# Package 'synergyfinder'

February 18, 2019

**Type** Package

**Title** Calculate and Visualize Synergy Scores for Drug Combinations

**Version** 1.8.0

**Date** 2016-04-15

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**Imports** drc (>= 2.5-12), reshape2 (>= 1.4.1), SpatialExtremes (>= 2.0-2), ggplot2 (>= 2.1.0), gridBase (>= 0.4-7), grid (>= 3.2.4), lattice (>= 0.20-33), gplots (>= 3.0.0), 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.

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**LazyData** TRUE

**RoxygenNote** 6.0.1

**Suggests** knitr, rmarkdown

**VignetteBuilder** knitr

**biocViews** Software, Statistical Method

**NeedsCompilation** no

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

**git_branch** RELEASE_3_8

**git_last_commit** 488b89f

**git_last_commit_date** 2018-10-30

**Date/Publication** 2019-02-17

## R topics documented:

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`BaselineCorrectionSD` *Baseline correction for the dose-response matrix of drug combinations*

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## Description

A function to do baseline correction on the dose-response matrix for drug combinations with a weighted correction fator

## Usage

```
BaselineCorrectionSD(response.mat, Emin = NA, Emax = NA,
  nan.handle = c("LL4", "L4"))
```

## Arguments

| | |
|---|---|
| `response.mat` | a dose-response matrix with concentrations as row names and column names. |
| `Emin` | 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. Defaults to NA. |
| `Emax` | 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. Defaults to NA. |
| `nan.handle` | a parameter to specify if L.4 function or LL.4 function is used when fitting with LL.4 produces NaNs. |

## Value

A list of the original dose-response matrix without correction and the corrected dose-response matrix.

## Author(s)

Liye He <liye.he@helsinki.fi>, Jing Tang <jing.tang@helsinki.fi>

## Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
data <- BaselineCorrectionSD(data$dose.response.mats[[1]])
```

`Bliss` *Synergy score based on Bliss model*

## Description

A function to calculate synergy score based on Bliss model

## Usage

```
Bliss(response.mat, correction = TRUE, Emin = NA, Emax = NA,
  nan.handle = c("LL4", "L4"))
```

## Arguments

| | |
|---|---|
| `response.mat` | a dose-response matrix with concentrations as row names and column names |
| `correction` | a parameter to specify if baseline correction is used or not. Defaults to TRUE. |
| `Emin` | 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. Defaults to NA. It is used only when correction is required. |
| `Emax` | 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. Defaults to NA. It is used only when correction is required. |
| `nan.handle` | a parameter to specify if L.4 function or LL.4 function is used when fitting with LL.4 produces NaNs. |

## Value

A matrix of Bliss synergy scores for all the dose pairs for a drug combination. For a does pair with at least one zero concentration, 0 is used as the synergy score.

## Author(s)

Liye He <liye.he@helsinki.fi>

## References

Yadav B, Wennerberg K, Aittokallio T, Tang J. Searching for Drug Synergy in Complex Dose-Response Landscape Using an Interaction Potency Model. Computational and Structural Biotechnology Journal 2015; 13: 504-513.

## Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
delta.score <- Bliss(data$dose.response.mats[[1]])
```

`CalculateSynergy` *Calculate the synergy scores for drug combinations*

## Description

A function to calculate the synergy scores for drug combinations using different models.

## Usage

```
CalculateSynergy(data, method = "ZIP", correction = TRUE, Emin = 0,
  Emax = 100, nan.handle = c("LL4", "L4"))
```

## 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". |
| `correction` | a parameter to specify if baseline correction is used or not. Defaults to TRUE. |
| `Emin` | 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. Defaults to 0. For "Bliss", "HSA" and "Loewe" model, it is used only when correction is required. |
| `Emax` | 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. Defaults to 100. For "Bliss", "HSA" and "Loewe" model, it is used only when correction is required. |
| `nan.handle` | a parameter to specify if L.4 function or LL.4 function is used when fitting with LL.4 produces NaNs. |

## Value

a list of the following components:

| | |
|---|---|
| `dose.response.mats` | the same as the input data component. |
| `drug.pairs` | the same as the input data component. |
| `scores` | a list of matrixes of synergy scores. |
| `method` | the method used to calculate the synergy scores. |

## Author(s)

Liye He <liye.he@helsinki.fi>

## References

Yadav B, Wennerberg K, Aittokallio T, Tang J. Searching for Drug Synergy in Complex Dose-Response Landscape Using an Interaction Potency Model. Computational and Structural Biotechnology Journal 2015; 13: 504-513.

## Examples

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

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`FittingSingleDrug` *Fitting single drug dose-response curve*

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## Description

A function to fit single drug dose-response curve with observed response data

## Usage

```
FittingSingleDrug(response.mat, fixed = c(NA, NA, NA, NA),
  nan.handle = c("LL4", "L4"))
```

## Arguments

| | |
|---|---|
| `response.mat` | a matrix with first column as the drug concentrations and second column as the observed responses |
| `fixed` | a parameter to specify which parameters are fixed and at what value they are fixed. NAs for parameter that are not fixed. |
| `nan.handle` | a parameter to specify if L.4 function or LL.4 function is used when fitting with LL.4 produces NaNs. |

## Details

Single drug dose-response curve is fitted with a commonly used 4-paramter log-losistic (4PL) function.

## Value

Fitted responses and fitted models are returned.

## Author(s)

Liye He <liye.he@helsinki.fi>

## References

Seber, G. A. F. and Wild, C. J (1989) Nonlinear Regression, New York: Wiley \& Sons (p. 330).

## Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
single.drug.fitted <- FittingSingleDrug(data$dose.response.mats[[1]])
```

HSA *HSA synergy score based on highest single agent (HSA) model*

## Description

A function to calculate HSA synergy score based on HSA model

## Usage

```
HSA(response.mat, correction = TRUE, Emin = NA, Emax = NA,
  nan.handle = c("LL4", "L4"))
```

## Arguments

| | |
|---|---|
| response.mat | a dose-response matrix with concentrations as row names and column names |
| correction | a parameter to specify if baseline correction is used or not. Defaults to TRUE. |
| Emin | 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. Defaults to NA. It is used only when correction is required. |
| Emax | 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. Defaults to NA. It is used only when correction is required. |
| nan.handle | a parameter to specify if L.4 function or LL.4 function is used when fitting with LL.4 produces NaNs. |

## Value

A matrix of HSA synergy scores for all the dose pairs for a drug combination. For a does pair with at least one zero concentration, 0 is used as the synergy score.

## Author(s)

Liye He <liye.he@helsinki.fi>

## Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
delta.score <- HSA(data$dose.response.mats[[1]])
```

Loewe *Delta synergy score based on Loewe model*

## Description

A function to calculate Loewe synergy score based on Loewe model

## Usage

```
Loewe(response.mat, correction = TRUE, Emin = NA, Emax = NA,
  nan.handle = c("LL4", "L4"))
```

## Arguments

| | |
|---|---|
| response.mat | a dose-response matrix with concentrations as row names and column names |
| correction | a parameter to specify if baseline correction is used or not. Defaults to TRUE. |
| Emin | 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. Defaults to NA. It is used only when correction is required. |
| Emax | 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. Defaults to NA. It is used only when correction is required. |
| nan.handle | a parameter to specify if L.4 function or LL.4 function is used when fitting with LL.4 produces NaNs. |

## Value

A matrix of Loewe synergy scores for all the dose pairs for a drug combination. For a does pair with at least one zero concentration, 0 is used as the synergy score.

## Author(s)

Liye He <liye.he@helsinki.fi>

## References

Yadav B, Wennerberg K, Aittokallio T, Tang J. Searching for Drug Synergy in Complex Dose-Response Landscape Using an Interaction Potency Model. Computational and Structural Biotechnology Journal 2015; 13: 504-513.

## Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
delta.score <- Loewe(data$dose.response.mats[[1]])
```

`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: BlockID, DrugRow, DrugCol, Row, Col, Response, Replicate, ConcRow, ConcCol, ConcUnit

## 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, save.file = FALSE, pair.index = NULL, Emin = NA,
  Emax = NA, ...)
```

## Arguments

| | |
|---|---|
| `data` | a list object generated by function `ReshapeData`. |
| `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. |
| `Emin` | 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. Defaults to NA. |
| `Emax` | 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. Defaults to NA. |
| `...` | 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>

## 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 are only displayed depending on the save.file parameter.

## Author(s)

Liye He <liye.he@helsinki.fi>

## Examples

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

---

# ReshapeData *Transform the response data from the data frame format to dose-response matrixes*

---

## Description

A function to transform the response data from the data frame format to dose-response matrixes

## Usage

```
ReshapeData(data, data.type = "viability")
```

## Arguments

| | |
|---|---|
| data | drug combination response data in a data frame format |
| 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: BlockID, DrugRow, DrugCol, Row, Col, Response, ConcRow, ConcCol, ConcUnit

## Value

a list of the following components:

| | |
|---|---|
| dose.response.mats | a list of the dose-response matrixes with %inhibition as the response data. Row names and column names are drug concentrations. |
| 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>

## Examples

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

---

ZIP *Delta synergy score based on zero interaction potency (ZIP) model*

---

## Description

A function to calculate delta synergy score based on zero interaction potency (ZIP) model

## Usage

```
ZIP(response.mat, correction = TRUE, Emin = 0, Emax = 100,
  nan.handle = c("LL4", "L4"))
```

## Arguments

| | |
|---|---|
| response.mat | a dose-response matrix with concentrations as row names and column names |
| correction | a parameter to specify if the baseline correction is used or not. Defaults to TRUE. |
| Emin | 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. Defaults to 0. |
| Emax | 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. Defaults to 100. |
| nan.handle | a parameter to specify if L.4 function or LL.4 function is used when fitting with LL.4 produces NaNs. |

## Value

A matrix of delta scores for all the dose pairs for a drug combination. For a does pair with at least one zero concentration, 0 is used as the synergy score.

## Author(s)

Liye He <liye.he@helsinki.fi>, Jing Tang <jing.tang@helsinki.fi>

## References

Yadav B, Wennerberg K, Aittokallio T, Tang J. Searching for Drug Synergy in Complex Dose-Response Landscape Using an Interaction Potency Model. Computational and Structural Biotechnology Journal 2015; 13: 504-513.

## Examples

```
data("mathews_screening_data")
data <- ReshapeData(mathews_screening_data)
delta.score <- ZIP(data$dose.response.mats[[1]])
```

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