Package 'metaLINCS'

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Title Enrichment analysis of LINCS L1000 drug signatures using meta-level connectivity mapping

Version 0.9.0

Description 'metaLINCS' calculates and visualises correlation between experimental gene expression profiles with pertubation signatures from the LINCS L1000 project that has collected gene expression profiles for thousands of perturbagens at a variety of time points, doses, and cell lines.

License GPL (>= 3)

URL https://github.com/bigomics/metaLINCS

BugReports https://github.com/bigomics/metaLINCS/issues

Depends R (>= 3.5.0)

Imports corrplot,
fgsea,
gplots,
graphics,
Matrix,
qlcMatrix,
stats,
utils,
uwot

Suggests knitr,
rmarkdown,
testthat (>= 3.0.0)

VignetteBuilder knitr

Config/testthat/edition 3

Encoding UTF-8

LazyData true

LazyDataCompression bzip2

Roxygen list(markdown = TRUE)

RoxygenNote 7.1.2

R topics documented:

`computeConnectivityEnrichment` *Compute Connectivity Enrichment*

Description

Compute Connectivity Enrichment

Usage

```
computeConnectivityEnrichment(
  mFC,
  names = NULL,
  mDrugEnrich = metaLINCS::mDrugEnrich,
  nmin = 15,
  nprune = 250
)
```

Arguments

`mFC`	A matrix of differential gene expression fold-change of own experiment, the rows name of the matrix must be the genes names
`names`	Names in case mFC is a vector
`mDrugEnrich`	a large matrix represents the gene expression fold change in the presence of different perturbations, either various drugs concentrations or other genetic engineering techniques as gene-knock-in etc..
`nmin`	the minimum number of experiments in the drug set
`nprune`	takes only the (nprune) top matching drugs for each comparison to reduce the size of the matrix. default is 0 to take the full matrix

Value

list of drugs enrichment statistics and annotations

Examples

```
# from the data-sets provided as examples within the package load the .rda files
# DrugsAnnot, mDrugEnrich, mFC
res <- computeConnectivityEnrichment(mFC, mDrugEnrich, nmin=15, nprune = 250)
```

`computeMoaEnrichment` *Get the mechanism of action object*

Description

Get the mechanism of action object

Usage

```
computeMoaEnrichment(res, annot = metaLINCS::DrugsAnnot)
```

Arguments

`res`	is the output object from `computeConnectivityEnrichment()`
`annot`	is a drug annotation table with `moa` and `target` columns

Value

MoA Mechanism of Action object

Examples

```
# from the data-sets provided as examples within the package load the .rda files
# DrugsAnnot, mDrugEnrich, mFC
res <- computeConnectivityEnrichment(mFC)
moa <- computeMoaEnrichment(res)
```

`DrugsAnnot` *Annotation of a set of drugs*

Description

This data set is a matrix represents the drugs annotation that contains drugs' names, targets, mechanism of action , clinical phase, disease area, and indication.

Usage

```
data("DrugsAnnot")
```

Format

A data frame with 6125 observations on the following 6 variables.

`pert_iname` a character vector

`clinical_phase` a character vector

`moa` a character vector

`target` a character vector

`disease_area` a character vector

`indication` a character vector

Details

L1000 repurposing drugs . For research use only. Do not use the Repurposing Hub to make clinical treatment decisions. BROAD DOES NOT GUARANTEE OR WARRANT THE ACCURACY OF THE DATA WITHIN THE REPURPOSING HUB.

Source

"The Drug Repurposing Hub, Broad Institute" http://www.broadinstitute.org/repurposing

References

Corsello SM, et al. Nature Medicine. 2017 Apr 7;23(4):405-408. doi: 10.1038/nm.4306

Examples

```
head(metaLINCS::DrugsAnnot)
## str(DrugsAnnot)
```

---

mDrugEnrich *The drugs activity on 1001 genes*

Description

Large matrix representing the gene expression fold change of 1001 genes in the presence of 20220 different drugs concentrations and working time.

Usage

```
metaLINCS::mDrugEnrich
```

Format

A gene expression matrix (log2FC) with 1001 rows and 20220 columns corresponding to 1001 genes and 20220 drug perturbation experiments.

Details

The LINCS L1000 project has collected gene expression profiles for thousands of perturbagens at a variety of time points, doses, and cell lines. A full list of the chemical and genetic perturbations used can be found on the CLUE website along with their descriptions.

Source

https://lincsproject.org/LINCS/tools/workflows/find-the-best-place-to-obtain-the-lincs-l1000-data

References

Duan Q et al. LINCS Canvas Browser: interactive web app to query, browse and interrogate LINCS L1000 gene expression signatures. Nucleic Acids Res. 2014 Jul;42 (Web Server issue):W449-60.

Examples

```
head(metaLINCS::mDrugEnrich)
## maybe str(mDrugEnrich) ; plot(mDrugEnrich) ...
```

`metaLINCS` *metaLINCS: is a new method to visualise correlations between experimental gene expression profiles and drug connectivity map profiles*

Description

The metaLINCS package provides three categories of important functions: computePeturbEnrichment, computeComboEnrichment and several plotting functions

metaLINCS functions

computeConnectivityEnrichment: Compute Connectivity Enrichment based on database and annotation provided as input parameter USAGE: computeConnectivityEnrichment(mFC = mFC, mDrugEnrich = mDrugEnrich, nprune = 250, contrast = NULL)

plotActivationMap: Plot drug Activity Map. USAGE: plotActivationMap(res, nterms = 50, nfc = 20)

computeMoaEnrichment: Compute mechanism-of-action enrichment USAGE: computeMoaEnrichment(dsea)

plotDrugConnectivity: Plot Drug Connectivity USAGE: plotDrugConnectivity(dsea)

plotMOA: Plot mechanism of action bargraph USAGE: plotMOA(dsea, ntop = 16)

mFC *Fold change matrix of differential gene expresion from RNA-seq data of multiple myeloma*

Description

Example signature data as query input for the analysis. This is the matrix that you probably want to replace. There are 6 contrasts:glucocorticoid sensitive vs glucocorticoid resistant ("Resistant.vs.Sensitive"); Treated with Withaferin-A vs untreated ("WithaferinA.vs.Untreated"); untreated glucocorticoid resistant cells vs untreated glucocorticoid sensitive cells ("UTR.vs.UTS"); Treated with Withaferin-A glucocorticoid resistant cells vs Treated with Withaferin-A glucocorticoid sensitive cells ("WAR.vs.WAS"); Treated Resistant vs Untreated Resistant ("WAR.vs.UTR"); Treated sensitive vs Untreated sensitive ("WAS.vs.UTS")

Usage

```
dim(mFC)
head(mFC)
```

Format

A data frame with 5332 observations on the following 6 variables.

`Resistant.vs.Sensitive` a numeric vector

`WithaferinA.vs.Untreated` a numeric vector

`UTR.vs.UTS` a numeric vector

`WAR.vs.WAS` a numeric vector

`WAR.vs.UTR` a numeric vector

`WAS.vs.UTS` a numeric vector

Details

The RNAseq data from (Logie et al 2021) study. They compared the therapeutic efficacy of the phytochemical kinase inhibitor withaferin A with the clinically approved BTK inhibitor ibrutinib to target hyperactivated tyrosine kinase signaling in glucocorticoid-resistant multiple myeloma cells. The results demonstrate that withaferin-A induced cell death of glucocorticoid-resistant MM1R cells involves covalent cysteine targeting of multiple Hinge-6 domain type tyrosine kinases of the kinase cysteinome classification, including BTK.

Source

GEO accession number GSE162475

References

Logie E, Chirumamilla CS, Perez-Novo C, Shaw P et al. Covalent Cysteine Targeting of Bruton's Tyrosine Kinase (BTK) Family by Withaferin-A Reduces Survival of Glucocorticoid-Resistant Multiple Myeloma MM1 Cell. Cancers (Basel) 2021 Mar 31;13(7). PMID: 33807411

Examples

```
data(mFC)
## maybe str(mFC) ; plot(mFC) ...
```

---

plotActivationMap *Plot drug Activity Map*

Description

Plot drug Activity Map

Usage

```
plotActivationMap(res, nterms = 60, nfc = 20, rot = FALSE)
```

Arguments

nterms	integer
nfc	integer
dsea	drugs set enrichment analysis object as output of getActiveDSEA
drugs	a list of drugs enrichment stats and annotations the output of computePeturbEnrichment()
method	the computation methods of Enrichment, either using GSEA algorithm or the rank correlation.
contr	is a character string represent the two compared conditions(contrast) as it is provided from the fold-change matrix

Value

plot of drug activity map

Examples

```
# from the data-sets provided as examples within the package load the .rda files
#DrugsAnnot, mDrugEnrich, mFC
res <- computeConnectivityEnrichment(mFC)
plotActivationMap(res, nterms = 50, nfc=20, rot=TRUE)
```

plotDrugConnectivity *Plot Drug Connectivity*

Description

Plot Drug Connectivity

Usage

```
plotDrugConnectivity(res, contr, drugs = NULL, nplots = 25)
```

Arguments

res	is a result object from the output of computeConnectivityEnrichment()
contr	is a index of the selected contrast
drugs	is a vector of selected drugs to show
nplots	is the number of plots to show

Value

a plot of drug connectivity

Examples

```
# from the data-sets provided as examples within the package load the .rda files
# DrugsAnnot, mDrugEnrich, mFC
res <- computeConnectivityEnrichment(mFC)
plotDrugConnectivity(res, contr=1, nplots=16)
```

plotMOA *Plot mechanism of action*

Description

Plot mechanism of action

Usage

```
plotMOA(moa, contr = NULL, type = c("drugClass", "targetGene"), ntop = 20)
```

Arguments

ntop	the number of the top enteries (genes or drug), ntop = 16 as a default value
dsea	is dsea object which is the output of the function getActiveDSEA()

Value

plot of mechanism of action

Examples

```
# from the data-sets provided as examples within the package load the .rda files
# DrugsAnnot, mDrugEnrich, mFC
res <- computeConnectivityEnrichment(mFC)
moa <- computeMoaEnrichment(res)
plotMOA(moa, contr=1, type="drugClass", ntop=25)
```

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selectResult *Select result*

Description

Select result

Usage

```
selectResult(res, contr)
```

Arguments

res	is the result from computeConnectivityEnrichment()
contr	contrast selection

Value

selected result for selected contrast

Examples

```
res1 <- selectResult(res,1)
```

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