Package 'synergyfinder'

October 16, 2019

Type Package

Title Calculate and Visualize Synergy Scores for Drug Combinations

Version 1.10.7

Date 2019-10-02

Author Liye He <liye.he@helsinki.fi>, Jing Tang <jing.tang@helsinki.fi>, Shuyu Zheng <shuyu.zheng@helsinki.fi>

Maintainer Shuyu Zheng <shuyu.zheng@helsinki.fi>

Depends R (>= 3.6.0)

Imports drc (>= 2.5-12), reshape2 (>= 1.4.1), SpatialExtremes (>= 2.0-2), ggplot2 (>= 2.1.0), grid (>= 3.2.4), lattice (>= 0.20-33), nleqslv(>= 3.0), stats (>= 3.3.0), graphics (>= 3.3.0), grDevices (>= 3.3.0)

Description Efficient implementations for all the popular synergy scoring models for drug combinations, including HSA, Loewe, Bliss and ZIP and visualization of the synergy scores as either a two-dimensional or a three-dimensional interaction surface over the dose matrix.

License Mozilla Public License 2.0

Encoding UTF-8

RoxygenNote 6.1.1

Suggests knitr, rmarkdown

VignetteBuilder knitr

biocViews Software, StatisticalMethod

NeedsCompilation no

git_url https://git.bioconductor.org/packages/synergyfinder

git_branch RELEASE_3_9

git_last_commit 4d5ec7f

git_last_commit_date 2019-10-02

Date/Publication 2019-10-15

R topics documented:

`AddNoise` *Add noise to response value*

Description

Function `AddNoise` calculates and add a noise to values in response matrix. The noises obey normal distribution ~N(0, 0.001) wich are generated by fucntion `rnorm`.

Usage

```
AddNoise(response.mat)
```

Arguments

`response.mat`	A matrix. It contains the response data for one drug combination.

Details

Note: If the analysis requires for reproductiblity, plesase set the random seed before calling this function.

Value

A matrix. It contains the response value added with noises.

Author(s)

Shuyu Zheng <shuyu.zheng@helsinki.fi>

Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
response.mat <- data$dose.response.mats[[1]]
set.seed(1)
adjusted.mat <- AddNoise(response.mat)
```

`Bliss` *Calculate Bliss synergy score*

Description

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

Usage

```
Bliss(response.mat)
```

Arguments

`response.mat`	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.

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".

Value

A matrix for synergy score calculated via reference model introduced by C. I. Bliss.

Author(s)

- Liye He <liye.he@helsinki.fi>
- Shuyu Zheng <shuyu.zheng@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)
Bliss.score <- Bliss(data$dose.response.mats[[1]])
```

`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) fron one dose-response **matrix**.

Usage

```
CalculateSynergy(data, method = "ZIP", adjusted = TRUE)
```

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".
`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.

Value

a list. It contains 4 elements:

- **dose.response.mats** The original input dose-response matrix
- **adjusted.response.mats** The dose response matrix adjusted by functions: `AddNoise`, `ImputeNA`, and `CorrectBaseLine`.
- **drug.pairs** a data frame contains the name of the row drug, the name of the column drug, concentration unit and block IDs.
- **scores** It contains the modified response value and 4 type of synergy scores of each drug dose response pair.
- **method** the method used to calculate the synergy scores.

Author(s)

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

Examples

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

CorrectBaseLine *Base line correction*

Description

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

Usage

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

Arguments

response.mat	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 to indicate using which method to do baseline correction. Available values ate: • **non** means no baseline corection. • **part** means only adjust the negative values in the matrix. • **all** means adjust all values in the matrix.

Value

A matrix which base line have been adjusted.

Author(s)

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

Examples

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

ExtractSingleDrug *Extract single drug response from matrix*

Description

ExtractSingleDrug extracts the dose-response values of single drug (drug added in column or row) from a drug combination dose-response matrix.

Usage

```
ExtractSingleDrug(response.mat, dim = "row")
```

Arguments

response.mat	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.
dim	A character. It should be either "col" or "row" to indicate which drug's dose-response value will be extracted.

Value

A data frame. It contains two variables:

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

Author(s)

Shuyu Zheng <shuyu.zheng@helsinki.fi>

Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
response.mat <- data$dose.response.mats[[1]]
drug.row <- ExtractSingleDrug(response.mat, dim = "row")
```

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>

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: • **conc** The concentration of drugs added in experiment. • **response** The response of cell lines to drug with different concentrations.
`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`.

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 imformation of fitted model.

Author(s)

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

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.mat)
```

Arguments

response.mat	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.

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 matrix for synergy score calculated via Highest Single Agent (HSA).

Author(s)

- Liye He <liye.he@helsinki.fi>
- Shuyu Zheng <shuyu.zheng@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)
HSA.score <- HSA(data$dose.response.mats[[1]])
```

ImputeNA *Impute missing value with nearest values*

Description

Function ImputeNA does missing value imputation by assigning the average of values in nearest 4 cells (top, bottom, left, right) to the NA cell. This pocess will be done repeadly until there is no missing values in the matrix.

Usage

```
ImputeNA(response.mat)
```

Arguments

response.mat	A matrix which has missing value.

Value

A matrix which is same as input matrix except the missing values are imputed.

Author(s)

Shuyu Zheng <shuyu.zheng@helsinki.fi>

Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
response.mat <- data$dose.response.mats[[1]]
# introduce some NA values into matrix
response.mat[3:4, 3:5] <- NA
adjusted.mat <- ImputeNA(response.mat)
```

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.mat, quiet = TRUE, drug.col.model = NULL,
  drug.row.model = NULL)
```

Arguments

response.mat	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.
quiet	A logical value. If it is TRUE then the warning message will not show during calculation.
drug.col.model	(optional) a character. It indicates the model used for fitting dose-response curve for drug added to columns.
drug.row.model	(optional) a character. It indicates the model type used for fitting dose-response curve for drug added to rows.

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 matrix for Synergy score calculated via reference model introduced by Loewe, S.

Author(s)

- Liye He <liye.he@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>
- Shuyu Zheng <shuyu.zheng@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

```
# No single drug fitted modle before
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
response.mat <- data$dose.response.mats[[1]]
Loewe.score <- Loewe(response.mat)

# Single drug dose response models have been fitted before.
drug.row.model <- FitDoseResponse(ExtractSingleDrug(response.mat, dim="row"))
drug.col.model <- FitDoseResponse(ExtractSingleDrug(response.mat, dim="col"))
Loewe.score <- Loewe(response.mat, drug.col.model=drug.col.model,
                     drug.row.model=drug.row.model)
```

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.

PlotDoseResponse *Visualize the drug combination dose-response data*

Description

A function to visualize the drug combination dose-response data

Usage

```
PlotDoseResponse(data, adjusted = TRUE, save.file = FALSE,
  pair.index = NULL, ...)
```

Arguments

data	a list object generated by function ReshapeData.
adjusted	a logical value. If it is FALSE, original response matrix will be plotted. If it is TRUE, adjusted response matrix will be plotted.
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.
pair.index	a parameter to specify which drug combination if there are many drug combinations in the data. By default, it is NULL so that the visualization of all the drug combinations in the data is returned.
...	further graphical parameters from plot for plotting the single drug dose-response curve. Use e.g., cex.lab to change the axis label size and cex.axis to change the tick size of axises.

Value

if save.file parameter is TRUE, pdf files are returned. Otherwise, the plots are only displayed.

Author(s)

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

Examples

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

`PlotSynergy` *Drug interaction landscape*

Description

A function to visualize the synergy scores for drug combinations as 2D or 3D interaction landscape over the dose-response matrix.

Usage

```
PlotSynergy(data, type = "2D", save.file = FALSE, len = 3,
  pair.index = NULL, legend.start = NULL, legend.end = NULL,
  row.range = NULL, col.range = NULL)
```

Arguments

`data`	a list object generated by function `CalculateSynergy`.
`type`	a parameter to specify the type of the interaction landscape, 2D, 3D or both. By default, 2D interaction landscape is returned.
`save.file`	a logical parameter to specify if the interaction landscape is saved as a pdf file in the current working directory or returned as an R object. By default, it is FALSE.
`len`	a parameter to specify how many values need to be predicted between two concentrations
`pair.index`	a parameter to specify which drug combination if there are many drug combinations in the data. By default, it is NULL so that the synergy score visualization of all the drug combinations in the data is returned.
`legend.start`	a parameter to specify the starting point of the legend. By defualt, it is NULL so the legend starting point is fixed by the data automatically.
`legend.end`	a parameter to specify the ending point of the legend. By defualt, it is NULL so the legend ending point is fixed by the data automatically.
`row.range`	a parameter to specify the starting and ending concentration of the drug on y-axis. Use e.g., c(1, 3) to specify that only from 1st to 3rd concentrations of the drug on y-axis are used. By default, it is NULl so all the concentrations are used.
`col.range`	a parameter to specify the starting and ending concentration of the drug on x-axis. Use e.g., c(1, 3) to specify that only from 1st to 3rd concentrations of the drug on x-axis are used. By default, it is NULl so all the concentrations are used.

Value

a pdf file or the interaction landscapes which are only displayed It depends on the `save.file` parameter.

Author(s)

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

Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
scores <- CalculateSynergy(data)
PlotSynergy(scores, "2D")
PlotSynergy(scores, "3D")
```

`ReshapeData` *Pre-processe the response data for furhter 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, noise = TRUE, correction = "non",
  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 `ImputeNA`. Default is `TRUE`.
`noise`	a logical value. It indicates whether or not adding noise to to the "response" values in the matrix. Default is `TRUE`.
`correction`	a character. This argument is extended from the argument `method` of `CorrectBaseLine` function. There are three available valuse: `non`, `part`, `all`. The default setting is `non`.
`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, drug_row, drug_col, response, conc_r, conc_c, conc_r_unit, conc_c_unit.

Value

a list of the following components:

- **dose.response.mats** a list of the dose-response matrices with %inhibition as the response data. Row names and column names are drug concentrations.
- **adjusted.response.mats** The dose response matrix adjusted. The processes are chosen by arguments `impute`, `noise`, and `correction`. If no process was chosen, the final result will not contain this result.
- **drug.pairs** a data frame contains the name of the row drug, the name of the column drug, concentration unit and block IDs.

Author(s)

- Liye He <liye.he@helsinki.fi>
- Shuyu Zheng <shuyu.zheng@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 Δ score matrix from a dose-response matrix by using Zero Interaction Potency (ZIP) method.

Usage

```
ZIP(response.mat, quiet = TRUE, drug.row.model = NULL,
  drug.col.model = NULL)
```

Arguments

`response.mat`	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.
`quiet`	A logical value. If it is `TRUE` then the warning message will not show during calculation.
`drug.row.model`	(optional) a character. It indicates the model type used for fitting dose-response curve for drug added to rows.
`drug.col.model`	(optional) a character. It indicates the model used for fitting dose-response curve for drug added to columns.

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 matrix of Δ score calculated via Zero Interaction Potency (ZIP) method.

Author(s)

- Liye He <liye.he@helsinki.fi>
- Jing Tang <jing.tang@helsinki.fi>
- Shuyu Zheng <shuyu.zheng@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.mat <- data$dose.response.mats[[1]]
ZIP.score <- ZIP(response.mat)

# Single drug dose response models have been fitted before.
drug.row.model <- FitDoseResponse(ExtractSingleDrug(response.mat, dim="row"))
drug.col.model <- FitDoseResponse(ExtractSingleDrug(response.mat, dim="col"))

ZIP.score <- ZIP(response.mat, drug.col.model=drug.col.model,
                 drug.row.model=drug.row.model)
```

Index