score sensitivities given either a single-agent or a fixed conc (combination) columns. The function calculates the AUC of the log10-scaled dose-response curve. **IMPORTANT:** note that with LL.4 calls, this value is already logged since the input concentrations are logged.

Usage

```
.ScoreCurve(b, c, d, m, c1, c2, t)
```

Arguments

b	A numeric value, fitted parameter b from LL.4 model.
c	A numeric value, fitted parameter c from LL.4 model.
d	A numeric value, fitted parameter d from LL.4 model.
m	A numeric value, relative IC50 for the curve. log10(e), where e is the fitted parameter e from LL.4 model.
c1	A numeric value, log10(min conc) (this is the minimal nonzero concentration).
c2	A numeric value, log10(max conc) (this is the maximal concentration).
t	A numeric value, threshold (usually set to zero).

Value

A numeric value, RI or CSS scores.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

`.ScoreCurve_L4` *CSS Facilitate Function - .ScoreCurve for Curves Fitted by L.4 Model*

Description

This function is used to score sensitivities given either a single-agent or a fixed conc (combination) columns. The function calculates the AUC of the log10-scaled dose-response curve.

Usage

```
.ScoreCurve_L4(b, c, d, e, c1, c2, t)
```

Arguments

`b`	A numeric value, fitted parameter b from `L.4` model.
`c`	A numeric value, fitted parameter c from `L.4` model.
`d`	A numeric value, fitted parameter d from `L.4` model.
`e`	A numeric value, fitted parameter e from `L.4` model.
`c1`	A numeric value, log10(min conc) (this is the minimal nonzero concentration).
`c2`	A numeric value, log10(max conc) (this is the maximal concentration).
`t`	A numeric value, threshold (usually set to zero).

Value

A numeric value, RI or CSS scores.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

.SolveExpDoesL4 *Solve the Expected Dose of Drug to Achieve Given Effect from L.4 Model*

Description

This function will solve the fitted four-parameter logistic dose-response model and output the dose of drug at which it could achieve the % inhibition to cell growth.

Usage

```
.SolveExpDoesL4(y, drug_par)
```

Arguments

y	The expected effect (% inhibition) of the drug to cell line
drug_par	The parameters for fitted dose-response model.

Value

A numeric value. It indicates the expected dose of drug.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

.SolveExpDoesLL4 *Solve the Expected Dose of Drug to Achieve Given Effect from LL.4 Model*

Description

This function will solve the fitted four-parameter log-logistic dose-response model and output the dose of drug at which it could achieve the % inhibition to cell growth.

Usage

```
.SolveExpDoesLL4(y, drug_par)
```

Arguments

y	The expected effect (% inhibition) of the drug to cell line
drug_par	The parameters for fitted dose-response model.

Value

A numeric value. It indicates the expected dose of drug.

Author(s)

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.SolveExpDose — *Solve the Expected Dose of Drug to Achieve Given Effect (% inhibition)*

Description

This function will solve the fitted dose-response model and output the dose of drug at which it could achieve the % inhibition to cell growth.

Usage

```
.SolveExpDose(y, drug_par, drug_type)
```

Arguments

y	The expected effect (% inhibition) of the drug to cell line.
drug_par	The parameters for fitted dose-response model.
drug_type	The type of model was used to fit the dose-response curve. Available values are "L.4" - four-parameter logistic model; "LL.4" - four-parameter log-logistic model.

Value

A numeric value. It indicates the expected dose of drug.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

.SolveLoewe — *Solve the Loewe Additive Effect for Concentration Combinations Isobologram*

Description

Solve the Loewe Additive Effect for Concentration Combinations Isobologram

Usage

```
.SolveLoewe(concs, drug_par, drug_type, nsteps = 100)
```

Arguments

`concs`	A numeric vector. It contains the concentrations of tested drugs.
`drug_par`	A numeric vector. The parameters in fitted dose response curve.
`drug_type`	The type of model used to fit dose response curve.
`nsteps`	The total steps to calculate concentration combinations approaching to the true Loewe effect.

Value

A list contains 3 items:

- y_loewe the predicted Loewe additive effect which closes to .
- x_select the expected concentrations for each drug to achieve y_loewe.
- distance the smallest distance

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
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`Bliss` *Calculate Bliss Synergy Score*

Description

`Bliss` calculates the synergy score matrix for a block of drug combination by using a drug interaction reference model introduced by C. I. Bliss in 1939.

Usage

```
Bliss(response, single_drug_data)
```

Arguments

`response`	A data frame. It must contain the columns: "conc1", "conc2", ..., for the concentration of the combined drugs and "response" for the observed %inhibition at certain combination.
`single_drug_data`	A list or NULL. It contains the monotherapy dose response data for all the tested drugs in the inputted block. If it is `NULL`, the data will extract the dose response table from inputted `response` table.

Details

This model is a reference model for evaluating the combination effect of two drugs. The basic assumption of this model is "The expected effect of two drugs acting independently". The Bliss reference effect y = 1 - product_all_drug(1-%Inhibition) * 100.

Value

A data frame containing the concentrations for drugs, reference effect and synergy score estimated by Bliss model.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

References

- Yadav B, Wennerberg K, Aittokallio T, Tang J. (2015). Searching for Drug Synergy in Complex Dose-Response Landscape Using an Interaction Potency Model. Comput Struct Biotechnol J, 13:504– 513.
- Bliss, C. I. (1939). The toxicity of poisons applied jointly. Annals of Applied Biology, 26(3):585–615.

Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
response <- data$response[data$response$block_id == 1,
                         c("conc1", "conc2", "response")]
Bliss.score <- Bliss(response)
```

CalculateCSS *Calculate Combination Sensitivity Score*

Description

This function will calculate the Combination Sensitivity Score (CSS) for a drug combination block.

Usage

```
CalculateCSS(response, ic50)
```

Arguments

response	A data frame. It must contain the columns: "conc1", "conc2", ..., for the concentration of the combined drugs and "response" for the observed %inhibition at certain combination.
ic50	A list. It contains the relative IC50 for all the drugs in the combination.

Value

A data frame. It contains the CSS for each drug will one of the other drugs is at its IC50 and summarized CSS for the whole block.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
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CalculateIC50 *Calculate Relative IC50 from Fitted Model*

Description

This function will calculate the relative IC50 from fitted 4-parameter log-logistic dose response model.

Usage

```
CalculateIC50(coef, type, max.conc)
```

Arguments

coef	A numeric vector. It contains the fitted coefficients for 4-parameter log-logistic dose response model.
type	A character value. It indicates the type of model was used for fitting the dose-response curve. Available values are "L.4" and "LL.4".
max.conc	A numeric value. It indicates the maximum concentration in the dose-response data

Value

A numeric value. It is the relative IC50.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

CalculateSens *Calculate Relative Inhibition (RI) for Dose-Response Curve*

Description

Function CalculateSens calculates cell line sensitivity to a drug or a combination of drugs from dose response curve.

Usage

```
CalculateSens(df)
```

Arguments

df	A data frame. It contains two variables: • **dose** the concentrations of drugs. • **response** the response of cell lines at corresponding doses. We use inhibition rate of cell line growth to measure the response.

Details

This function measures the sensitivity by calculating the Area Under Curve (AUC) according to the dose response curve. The lower border is chosen as lowest non-zero concentration in the dose response data.

Value

A numeric value. It is the RI score for input dose-response curve.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
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Examples

```
# LL.4
df <- data.frame(dose = c(0, 0.1954, 0.7812, 3.125, 12.5, 50),
                 response = c(2.95, 3.76, 18.13, 28.69, 46.66, 58.82))
RI <- CalculateSens(df)
```

CalculateSensitivity *Calculate the Synergy Scores for Drug Combinations*

Description

CalculateSynergy is the main function for calculating synergy scores based on model(ZIP, Bliss, Loewe, and HSA) fron one dose-response **matrix**.

Usage

```
CalculateSensitivity(data, adjusted = TRUE, iteration = 10, seed = 123)
```

Arguments

data	A list object generated by function ReshapeData.
adjusted	A logical value. If it is TRUE, the 'adjusted.response.mats' will be used to calculate synergy scores. If it is FALSE, the raw data ('dose.response.mats') will be used to calculate synergy scores.
iteration	An integer. It indicates the number of iterations for synergy scores calculation on data with replicates.
seed	An integer or NULL. It is used to set the random seed in synergy scores calculation on data with replicates.

Value

This function will add columns into `data$drug_pairs` table. The columns are:

- **ic50_1/2/...** Relative IC50 for drug 1, 2, ...
- **ri_1/2/...** Relative Inhibition (RI) for drug 1, 2, ...
- **css1_ic502/...** CSS score of drug 1 while fixing drug 2 at its IC50.
- **css** Over all CSS score for the whole block. It's the mean value of the CSS for all drug pairs in the combination.

If there are replicates in the block, this function will add one table named as "sensitivity_scores_statistics" for the statistics of the values mentioned about into the input `data` list.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
data <- CalculateSensitivity(data)
```

CalculateSynergy *Calculate the Synergy Scores for Drug Combinations*

Description

`CalculateSynergy` is the main function for calculating synergy scores based on model(ZIP, Bliss, Loewe, and HSA) from one dose-response **matrix**.

Usage

```
CalculateSynergy(
  data,
  method = c("ZIP", "HSA", "Bliss", "Loewe"),
  Emin = NA,
  Emax = NA,
  adjusted = TRUE,
  correct_baseline = "non",
  iteration = 10,
  seed = 123
)
```

Arguments

data	A list object generated by function ReshapeData.
method	A parameter to specify which models to use to calculate the synergy scores. Choices are "ZIP", "Bliss", "HSA" and "Loewe". Defaults to "ZIP".
Emin	The expected minimum response value in the 4 parameter log-logistic model. It is used while calling ZIP and Loewe.
Emax	The expected maximum response value in the 4 parameter log-logistic model. It is used while calling ZIP and Loewe.
adjusted	A logical value. If it is TRUE, the 'adjusted.response.mats' will be used to calculate synergy scores. If it is FALSE, the raw data ('dose.response.mats') will be used to calculate synergy scores.
correct_baseline	A character value. It indicates the method used for baseline correction. Available values are: • **non** No baseline correction. • **part** Adjust only the negative values in the matrix. • **all** Adjust all values in the matrix.
iteration	An integer value. It indicates the number of iterations for synergy scores calculation on data with replicates.
seed	An integer or NULL. It is used to set the random seed in synergy scores calculation on data with replicates.

Value

This function will add 1 or 2 elements into inputted data list:

- **scores** A data frame. It contains synergy scores, reference effects and fitted response values (only for "ZIP" model) calculated by selected method. If there are replicates in the block, the mean values across all iterations for all the metrics mentioned above will be output.
- **scores_statistics** A data frame. It will be output if there is block have replicated response values. It contains the the statistics (including mean, standard deviation, standard error of mean and 95 and fitted response values (only for "ZIP" model) across results from iterations.

This function also add mean of synergy scores across whole combination matrix to the data$drug_pair table.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
scores <- CalculateSynergy(data)
```

CorrectBaseLine *Base Line Correction for Drug Combination Matrix*

Description

CorrectBaseLine adjusts the base line of drug combination dose-response matrix to make it closer to 0.

Usage

```
CorrectBaseLine(response, method = c("non", "part", "all"))
```

Arguments

response	A drug cobination dose-response matrix. It's column name and row name are representing the concerntrations of drug added to column and row, respectively. The values in matrix indicate the inhibition rate to cell growth.
method	A character value. It indicates the method used for baseline correction. Available values are: • **non** No baseline correction. • **part** Adjust only the negative values in the matrix. • **all** Adjust all values in the matrix.

Value

A matrix which base line have been adjusted.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
response <- data$response[data$response$block_id == 1, ]
adjusted <- CorrectBaseLine(response, method = "part")
```

DimensionReduction *Dimension Reduction for Multi-drug Combination Visualization*

Description

This function will take the multi-drug combination data, project the concentrations of all the drugs into 2 dimensions. It is an auxiliary function for PlotMultiDrugSurface

Usage

```
DimensionReduction(plot_table, drug_pair, plot_value, distance_method)
```

Arguments

plot_table	A data frame contains concentrations for all drugs, the values for plot_value.
drug_pair	A data frame contains the drug names and concentration unites, whither the block is replicate or not.
plot_value	A vector of characters. It contains the name of one or more metrics to be visualized. If the data is the direct output from ReshapeData, the values for this parameter are: • **response_origin** The original response value in input data. It might be % inhibition or % viability. • **response** The % inhibition after preprocess by function ReshapeData If the data is the output from CalculateSynergy, following values are also available: • **ZIP_ref, Bliss_ref, HSA_ref, Loewe_ref** The reference additive effects predicted by ZIP, Bliss, HSA or Loewe model, respectively. • **ZIP_synergy, Bliss_synergy, HSA_synergy, Loewe_synergy** The synergy score calculated by ZIP, Bliss, HSA or Loewe model, respectively. • **ZIP_fit** The response fitted by ZIP model.
distance_method	The methods to calculate the distance between different data points from the concentration of drugs. The distance matrix is used for dimension reduction. This parameter is used to set the parameter method for vegdist. The default values is "euclidean".

Value

A data frame. It contains the plot information required by function GenerateSurface

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

ExtractSingleDrug *Extract Single Drug Dose Response*

Description

ExtractSingleDrug extracts the dose-response values of single drug from a drug combination dose-response matrix.

Usage

```
ExtractSingleDrug(response)
```

Arguments

response	A data frame. It must contain the columns: "conc1", "conc2", ..., for the concentration of the combined drugs and "response" for the observed %inhibition at certain combination.

Value

A list contains several data frames each of which contains 2 columns:

- **dose** The concertration of drug.
- **response** The cell's response (inhibation rate) to corresponding drug concertration.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
response <- data$response[data$response$block_id == 1,
                         c("conc1", "conc2", "response")]
single <- ExtractSingleDrug(response)
```

`FindModelPar` *Find the Fitted Parameters from 4-Parameter Log-Logistic Model*

Description

Find the Fitted Parameters from 4-Parameter Log-Logistic Model

Usage

```
FindModelPar(model)
```

Arguments

`model`	A object of class "drc".

Value

A numeric vector. It contains 4 fitted parameters.

FindModelType *Find the Type of Model Used for Fitting Dose Response Data*

Description

FindModelType will extract the model type ("LL.4" or "L.4) eventually used in funciton FitDoseResponse

Usage

```
FindModelType(model)
```

Arguments

model	An object of class 'drc'. It is generated by function FitDoseResponse

Value

A character either "LL.4" or "L.4". It indicates the type of model used for fitting dose response data.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

Examples

```
df <- data.frame(
  response = c(0, 29, 59, 60, 75, 90),
  dose = c(0.00, 9.7656, 39.0626, 156.25, 625, 2500)
)
model <- FitDoseResponse(df)
model.type <- FindModelType(model)
```

FitDoseResponse *Fitting Single Drug Dose-Response Model*

Description

Function FitDoseResponse fits dose-response model by using drm function.

Usage

```
FitDoseResponse(data, Emin = NA, Emax = NA)
```

Arguments

data	A data frame. It contains two columns: • **dose** The concentration of drugs added in experiment. • **response** The response (with different concentrations.
Emin	A numeric value or NA. the minimal effect of the drug used in the 4-parameter log-logistic function to fit the dose-response curve. If it is not NA, it is fixed the value assigned by the user. Default setting is NA.
Emax	A numeric or NA. the maximal effect of the drug used in the 4-parameter log-logistic function to fit the dose-response curve. If it is not NA, it is fixed the value assigned by the user. Default setting is NA.

Details

Pre-fitting process: 1. Change the 0 value in concentration into 10^-10 to avoide raising error when taking log. 2. If the variance of "response" values equal to 0, add 10^-10 to the last "response" value.

Model choice: First use "L.4" model to fit the raw data. If error or waring occurs, use "LL.4" model to fit log(raw data).

Value

An object of class 'drc'. It contains information of fitted model.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

References

Seber, G. A. F. and Wild, C. J (1989) hrefhttps://onlinelibrary.wiley.com/doi/book/10.1002/0471725315Nonlinear Regression, New York: Wiley \& Sons (p. 330).

Examples

```
df <- data.frame(
  response = c(0, 29, 59, 60, 75, 90),
  dose = c(0.00, 9.7656, 39.0626, 156.25, 625, 2500)
)
model <- FitDoseResponse(df)
```

GenerateSurface *3D Surface Plot for Nulti-drug Combination Dose-Response/Synergy Scores*

Description

This function will generate a surface plot for multi-drug combinations from the output of DimensionReduction. It is an auxiliary function for PlotMultiDrugSurface

Usage

```
GenerateSurface(
  dim_reduced_data,
  high_value_color,
  low_value_color,
  point_color,
  plot_title,
  legend_title,
  z_axis_title
)
```

Arguments

dim_reduced_data	A list of data frame. It contains the dimension reduced data for all the data points and other information for plotting. It is the output of DimensionReduction (combination of concentrations). It is
high_value_color	An R color value. It indicates the color for the high values.
low_value_color	An R color value. It indicates the color for low values.
point_color	An R color value. It indicates the color for data points.
plot_title	A character value. It is the title for plot.
legend_title	A character value. It is the title for legend.
z_axis_title	A character value. It is the title for z-axis.

Value

A ggplot object.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

HighlightBarPlot *Highlight Bars*

Description

It is an auxiliary function for PlotMultiDrugBar

Usage

```
HighlightBarPlot(selected_data)
```

Arguments

selected_data	A data frame. It contain the information for the bars to be highlighted.

Value

A ggplot object

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

HSA *Calculate HSA Synergy Score*

Description

HSA calculates the synergy score matrix for a block of drug combination by using Highest Single Agent (HSA) reference model.

Usage

```
HSA(response)
```

Arguments

response	A data frame. It must contain the columns: "conc1", "conc2", ..., for the concentration of the combined drugs and "response" for the observed %inhibition at certain combination.

Details

This model is a reference model for evaluating the combination effect of two drugs. The basic assumption of this model is "The reference effect of drug combination is the maximal single drug effect".

Value

A data frame containing the concentrations for drugs, reference effect and synergy score estimated by HSA model.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

References

- Yadav B, Wennerberg K, Aittokallio T, Tang J.(2015). Searching for Drug Synergy in Complex Dose-Response Landscape Using an Interaction Potency Model.Comput Struct Biotechnol J, 13:504– 513.
- Berenbaum MC. (1989). What is synergy? Pharmacol Rev 1990 Sep;41(3):422.

Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
response <- data$response[data$response$block_id == 1,
                         c("conc1", "conc2", "response")]
HSA.score <- HSA(response)
```

`ImputeIC50` *Impute Missing Value at IC50 Concentration of Drug*

Description

`ImputeIC50` uses the particular experiment's values to predict the missing values at the desired IC50 concentration of the drug. This function is only called when trying to fix a drug at its selected IC50 concentration where the response values have not been tested in experiment.

Usage

```
ImputeIC50(response.mat, col.ic50, row.ic50)
```

Arguments

`response.mat`	A matrix. It contains response value of a block of drug combination.
`col.ic50`	A numeric value. The IC50 value of drug added to columns.
`row.ic50`	A numeric value. The IC50 value of drug added to rows.

Details

`ImputeIC50` fits dose-response models (with `drm` function) by fixing the concentrations of the **other** drug successively, and uses each fit to predict the missing value at the combination (missing IC50, fixed conc).

Value

A data frame contains all response value at the IC50 concentration of certein drug. It could be directly passed to function `CalculateSens` for scoring.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

Loewe *Calculate Loewe Synergy Score*

Description

Loewe calculates the synergy score matrix from a dose-response matrix by using a druginteraction reference model introduced by Loewe in 1953.

Usage

```
Loewe(response, Emin = NA, Emax = NA, quiet = TRUE)
```

Arguments

response	A data frame. It must contain the columns: "conc1", "conc2", ..., for the concentration of the combined drugs and "response" for the observed %inhibition at certain combination.
Emin	The expected minimum response value in the 4 parameter log-logistic model.
Emax	The expected maximum response value in the 4 parameter log-logistic model.
quiet	A logical value. If it is TRUE then the warning message will not show during calculation.

Details

Loewe model is a reference model for evaluating the combination effect of two drugs. The basic assumption of this model is "The referece effect of drug combination is the expected effect of a drug combined with itself".

The optional arguments drug.col.model, drug.row.model are designed for reuse the single drug dose response model fitting results, if it has been down before. Functions FitDoseResponse and ExtractSingleDrug could be used to calculate these arguments.

Value

A data frame containing the concentrations for drugs, reference effect and synergy score estimated by Loewe model.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

References

- Yadav B, Wennerberg K, Aittokallio T, Tang J.(2015). Searching for Drug Synergy in Complex Dose-Response Landscape Using an Interaction Potency Model.Comput Struct Biotechnol J, 13:504– 513.
- [Loewe, 1953] Loewe, S. (1953). The problem of synergism and antagonism of combined drugs. Arzneimittelforschung, 3(6):285–290.

Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
response <- data$response[data$response$block_id == 1,
                         c("conc1", "conc2", "response")]
Loewe.score <- Loewe(response)
```

`mathews_screening_data` *A high-throughput drug combination screening data*

Description

A recent drug combination screening for the treatment of diffuse large B-cell lymphoma (DLBCL).

Format

A data frame with the following columns: block_id, drug_row, drug_col, conc_r, conc_c, response, conc_r_unit, conc_c_unit.

References

Mathews Griner LA, Guha R, Shinn P, Young RM, Keller JM, et al. High-throughput combinatorial screening identifies drugs that cooperate with ibrutinib to kill activated B-cell-like diffuse large B-cell lymphoma cells. Proc Natl Acad Sci USA 2014; 111:2349-54.

`NCATS_10023_data` *A high-throughput 3 drug combination screening data*

Description

A 3-drug combination screening data on Malaria. It is downloaded from [NCATS Matrix](https://matrix.ncats.nih.gov/) project 2321 "Malaria TACT", assay 10023.

Format

A data frame with the following columns: BlockId, Drug1, Drug2, Drug3, Conc1, Conc2, Conc3, Response..

`Plot2DrugHeatmap` *Heatmap Plot for 2-drug Combination Dose-Response/Synergy Scores*

Description

This function will generate a plot for 2-drug combinations. The axes are the dosage at which drugs are tested. The values could be observed response, synergy scores or the reference effects calculated from different models.

Usage

```
Plot2DrugHeatmap(
  data,
  plot_block = 1,
  drugs = c(1, 2),
  plot_value = "response",
  statistic = NULL,
  summary_statistic = NULL,
  high_value_color = "#A90217",
  low_value_color = "#2166AC"
)
```

Arguments

`data`	A list object generated by function `ReshapeData`.
`plot_block`	A character/integer. It indicates the block ID for the block to visualize.
`drugs`	A vector of characters or integers with length of 2. It contains the index for two drugs to plot. For example, `c(1,2)` indicates to plot "drug1" and "drug2" in the input `data`.
`plot_value`	A character value. It indicates the value to be visualized. If the `data` is the direct output from ReshapeData, the values for this parameter are: • **response_origin** The original response value in input data. It might be % inhibition or % viability. • **response** The % inhibition after preprocess by function ReshapeData If the `data` is the output from CalculateSynergy, following values are also available: • **ZIP_ref, Bliss_ref, HSA_ref, Loewe_ref** The reference additive effects predicted by ZIP, Bliss, HSA or Loewe model, respectively. • **ZIP_synergy, Bliss_synergy, HSA_synergy, Loewe_synergy** The synergy score calculated by ZIP, Bliss, HSA or Loewe model, respectively. • **ZIP_fit** The response fitted by ZIP model.
`statistic`	A character or NULL. It indicates the statistics printed in the plot while there are replicates in input data. Available values are: • **sem** Standard error of mean; • **ci** 95% confidence interval. If it is `NULL`, no statistics will be printed.

summary_statistic
: A vector of characters or NULL. It indicates the summary statistics for all the plot_value in whole combination matrix. Available values are:
  - **mean** Median value for all the responses or synergy scores in the matrix;
  - **median** Median value for all the responses or synergy scores in the matrix;
  - **quantile_90** 90% quantile. User could change the number to print different sample quantile. For example quantile_50 equal to median.

  If it is NULL, no statistics will be printed.

high_value_color
: An R color value. It indicates the color for the high values.

low_value_color
: An R color value. It indicates the color for low values.

Value

A ggplot plot object.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
Plot2DrugHeatmap(data)
```

Plot2DrugSurface *3D Surface Plot for 2-drug Combination Dose-Response/Synergy Scores*

Description

This function will generate a surface plot for 2-drug combinations. The axes are the dosage for each drug. The values could be observed response, synergy scores or the reference effects calculated from different models.

Usage

```
Plot2DrugSurface(
  data,
  plot_block = 1,
  drugs = c(1, 2),
  plot_value = "response",
  summary_statistic = NULL,
  dynamic = FALSE,
  high_value_color = "#A90217",
  low_value_color = "#2166AC"
)
```

Arguments

`data`	A list object generated by function `ReshapeData`.
`plot_block`	A character/integer. It indicates the block ID for the block to visualize.
`drugs`	A vector of characters or integers with length of 2. It contains the index for two drugs to plot. For example, `c(1,2)` indicates to plot "drug1" and "drug2" in the input `data`.
`plot_value`	A character value. It indicates the score or response value to be visualized. If the `data` is the direct output from ReshapeData, the available values for this parameter are: • **response_origin** The original response value in input data. It might be % inhibition or % viability. • **response** The % inhibition after preprocess by function ReshapeData If the `data` is the output from CalculateSynergy, following values are also available: • **ZIP_ref, Bliss_ref, HSA_ref, Loewe_ref** The reference additive effects predicted by ZIP, Bliss, HSA or Loewe model, respectively. • **ZIP_synergy, Bliss_synergy, HSA_synergy, Loewe_synergy** The synergy score calculated by ZIP, Bliss, HSA or Loewe model, respectively. • **ZIP_fit** The response fitted by ZIP model.
`summary_statistic`	A vector of characters or NULL. It indicates the summary statistics for all the `plot_value` in whole combination matrix. Available values are: • **mean** Median value for all the responses or synergy scores in the matrix; • **median** Median value for all the responses or synergy scores in the matrix; • **quantile_90** 90% quantile. User could change the number to print different sample quantile. For example quantile_50 equal to median. If it is `NULL`, no statistics will be printed.
`dynamic`	A logical value. If it is `TRUE`, this function will use plot_ly to generate an interactive plot. If it is `FALSE`, this function will use wireframe to generate a static plot.
`high_value_color`	An R color value. It indicates the color for the high values.
`low_value_color`	An R color value. It indicates the color for low values.

Value

If `dynamic = FALSE`, this function will return a plot project recorded by recordPlot. If `dynamic = FALSE`, this function will return a plotly plot object.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
Plot2DrugSurface(data)
Plot2DrugSurface(data, dynamic = TRUE)
```

`PlotBarometer` *Plot Barometer for Responses at One Data Point*

Description

This function will plot a barometer. The needle will point at the response (% inhibition) at the data point specified by `plot_concs`. The reference additive effects calculated by different models will be marked on the bar if they are included in input `data`.

Usage

```
PlotBarometer(
  data,
  plot_block = 1,
  plot_concs,
  graduation_color = "#6C6C6C",
  needle_color = "#6C6C6C",
  needle_text_size = 5,
  needle_text_offset = 50,
  graduation_label_size = 4,
  graduation_label_offset = 0.7,
  annotation_label_size = 4,
  annotation_label_offset = 0.6,
  annotation_label_color = "#6C6C6C",
  font_family = "",
  color_bar_color = "#8f1b01",
  color_bar_outer = 9,
  color_bar_inner = 8,
  major_graduation_outer = 7.8,
  minor_graduation_inner = 7.5,
  major_graduation_inner = 7
)
```

Arguments

`data`	A list object generated by function `ReshapeData`.
`plot_block`	An integer or character. It indicates the block id for the combination matrix to visualize.
`plot_concs`	A vector of numeric values with the length same as the number of drugs in selected block. It contains the concentrations for "drug1", "drug2", ... The data point selected by these concentrations will be highlighted in the plot.
`graduation_color`	An R color value. It indicates the color of the graduation texts and ticks.
`needle_color`	An R color value. It indicates the color of the needle.

needle_text_size
: A numeric value. It indicates the size of the text near the center of barometer which showing the response value. The unit is "mm".

needle_text_offset
: A numeric value. It is used to set the position of the response values text. Smaller value means the text is closer to the center.

graduation_label_size
: A numeric value. It indicates the size of the graduation texts. The unit is "mm".

graduation_label_offset
: A numeric value. It is used to set the position of graduation texts. Smaller values means the graduation texts is closer to the ticks. It ranges from 0 to 1.

annotation_label_size
: A numeric value. It indicates the size of the labels for the additive effects at the out-most layer. The unit is "mm".

annotation_label_offset
: A numeric value. It is used to set the position of additive effect labels. Smaller values means the labels is closer to the color bar. It ranges from 0 to 1.

annotation_label_color
: An R color value. It indicates the color of the additive effects at the out-most layer.

font_family
: The font family for all the texts in the plot.

color_bar_color
: An R color value. It indicates the color of the largest value in the color bar.

color_bar_outer
: A numerical value. It indicates the proportion of the radius for the outer side of color bar comparing to the outermost edge for plotting area. It ranges from 0 to 1.

color_bar_inner
: A numerical value. It indicates the proportion of the radius for the inner side of color bar comparing to the outermost edge for plotting area. It ranges from 0 to 1.

major_graduation_outer
: A numerical value. It indicates the proportion of the radius for the outer side of graduation comparing to the outermost edge for plotting area. It ranges from 0 to 1.

minor_graduation_inner
: A numerical value. It indicates the proportion of the radius for the outer side of graduation comparing to the outermost edge for plotting area. It ranges from 0 to 1.

major_graduation_inner
: A numerical value. It indicates the proportion of the radius for the outer side of graduation comparing to the outermost edge for plotting area. It ranges from 0 to 1.

Value

A ggplot object.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

References

Tang J, Wennerberg K and Aittokallio T (2015) hrefhttps://www.frontiersin.org/articles/10.3389/fphar.2015.00181/fullW is synergy? The Saariselkä agreement revisited. Front. Pharmacol. 6:181. doi: 10.3389/fphar.2015.00181

Examples

```
data("NCATS_10023_data")
data <- ReshapeData(NCATS_10023_data)
data <- CalculateSynergy(data, method = c("ZIP", "HSA", "Bliss", "Loewe"))
p <- PlotBarometer(data, plot_block = 1, c(0.009375, 0.0125, 0.75))
p
```

PlotDoseResponse *Visualize the Drug Combination Dose-response Data*

Description

A function to visualize the drug combination dose-response data

Usage

```
PlotDoseResponse(
  data,
  block_ids = NULL,
  drugs = c(1, 2),
  adjusted = TRUE,
  statistic = NULL,
  summary_statistic = "mean",
  high_value_color = "#A90217",
  low_value_color = "#2166AC",
  point_color = "#C24B40",
  curve_color = "black",
  Emin = NA,
  Emax = NA,
  save_file = FALSE,
  file_type = "pdf",
  file_name = NULL,
  width = 12,
  height = 6
)
```

Arguments

data	A list object generated by function ReshapeData.
block_ids	A vector of characters/integers or NULL. It contains the block IDs for the blocks to visualize. By default, it is NULL so that the visualization of all the drug combinations in input data.
drugs	A vector of characters or integers with length of 2. It contains the index for two drugs to plot. For example, c(1,2) indicates to plot "drug1" and "drug2" in the input data.

adjusted
: A logical value. If it is FALSE, original response matrix will be plotted. If it is TRUE, adjusted response matrix will be plotted.

statistic
: A character or NULL. It indicates the statistics printed in the plot while there are replicates in input data. Available values are:

  - **sem** Standard error of mean;
  - **ci** 95

  If it is NULL, no statistics will be printed.

summary_statistic
: A vector of characters or NULL. It indicates the summary statistics printed in heatmap for all the plot_value in whole combination matrix. Available values are:

  - **mean** Median value for all the responses or synergy scores in the matrix;
  - **median** Median value for all the responses or synergy scores in the matrix;
  - **quantile_90** 90 print different sample quantile. For example quantile_50 equal to median.

  If it is NULL, no statistics will be printed.

high_value_color
: An R color value. It indicates the color for the high values.

low_value_color
: An R color value. It indicates the color for low values.

point_color
: An R color value. It indicates the color for points in dose response curve plots.

curve_color
: An R color value. It indicates the color for curves in dose response curve plots.

Emin
: A numeric or NA. the minimal effect of the drug used in the 4-parameter log-logistic function to fit the dose-response curve. If it is not NA, it is fixed the value assigned by the user. Default setting is NA.

Emax
: A numeric or NA. the maximal effect of the drug used in the 4-parameter log-logistic function to fit the dose-response curve. If it is not NA, it is fixed the value assigned by the user. Default setting is NA.

save_file
: A parameter to specify if the visualization results are saved as pdf files in current working directory or not. If it is FALSE, the results are returned as a list of the plots. It is FALSE by default.

file_type
: A character. It indicates the format of files you want to save as. Default is "pdf". Available values are "jpeg", "bmp", "png", "tiff", "pdf", "svg".

file_name
: A character vector. It indicates the file names, if user chose to save the plot to local directory.If it is not defined by user, a default name will be assigned.

width
: a numeric value. It indicates the width of saved file.

height
: a numeric value. It indicates the height of saved file.

Value

A list of plot objects recorded by recordPlot. The plot will be saved into a local file if save.file = TRUE. If save.file = FALSE, the plot will be printed in default graphic device.

Author(s)

- Liye He <liye.he@helsinki.fi>,
- Shuyu Zheng <shuyu.zheng@helsinki.fi>

Examples

```
## Not run:
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
plots <- PlotDoseResponse(data)

## End(Not run)
```

`PlotDoseResponseCurve` *Plot Dose Response Curve for Single Drug*

Description

This function will pot the dose response curve fitted by 4 parameters log-logistic curve.

Usage

```
PlotDoseResponseCurve(
  data,
  plot_block = 1,
  drug_index = 1,
  adjusted = TRUE,
  Emin = NA,
  Emax = NA,
  grid = expression(graphics::grid(col = "#DFDFDF", lty = 1)),
  point_color = "#C24B40",
  curve_color = "black",
 plot_setting = list(cex.lab = 1, cex.axis = 1, mgp = c(2, 0.5, 0), font.main = 2,
    font.lab = 3, cex.main = 14/12, bty = "l", lwd = 1.5)
)
```

Arguments

`data`	A list object generated by function `ReshapeData`.
`plot_block`	A character/integer. It indicates the block ID for the block to visualize.
`drug_index`	A character/integer. It indicates the index of the drug to plot. For example, 1 or "1" indicates to plot "drug1" in the input `data`.
`adjusted`	A logical value. If it is `FALSE`, original response value will be used to fit the curve. If it is `TRUE`, the response values adjusted by (adding noise and/or imputation) will be plotted.
`Emin`	A numeric or `NA`. the minimal effect of the drug used in the 4-parameter log-logistic function to fit the dose-response curve. If it is not NA, it is fixed the value assigned by the user. Default setting is `NA`.
`Emax`	A numeric or `NA`. the maximal effect of the drug used in the 4-parameter log-logistic function to fit the dose-response curve. If it is not NA, it is fixed the value assigned by the user. Default setting is `NA`.
`grid`	A expression for grid function of `NULL`. If it is `NULL`, no grids will be shown in the plot.
`point_color`	An R color value. It indicates the color for points in dose response curve plots.

curve_color	An R color value. It indicates the color for curves in dose response curve plots.
plot_setting	A list of graphical arguments. The arguments are passed to par function to modify the appearance of plots.

Value

A plot object recorded by recordPlot.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
PlotDoseResponseCurve(data, grid = NULL)
```

PlotMultiDrugBar *Bar Plot for Multi-drug Combination Dose-Response/Synergy Scores*

Description

This function will generate a group of bar plots for one drug combination block. Each panel (columns) visualize the concentrations for all the drugs and metrics specified by plot_values. Each row represents a data point in the combination data. The data point specified by highlight_row will be highlighted in different color.

Usage

```
PlotMultiDrugBar(
  data,
  plot_block,
  plot_value,
  sort_by = "conc1",
  highlight_row = NULL,
  pos_value_color = "#CC3311",
  neg_value_color = "#448BD4",
  highlight_pos_color = "#A90217",
  highlight_neg_color = "#2166AC"
)
```

Arguments

data	A list object generated by function ReshapeData.
plot_block	A character/integer. It indicates the block ID for the block to visualize.
plot_value	A vector of characters. It contains the name of one or more metrics to be visualized. If the data is the direct output from ReshapeData, the values for this parameter are:

- **response_origin** The original response value in input data. It might be % inhibition or % viability.
- **response** The % inhibition after preprocess by function ReshapeData

If the `data` is the output from CalculateSynergy, following values are also available:

- **ZIP_ref, Bliss_ref, HSA_ref, Loewe_ref** The reference additive effects predicted by ZIP, Bliss, HSA or Loewe model, respectively.
- **ZIP_synergy, Bliss_synergy, HSA_synergy, Loewe_synergy** The synergy score calculated by ZIP, Bliss, HSA or Loewe model, respectively.
- **ZIP_fit** The response fitted by ZIP model.

`sort_by` A character. It indicates by which metric the bars (data points) will be sorted. It could be one of the available values for `plot_value` or one of the concentration columns (e.g. "cocn1", "conc2", ...)

`highlight_row` A vector of numeric values with the length same as the number of drugs in selected block. It contains the concentrations for "drug1", "drug2", ... The data point selected by these concentrations will be highlighted in the plot.

`pos_value_color`
An R color value. It indicates the color for the positive values.

`neg_value_color`
An R color value. It indicates the color for the negative values.

`highlight_pos_color`
An R color value. It indicates the highlight color for the positive values.

`highlight_neg_color`
An R color value. It indicates the highlight color for the negative values.

Value

A ggplot object.

Author(s)

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- Jing Tang <jing.tang@helsinki.fi>

Examples

```
data("NCATS_10023_data")
data <- ReshapeData(NCATS_10023_data)
data <- CalculateSynergy(data, method = c("HSA"))
p <- PlotMultiDrugBar(data,
  plot_block = 1,
  plot_value = c("response", "HSA_ref", "HSA_synergy"),
  highlight_row = c(0, 0, 0),
  sort_by = "HSA_synergy"
)
p
```

`PlotMultiDrugSurface` *3D Plot for Multi-drug Combination Dose-Response/Synergy Scores*

Description

This function will generate a dynamic 3D plot response values or synergy scores for all the observed data points in a multi-drug combination block. The concentrations of drugs will be projected to 2 dimensions and plot along x an y axis. A surface for the selected `plot_value` and points for all the concentration combinations will be plotted.

Usage

```
PlotMultiDrugSurface(
  data,
  plot_block,
  plot_value,
  statistic = NULL,
  distance_method = "euclidean",
  high_value_color = "#A90217",
  low_value_color = "#2166AC",
  point_color = "#DDA137"
)
```

Arguments

`data`	A list object generated by function `ReshapeData`.
`plot_block`	A character/integer. It indicates the block ID for the block to visualize.
`plot_value`	A vector of characters. It contains the name of one or more metrics to be visualized. If the `data` is the direct output from ReshapeData, the values for this parameter are: • **response_origin** The original response value in input data. It might be % inhibition or % viability. • **response** The % inhibition after preprocess by function ReshapeData If the `data` is the output from CalculateSynergy, following values are also available: • **ZIP_ref, Bliss_ref, HSA_ref, Loewe_ref** The reference additive effects predicted by ZIP, Bliss, HSA or Loewe model, respectively. • **ZIP_synergy, Bliss_synergy, HSA_synergy, Loewe_synergy** The synergy score calculated by ZIP, Bliss, HSA or Loewe model, respectively. • **ZIP_fit** The response fitted by ZIP model.
`statistic`	A character or NULL. It indicates the statistics printed in the plot while there are replicates in input data. Available values are: • **sem** Standard error of mean; • **ci** 95% confidence interval. If it is `NULL`, no statistics will be printed.

distance_method
: The methods to calculate the distance between different data points from the concentration of drugs. The distance matrix is used for dimension reduction. This parameter is used to set the parameter method for vegdist. The default values is "euclidean".

high_value_color
: An R color value. It indicates the color for the high values.

low_value_color
: An R color value. It indicates the color for low values.

point_color
: An R color value. It indicates the color for data points.

Value

A plotly plot object.

Author(s)

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- Jing Tang <jing.tang@helsinki.fi>

Examples

```
data("NCATS_10023_data")
data <- ReshapeData(NCATS_10023_data)
p <- PlotMultiDrugSurface(
  data,
  plot_block = 1,
  plot_value = "response",
  statistic = NULL,
  distance_method = "euclidean"
)
p
```

PlotSensitiveSynergy *Plot Sensitive-Synergy Plot for All the Combinations in the Input Data*

Description

This function will generate a scatter plot for all the combinations in the input data. The x-axis is the Combination Sensitive score (CSS).

Usage

```
PlotSensitiveSynergy(
  data,
  plot_synergy,
  point_color = "#2D72AD",
  point_label_color = "#2D72AD"
)
```

Arguments

data	A list object generated by function ReshapeData.
plot_synergy	A character value. It indicates the synergy score for visualization. The available values are: "ZIP", "HSA", Bliss", "Leowe".
point_color	An R color value. It indicates the color for the points.
point_label_color	An R color value. It indicates the color for the label of data points.

Value

A ggplot object.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
data <- CalculateSynergy(data, method = c("ZIP"))
data <- CalculateSensitivity(data)
PlotSensitiveSynergy(data, plot_synergy = "ZIP")
```

PredictModelSpecify *Predict Response Value at Certain Drug Dose*

Description

PredictModelSpecify uses drm function to fit the dose response model and generate the predict response value at the given dose.

Usage

```
PredictModelSpecify(model, dose)
```

Arguments

model	An object for fitted model from drm::drc function L.4 or LL.4 model.
dose	A numeric value. It indicates the concentration of drug at which the response will be predicted.

Details

Note: Random number generator used in AddNoise with method = "random". If the analysis requires reproducibility, please set the random seed before calling this function.

Value

A numeric value. It is the response value of cell line to the drug at inputted dose.

Author(s)

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`PredictResponse` *Predict Response Value at Certain Drug Dose*

Description

`PredictResponse` uses `drm` function to fit the dose response model and generate the predict response value at the given dose.

Usage

```
PredictResponse(df, dose)
```

Arguments

`df`	A data frame. It contains two variable: • **dose** a serial of concentration of drug; • **response** the cell line response to each concentration of drug. It should be the inhibition rate according to negative control.
`dose`	A numeric value. It specifies the dose at which user want to predict the response of cell line to the drug.

Details

Note: Random number generator used in `AddNoise` with `method = "random"`. If the analysis requires for reproductiblity, plesase set the random seed before calling this function.

Value

A numeric value. It is the response value of cell line to the drug at inputted dose.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

ReshapeData *Pre-process the Response Data for Further Calculation and Plot*

Description

A function to transform the response data from data frame format to dose-response matrices. Several processes could be chose to add noise, impute missing values or correct base line to the dose-response matrix.

Usage

```
ReshapeData(
  data,
  impute = TRUE,
  impute_method = NULL,
  noise = TRUE,
  seed = NULL,
  data_type = "viability"
)
```

Arguments

data	drug combination response data in a data frame format
impute	a logical value. If it is TRUE, the NA values will be imputed by mice. Default is TRUE.
impute_method	a single string. It sets the method parameter in function mice to specify the imputation method. Please check the documentation of mice to find the available methods.
noise	a logical value. It indicates whether or not adding noise to to the "response" values in the matrix. Default is TRUE.
seed	a single value, interpreted as an integer, or NULL. It is the random seed for calculating the noise. Default setting is NULL
data_type	a parameter to specify the response data type which can be either "viability" or "inhibition".

Details

The input data must contain the following columns: (block_id/BlockId/PairIndex), (drug_row/DrugRow/Drug1), (drug_col/DrugCol/Drug2), (response/Response/inhibition/Inhibition), (conc_r/ConcRow/Conc1), (conc_c/ConcCol/Conc2), and (ConcUnit/conc_r_unit, conc_c_unit/ConcUnit1, ConcUnit2, ConcUnit3)

Value

a list of the following components:

- **drug_pairs** A data frame contains the name of all the tested drugs, concentration unit, block IDs and a logical column "replicate" to indicate whether there are replicates in the corresponding block.

- **response** A data frame contains the columns: "concX" concentrations for drugs from input data; "response_origin" response values from input data; "response" % inhibition value for downstream analysis.
- **response_statistics** A data frame. It will be output if there is block have replicated response values. It contains the block ID, the concentrations for all the tested drugs, and statistics for % inhibition values across replicates (including mean, standard deviation, standard error of mean and 95% confidence interval).

Author(s)

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- Jing Tang <jing.tang@helsinki.fi>

Examples

```
data("mathews_screening_data")
# set a random number seed for generating the noises
set.seed(1)
data <- ReshapeData(mathews_screening_data)
```

`ZIP` *Calculate Delta Synergy Score Based on ZIP Model*

Description

`ZIP` calculates the Delta score matrix from a dose-response matrix by using Zero Interaction Potency (ZIP) method.

Usage

```
ZIP(response, Emin = NA, Emax = NA, quiet = TRUE)
```

Arguments

`response`	A data frame. It must contain the columns: "conc1", "conc2", ..., for the concentration of the combined drugs and "response" for the observed %inhibition at certain combination.
`Emin`	The expected minimum response value in the 4 parameter log-logistic model.
`Emax`	The expected maximum response value in the 4 parameter log-logistic model.
`quiet`	A logical value. If it is `TRUE` then the warning message will not show during calculation.

Details

Zero Interaction Potency (ZIP) is a reference model for evaluating the conbimation effect of two drugs. It captures the effect of drug combination by comparing the change in the potency of the dose-response curves between individual drugs and their combinations.

The optional arguments `drug.col.model`, `drug.row.model` are designed for reuse the single drug dose response model fitting results, if it has been down before. Functions `FitDoseResponse` and `ExtractSingleDrug` could be used to calculate these arguments.

Value

A data frame containing the concentrations for drugs, reference effect, fitted response and synergy score estimated by ZIP model.

Author(s)

- Shuyu Zheng <shuyu.zheng@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>

References

- Yadav B, Wennerberg K, Aittokallio T, Tang J. (2015). Searching for Drug Synergy in Complex Dose-Response Landscape Using an Interaction Potency Model. Comput Struct Biotechnol J, 13:504– 513.

Examples

```
# No single drug fitted modle before
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
response <- data$response[data$response$block_id == 1,
                         c("conc1", "conc2", "response")]
ZIP_score <- ZIP(response)

## Not run:
# Parallel processing:
if (future::supportsMulticore()) {
  future::plan(future::multicore)
} else {
  future::plan(future::multisession)
}
ZIP(response)
# future::plan(future::sequential) # Turn off the multicore setting

## End(Not run)
```

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