Package 'signatureSearch'

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Title Environment for Gene Expression Searching Combined with Functional Enrichment Analysis

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Description This package implements algorithms and data structures for performing gene expression signature (GES) searches, and subsequently interpreting the results functionally with specialized enrichment methods.

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Author Yuzhu Duan [cre, aut], Thomas Girke [aut]

Maintainer Yuzhu Duan <yduan004@ucr.edu>

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Environment for Gene Expression Signature Searching Combined with Functional Enrichment Analysis

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Description

Welcome to the signatureSearch package! This package implements algorithms and data structures for performing gene expression signature (GES) searches, and subsequently interpreting the results functionally with specialized enrichment methods. These utilities are useful for studying the effects of genetic, chemical and environmental perturbations on biological systems. Specifically, in drug discovery they can be used for identifying novel modes of action (MOA) of bioactive compounds from reference databases such as LINCS containing the genome-wide GESs from tens of thousands of drug and genetic perturbations (Subramanian et al. 2017)

A typical GES search (GESS) workflow can be divided into two major steps. First, GESS methods are used to identify perturbagens such as drugs that induce GESs similar to a query GES of interest. The queries can be drug-, disease- or phenotype-related GESs. Since the MOAs of most drugs in the corresponding reference databases are known, the resulting associations are useful to gain insights into pharmacological and/or disease mechanisms, and to develop novel drug repurposing approaches.

Second, specialized functional enrichment analysis (FEA) methods using annotations systems, such as Gene Ontologies (GO), pathways or Disease Ontologies (DO), have been developed and implemented in this package to efficiently interpret GESS results. The latter are usually composed of lists of perturbagens (e.g. drugs) ranked by the similarity metric of the corresponding GESS method.

Finally, network resconstruction functionalities are integrated for visualizing the final results, e.g. in form of drug-target networks.

Details

The GESS methods include `CMAP`, `LINCS`, `gCMAP`, `Fisher` and `Cor`. For detailed description, please see help files of each method. Most methods can be easily paralleled for multiple query signatures.

GESS results are lists of perturbagens (here drugs) ranked by their signature similarity to a query signature of interest. Interpreting these search results with respect to the cellular networks and pathways affected by the top ranking drugs is difficult. To overcome this challenge, the knowledge of the target proteins of the top ranking drugs can be used to perform functional enrichment analysis (FEA) based on community annotation systems, such as Gene Ontologies (GO), pathways (e.g. KEGG, Reactome), drug MOAs or Pfam domains. For this, the ranked drug sets are converted into target gene/protein sets to perform Target Set Enrichment Analysis (TSEA) based on a chosen

annotation system. Alternatively, the functional annotation categories of the targets can be assigned to the drugs directly to perform Drug Set Enrichment Analysis (DSEA). Although TSEA and DSEA are related, their enrichment results can be distinct. This is mainly due to duplicated targets present in the test sets of the TSEA methods, whereas the drugs in the test sets of DSEA are usually unique. Additional reasons include differences in the universe sizes used for TSEA and DSEA.

Importantly, the duplications in the test sets of the TSEA are due to the fact that many drugs share the same target proteins. Standard enrichment methods would eliminate these duplications since they assume uniqueness in the test sets. Removing duplications in TSEA would be inappropriate since it would erase one of the most important pieces of information of this approach. To solve this problem, we have developed and implemented in this package weighting methods (`dup_hyperG`, `mGSEA` and `meanAbs`) for duplicated targets, where the weighting is proportional to the frequency of the targets in the test set.

Instead of translating ranked lists of drugs into target sets, as for TSEA, the functional annotation categories of the targets can be assigned to the drugs directly to perform DSEA instead. Since the drug lists from GESS results are usually unique, this strategy overcomes the duplication problem of the TSEA approach. This way classical enrichment methods, such as GSEA or tests based on the hypergeometric distribution, can be readily applied without major modifications to the underlying statistical methods. As explained above, TSEA and DSEA performed with the same enrichment statistics are not expected to generate identical results. Rather they often complement each other's strengths and weaknesses.

To perform TSEA and DSEA, drug-target annotations are essential. They can be obtained from several sources, including DrugBank, ChEMBL, STITCH, and the Touchstone dataset from the LINCS project (https://clue.io/). Most drug-target annotations provide UniProt identifiers for the target proteins. They can be mapped, if necessary via their encoding genes, to the chosen functional annotation categories, such as GO or KEGG. To minimize bias in TSEA or DSEA, often caused by promiscuous binders, it can be beneficial to remove drugs or targets that bind to large numbers of distinct proteins or drugs, respectively.

Note, most FEA tests involving proteins in their test sets are performed on the gene level in `signatureSearch`. This way one can avoid additional duplications due to many-to-one relationships among proteins and their encoding gents. For this, the corresponding functions in signatureSearch will usually translate target protein sets into their encoding gene sets using identifier mapping resources from R/Bioconductor such as the `org.Hs.eg.db` annotation package. Because of this as well as simplicity, the text in the vignette and help files of this package will refer to the targets of drugs almost interchangeably as proteins or genes, even though the former are the direct targets and the latter only the indirect targets of drugs.

Terminology

The term Gene Expression Signatures (GESs) can refer to at least four different situations of preprocessed gene expression data: (1) normalized gene expression intensity values (or counts for RNA-Seq); (2) log2 fold changes (LFC), z-scores or p-values obtained from analysis routines of differentially expressed genes (DEGs); (3) rank transformed versions of the expression values obtained under (1) and (2); and (4) gene identifier sets extracted from the top and lowest ranks under (3), such as n top up/down regulated DEGs.

Author(s)

- Yuzhu Duan (yduan004@ucr.edu)
- Thomas Girke (thomas.girke@ucr.edu)

References

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Subramanian, Aravind, Pablo Tamayo, Vamsi K Mootha, Sayan Mukherjee, Benjamin L Ebert, Michael A Gillette, Amanda Paulovich, et al. 2005. Gene Set Enrichment Analysis: A Knowledge-Based Approach for Interpreting Genome-Wide Expression Profiles. Proc. Natl. Acad. Sci. U. S. A. 102 (43): 15545-50. http://dx.doi.org/10.1073/pnas.0506580102

See Also

Methods for GESS:

- gess_cmap, gess_lincs, gess_gcmap gess_fisher, gess_cor

Methods for FEA:

- TSEA methods: tsea_dup_hyperG, tsea_mGSEA, tsea_mabs
- DSEA methods: dsea_hyperG, dsea_GSEA

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append2H5 *Append Matrix to HDF5 File*

Description

Function to write matrix data to an existing HDF5 file. If the file contains already matrix data then both need to have the same number of rows. The append will be column-wise.

Usage

```
append2H5(x, h5file, name = "assay", printstatus = TRUE)
```

Arguments

x	matrix object to write to an HDF5 file. If the HDF5 file is not empty, the exported matrix data needs to have the same number rows as the matrix stored in the HDF5 file, and will be appended column-wise to the existing one.
h5file	character(1), path to existing HDF5 file that can be empty or contain matrix data
name	The name of the dataset in the HDF5 file.
printstatus	logical, whether to print status

Value

HDF5 file storing exported matrix

Examples

```
mat <- matrix(1:12, nrow=3)
rownames(mat) <- paste0("r", 1:3); colnames(mat) <- paste0("c", 1:4)
tmp_file <- tempfile(fileext=".h5")
create_empty_h5(tmp_file)
append2H5(mat, tmp_file)
rhdf5::h5ls(tmp_file)
```

`build_custom_db` *build_custom_db*

Description

Build custom reference signature database for GESS methods

Usage

```
build_custom_db(df, h5file)
```

Arguments

`df`	data.frame or matrix containing genome-wide or close to genome-wide GESs of perturbation experiments. The row name slots are expected to contain gene or transcript IDs (e.g. Entrez ids), while the column names are expected to have this structure: '(drug)__(cell)__(factor)', e.g. 'sirolimus__MCF7__trt_cp'. This format is flexible enough to encode most perturbation types of biological samples. For example, gene knockdown or over expression treatments can be specified by assigning the ID of the affected gene to 'drug', and 'ko' or 'ov' to 'factor', respectively. An example for a knockdown treatment would look like this: 'P53__MCF7__ko'.
`h5file`	character vector of length 1 containing the path to the destination hdf5 file

Details

The perturbation-based gene expression data, here provided as data.frame or matrix, will be stored in an HDF5 file. The latter can be used as reference database by compatible GESS methods of signatureSearch. Various types of pre-processed gene expression data can be used here, such as normalized gene expression intensities (or counts for RNA-Seq); log2 fold changes (LFC), Z-scores or p-values obtained from analysis routines of differentially expressed genes (DEGs).

Value

HDF5 file

Examples

```
# Generate a data.frame
df <- data.frame(sirolimus__MCF7__trt_cp=rnorm(1000),
                 vorinostat__SKB__trt_cp=rnorm(1000))
data(targetList)
rownames(df) = names(targetList)
h5file = tempfile(fileext=".h5")
```

```
build_custom_db(df, h5file)
library(SummarizedExperiment)
tmp <- SummarizedExperiment(HDF5Array::HDF5Array(h5file, name="assay"))
rownames(tmp) <- HDF5Array::HDF5Array(h5file, name="rownames")
colnames(tmp) <- HDF5Array::HDF5Array(h5file, name="colnames")
```

`calcGseaStatBatchCpp` *Calculates GSEA statistic valus for all gene sets in 'selectedStats' list.*

Description

Takes *O(n + mKlogK)* time, where n is the number of genes, m is the number of gene sets, and k is the mean gene set size.

Usage

```
calcGseaStatBatchCpp(stats, selectedGenes, geneRanks)
```

Arguments

`stats`	Numeric vector of gene-level statistics sorted in decreasing order
`selectedGenes`	List of integer vector with integer gene IDs (from 1 to n)
`geneRanks`	Integer vector of gene ranks

Value

Numeric vector of GSEA statistics of the same length as 'selectedGenes' list

---

`cell_info` *Cell Type Information*

Description

It contains cell type (tumor or normal), primary site and subtype annotations of cells in LINCS database.

Usage

```
cell_info
```

Format

A `tibble` object with 30 rows and 4 columns.

Examples

```
# Load object
data(cell_info)
head(cell_info)
```

chembl_moa_list *MOA to Gene Mappings*

Description

It is a list containing MOA terms to gene Entrez id mappings from ChEMBL database

Usage

```
chembl_moa_list
```

Format

An object of class `list` of length 1099.

Examples

```
# Load object
data(chembl_moa_list)
head(chembl_moa_list)
```

clue_moa_list *MOA to Drug Name Mappings*

Description

It is a list containing MOA terms to drug name mappings obtained from Touchstone database at CLUE website (https://clue.io/)

Usage

```
clue_moa_list
```

Format

An object of class `list` of length 345.

Examples

```
# Load object
data(clue_moa_list)
head(clue_moa_list)
```

comp_fea_res *Plot for Comparing Ranking Results of FEA Methods*

Description

Dot plot for comparing the top ranking functional categories from different functional enrichment analysis (FEA) results. The functional categories are plotted in the order defined by their mean rank across the corresponding FEA results.

Usage

```
comp_fea_res(
  table_list,
  rank_stat = "pvalue",
  Nshow = 20,
  Nchar = 50,
  scien = FALSE,
  ...
)
```

Arguments

table_list	a named list of tibbles extracted from feaResult objects, e.g. generated with different FEA methods.
rank_stat	character(1), column name of the enrichment statisic used for ranking the functional categories, e.g. 'pvalue' or 'p.adjust'. Note, the chosen column name needs to be present in each tibble of 'table_list'.
Nshow	integer defining the number of the top functional categories to display in the plot after re-ranking them across FEA methods
Nchar	integer defining number of characters displayed (exceeded characters were replaced by '...') in the description of each item
scien	TRUE or FALSE, indicating whether the rank_stat is rounded to the scientific format with 3 digits
...	Other arguments passed on to geom_point

Details

The 'comp_fea_res' function computes the mean rank for each functional category across different FEA result instances and then re-ranks them based on that. Since the functional categories are not always present in all enrichment results, the mean rank of a functional category is corrected by an adjustment factor that is the number of enrichment result methods used divided by the number of occurences of a functional category. For instance, if a functional category is only present in the result of one method, its mean rank will be increased accordingly. Subsequently, the re-ranked functional categories are compared in a dot plot where the colors represent the values of the enrichment statistic chosen under the rank_stat argument.

Value

ggplot2 graphics object

Examples

```
method1 <- data.frame("ID"=paste0("GO:", 1:5),
                      "Description"=paste0("desc", 1:5),
                      "pvalue"=c(0.0001, 0.002, 0.004, 0.01, 0.05))
method2 <- data.frame("ID"=paste0("GO:", c(1,3,5,4,6)),
                      "Description"=paste0("desc", c(1,3,5,4,6)),
                      "pvalue"=c(0.0003, 0.0007, 0.003, 0.006, 0.04))
table_list <- list("method1" = method1, "method2"=method2)
comp_fea_res(table_list, rank_stat="pvalue", Nshow=20)
```

`create_empty_h5` *Create Empty HDF5 File*

Description

This function can be used to create an empty HDF5 file where the user defines the file path and compression level. The empty HDF5 file has under its root group three data slots named 'assay', 'colnames' and 'rownames' for storing a `numeric matrix` along with its column names (`character`) and row names (`character`), respectively.

Usage

```
create_empty_h5(h5file, delete_existing = FALSE, level = 6)
```

Arguments

`h5file`	character(1), path to the HDF5 file to be created
`delete_existing`	logical, whether to delete an existing HDF5 file with identical path
`level`	The compression level used, here given as integer value between 0 (no compression) and 9 (highest and slowest compression).

Value

empty HDF5 file

Examples

```
tmp_file <- tempfile(fileext=".h5")
create_empty_h5(tmp_file, level=6)
```

dim *Dimensions of an Object*

Description

Retrieve dimension of the result table in the gessResult, and feaResult objects

Usage

```
## S4 method for signature 'gessResult'
dim(x)

## S4 method for signature 'feaResult'
dim(x)
```

Arguments

x	an R object

Value

dim attribute of the result table

Examples

```
gr <- gessResult(result=dplyr::tibble(pert=letters[seq_len(10)],
                                      val=seq_len(10)),
                 query=list(up=c("g1","g2"), down=c("g3","g4")),
                 gess_method="LINCS", refdb="path/to/lincs/db")
dim(gr)
fr <- feaResult(result=dplyr::tibble(id=letters[seq_len(10)],
                                     val=seq_len(10)),
                organism="human", ontology="MF", drugs=c("d1", "d2"),
                targets=c("t1","t2"))
dim(fr)
```

drugs *Extract/Assign Drug Names for feaResult*

Description

The drugs generic extracts or assign the drug names/ids stored in the drugs slot of an feaResult object.

Usage

```
drugs(x)

drugs(x) <- value

## S4 method for signature 'feaResult'
drugs(x)

## S4 replacement method for signature 'feaResult'
drugs(x) <- value
```

Arguments

x	feaResult object
value	A character vector of drug names

Value

character vector

An feaResult object with new assigned drugs slot

Examples

```
fr <- feaResult(result=dplyr::tibble(id=letters[seq_len(10)],
                                     val=seq_len(10)),
                organism="human", ontology="MF", drugs=c("d1", "d2"),
                targets=c("t1","t2"))
drugs(fr)
drugs(fr) <- c("d3", "d4")
```

---

drugs10 *Drug Names Used in Examples*

Description

A character vector containing the names of the top 10 drugs in the GESS result from the gess_lincs method used in the vignette of signatureSearch.

Usage

```
drugs10
```

Format

An object of class character of length 10.

Examples

```
# Load drugs object
data(drugs10)
drugs10
```

drug_cell_ranks *Summary ranking statistics across cell types*

Description

The drug_cell_ranks function returns from a gessResult object the ranks of the perturbagens (e.g. drugs) for each cell type. The results are arranged in separate columns of a data.frame. Additionally, it includes in the last columns summary ranking statistics across all cell types, such as min, mean and max values.

Usage

```
drug_cell_ranks(gessResult)
```

Arguments

gessResult	'gessResult' object

Value

data.frame

Examples

```
gr <- gessResult(result=dplyr::tibble(pert=c("p1", "p1", "p2", "p3"),
                                      cell=c("MCF7", "SKB", "MCF7", "SKB"),
                                      type=rep("trt_cp", 4),
                                      NCS=c(1.2, 1, 0.9, 0.6)),
                 query=list(up="a", down="b"),
                 gess_method="LINCS", refdb="path/to/refdb")
df <- drug_cell_ranks(gr)
```

dsea_GSEA *Drug Set Enrichment Analysis (DSEA) with GSEA Algorithm*

Description

The dsea_GSEA function performs Drug Set Enrichment Analysis (DSEA) with the GSEA algorithm from Subramanian et al. (2005). In case of DSEA, drug identifiers combined with their ranking scores of an upstream GESS method are used, such as the NCS values from the LINCS method. To use drug instead of gene labels for GSEA, the former are mapped to functional categories, including GO or KEGG, based on drug-target interaction annotations provided by databases such as DrugBank, ChEMBL, CLUE or STITCH.

Usage

```
dsea_GSEA(
  drugList,
  type = "GO",
  ont = "BP",
  exponent = 1,
  nPerm = 1000,
  minGSSize = 10,
  maxGSSize = 500,
  pvalueCutoff = 0.05,
  pAdjustMethod = "BH"
)
```

Arguments

drugList	named numeric vector, where the names represent drug labels and the numeric component scores. This can be all drugs of a GESS result that are ranked by GESS scores, such as NCSs of the LINCS method. Note, drugs with scores of zero are ignored by this method.
type	one of 'GO', 'KEGG' or 'MOA'
ont	character(1). If type is 'GO', assign ont (ontology) one of 'BP','MF', 'CC' or 'ALL'. If type is 'KEGG', ont is ignored.
exponent	integer value used as exponent in GSEA algorithm. It defines the weight of the items in the item set *S*. Note, in DSEA the items are drug labels, while it is gene labels in the original GSEA.
nPerm	integer defining the number of permutation iterations for calculating p-values
minGSSize	integer, annotation categories with less than minGSize drugs annotated will be ignored by enrichment test. If type is 'MOA', it may be beneficial to set 'minGSSize' to lower values (e.g. 2) than for other functional annotation systems. This is because certain MOA categories contain only 2 drugs.
maxGSSize	integer, annotation categories with more drugs annotated than maxGSize will be ignored by enrichment test.
pvalueCutoff	double, p-value cutoff to return only enrichment results for drugs meeting a user definable confidence threshold
pAdjustMethod	p-value adjustment method, one of 'holm', 'hochberg', 'hommel', 'bonferroni', 'BH', 'BY', 'fdr'

Details

The DSEA results stored in the feaResult object can be returned with the result method in tabular format, here tibble. The columns of this tibble are described in the help of the tsea_mGSEA function.

Value

feaResult object containing the enrichment results of functional categories (e.g. GO terms or KEGG pathways) ranked by the corresponding enrichment statistic.

References

GSEA algorithm: Subramanian, A., Tamayo, P., Mootha, V. K., Mukherjee, S., Ebert, B. L., Gillette, M. A., Mesirov, J. P. (2005). Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. Proceedings of the National Academy of Sciences of the United States of America, 102(43), 15545-15550. URL: https://doi.org/10.1073/pnas.0506580102

See Also

feaResult, fea, GO_DATA_drug

Examples

```
data(drugs10)
dl <- c(rev(seq(0.1, 0.5, by=0.05)), 0)
names(dl)=drugs10
## KEGG annotation system
#gsea_k_res <- dsea_GSEA(drugList=dl, type="KEGG", exponent=1, nPerm=100,
#                        pvalueCutoff=0.5, minGSSize=2)
#result(gsea_k_res)
```

---

dsea_hyperG *Drug Set Enrichment Analysis (DSEA) with Hypergeometric Test*

Description

The dsea_hyperG function performs Drug Set Enrichment Analysis (DSEA) based on the hypergeomtric distribution. In case of DSEA, the identifiers of the top ranking drugs from a GESS result table are used. To use drug instead of gene labels for this test, the former are mapped to functional categories, including GO, KEGG or Mode of Action (MOA) categories, based on drug-target interaction annotations provided by databases such as DrugBank, ChEMBL, CLUE or STITCH. Currently, the MOA annotation used by this function are from the CLUE website (https://clue.io).

Usage

```
dsea_hyperG(
  drugs,
  type = "GO",
  ont = "BP",
  pvalueCutoff = 0.05,
  pAdjustMethod = "BH",
  qvalueCutoff = 0.2,
  minGSSize = 10,
  maxGSSize = 500
)
```

Arguments

drugs	character vector, query drug identifier set used for functional enrichment testing. This can be the top ranking drugs from a GESS result.
type	one of 'GO', 'KEGG' or 'MOA'

ont	character(1). If type is 'GO', assign ont (ontology) one of 'BP','MF', 'CC' or 'ALL'. If type is 'KEGG', ont is ignored.
pvalueCutoff	double, p-value cutoff to return only enrichment results for drugs meeting a user definable confidence threshold
pAdjustMethod	p-value adjustment method, one of 'holm', 'hochberg', 'hommel', 'bonferroni', 'BH', 'BY', 'fdr'
qvalueCutoff	double, qvalue cutoff, similar to pvalueCutoff
minGSSize	integer, annotation categories with less than minGSize drugs annotated will be ignored by enrichment test. If type is 'MOA', it may be beneficial to set 'minGSSize' to lower values (e.g. 2) than for other functional annotation systems. This is because certain MOA categories contain only 2 drugs.
maxGSSize	integer, annotation categories with more drugs annotated than maxGSize will be ignored by enrichment test.

Details

Compared to the related Target Set Enrichment Analysis (TSEA; see help tsea_dup_hyperG or tsea_mGSEA), the DSEA approach has the advantage that the drugs in the query test sets are usually unique allowing to use them without major modifications to the underlying statistical method(s).

The DSEA results stored in the feaResult object can be returned with the result method in tabular format, here tibble. The columns of this tibble are described in the help of the tsea_dup_hyperG function.

Value

feaResult object containing the enrichment results of functional categories (e.g. GO terms or KEGG pathways) ranked by the corresponding enrichment statistic.

See Also

feaResult, fea, GO_DATA_drug

Examples

```
data(drugs10)
## GO annotation system
# hyperG_res <- dsea_hyperG(drugs = drugs10, type = "GO", ont="MF")
# result(hyperG_res)
## KEGG annotation system
#hyperG_k_res <- dsea_hyperG(drugs = drugs10, type = "KEGG",
#                            pvalueCutoff = 1, qvalueCutoff = 1,
#                            minGSSize = 10, maxGSSize = 500)
#result(hyperG_k_res)
```

dtnetplot *Drug-Target Network Visualization*

Description

Functional modules of GESS and FEA results can be rendered as interactive drug-target networks using the `dtnetplot` function form `signatureSearch`. For this, a character vector of drug names along with an identifier of a chosen functional category are passed on to the drugs and set arguments, respectively. The resulting plot depicts the corresponding drug-target interaction network. Its interactive features allow the user to zoom in and out of the network, and to select network components in the drop-down menu located in the upper left corner of the plot.

Usage

```
dtnetplot(drugs, set, ont = NULL, desc = NULL, verbose = FALSE, ...)
```

Arguments

`drugs`	A character vector of drug names
`set`	character(1) GO term ID or KEGG pathway ID. Alternatively, a character vector of gene SYMBOLs can be assigned.
`ont`	if 'set' is a GO term ID, 'ont' is the corresponding ontology that GO term belongs to. One of 'BP', 'MF' or 'CC'
`desc`	character(1), description of the chosen functional category or target set
`verbose`	TRUE or FALSE, whether to print messages
`...`	Other arguments passed on to `visNetwork` function.

Value

visNetwork plot

Examples

```
data(drugs10)
dtnetplot(drugs=drugs10,
    set=c("HDAC1", "HDAC2", "HDAC3", "HDAC11", "FOX2"),
    desc="NAD-dependent histone deacetylase activity (H3-K14 specific)")
```

enrichGO2 *GO Term Enrichment with Hypergeometric Test*

Description

Given a vector of gene identifiers, this function returns GO term enrichment results based on a hypergeometric test with duplication support in the test set.

Usage

```
enrichGO2(
  gene,
  OrgDb,
  keytype = "SYMBOL",
  ont = "MF",
  pvalueCutoff = 0.05,
  pAdjustMethod = "BH",
  universe,
  qvalueCutoff = 0.2,
  minGSSize = 5,
  maxGSSize = 500,
  pool = FALSE
)
```

Arguments

gene	a vector of gene SYMBOL ids (here the test set)
OrgDb	OrgDb
keytype	Gene ID type of test set
ont	One of "MF", "BP", "CC" or "ALL"
pvalueCutoff	pvalue cutoff
pAdjustMethod	one of "holm", "hochberg", "hommel", "bonferroni", "BH", "BY", "fdr", "none"
universe	background genes
qvalueCutoff	qvalue cutoff
minGSSize	minimum size of each gene set in annotation system
maxGSSize	maximum size of each gene set in annotation system
pool	If ont='ALL', whether 3 GO ontologies should be combined

Value

A feaResult instance.

See Also

feaResult-class

Examples

```
# The method supports duplicated elements in 'gene',
# which should be gene SYMBOL ids for GO term enrichment.
gene <- c(rep("HDAC1",4), rep("HDAC3",2), "SOX8", "KLK14")
# data(targetList)
# ego <- enrichGO2(gene = gene, OrgDb="org.Hs.eg.db", ont="MF",
#                  universe=names(targetList))
```

enrichKEGG2 *KEGG Pathway Enrichment with Hypergeometric Test*

Description

Given a vector of gene identifiers, this function returns KEGG pathway enrichment results based on a hypergeometric test with duplication support in the test set.

Usage

```
enrichKEGG2(
  gene,
  organism = "hsa",
  keyType = "kegg",
  pvalueCutoff = 0.05,
  pAdjustMethod = "BH",
  universe,
  minGSSize = 5,
  maxGSSize = 500,
  qvalueCutoff = 0.2
)
```

Arguments

gene	a vector of entrez gene ids (here the test set)
organism	supported organism are listed in http://www.genome.jp/kegg/catalog/org_list.html
keyType	one of "kegg", 'ncbi-geneid', 'ncbi-proteinid' or 'uniprot'
pvalueCutoff	pvalue cutoff
pAdjustMethod	one of "holm", "hochberg", "hommel", "bonferroni", "BH", "BY", "fdr", "none"
universe	background genes
minGSSize	minimal size of genes annotated by ontology term for testing.
maxGSSize	maximal size of genes annotated for testing
qvalueCutoff	qvalue cutoff

Value

A feaResult instance.

Examples

```
# Method supports duplicated elements in "gene", which should be entrez ids
gene <- c(rep("4312",4), rep("8318",2), "991", "10874")
#data(geneList, package="DOSE")
#kk <- enrichKEGG2(gene = gene, universe=names(geneList))
#head(kk)
```

enrichMOA *MOA Category Enrichment with Hypergeometric Test*

Description

Given a vector of gene identifiers, this function returns MOA category enrichment results based on a hypergeometric test with duplication support in the test set. The universe for the test is set to the unique genes encoding the target proteins present in the MOA annotation system from the ChEMBL database.

Usage

```
enrichMOA(gene, pvalueCutoff = 0.05, pAdjustMethod = "BH", qvalueCutoff = 0.2)
```

Arguments

gene	a vector of entrez gene ids (here the test set)
pvalueCutoff	pvalue cutoff
pAdjustMethod	one of "holm", "hochberg", "hommel", "bonferroni", "BH", "BY", "fdr", "none"
qvalueCutoff	qvalue cutoff

Value

A feaResult instance.

See Also

feaResult-class

Examples

```
data(geneList, package="DOSE")
emoa <- enrichMOA(gene = names(geneList)[seq(3)])
head(emoa)
```

feaResult *Constructor for* feaResult-class

Description

This is a helper function to construct a feaResult object. For detail description, please consult the help file of the feaResult-class.

Usage

```
feaResult(
  result,
  organism = "UNKNOWN",
  ontology = "UNKNOWN",
  drugs = "UNKNOWN",
  targets = "UNKNOWN"
)
```

Arguments

result	tibble object containing the FEA results
organism	character(1), organism information of the annotation system
ontology	character(1), ontology type of the GO annotation system. If the annotation system is KEGG, it will be 'KEGG'
drugs	character vector, input drug names used for the enrichment test
targets	character vector, gene labels of the gene/protein targets for the drugs

Value

feaResult object

Examples

```
fr <- feaResult(result=dplyr::tibble(id=letters[seq_len(10)],
                                     val=seq_len(10)),
                organism="human", ontology="MF", drugs=c("d1", "d2"),
                targets=c("t1","t2"))
```

---

feaResult-class *feaResult object*

Description

The feaResult object stores Functional Enrichment Analysis (FEA) results generated by the corresponding Target and Drug Set Enrichment methods (here TSEA and DSEA) defined by signatureSearch. This includes slots for the FEA results in tabular format, the organism information, and the type of functional annotation used (e.g. GO or KEGG). It also includes the drug information used for the FEA, as well as the corresponding target protein information.

Slots

result tibble object, this tabular result contains the enriched functional categories (e.g. GO terms or KEGG pathways) ranked by the corresponding enrichment statistic. The result table can be extracted via the result accessor function.

Description of the columns that are shared among the result tables generated by the different FEA methods:

- ont: in case of GO, one of BP, MF, CC, or ALL
- ID: GO or KEGG IDs
- Description: description of functional category
- p.adjust: p-value adjusted for multiple hypothesis testing based on method specified under pAdjustMethod argument
- qvalue: q value calculated with R's qvalue function to control FDR
- itemID: IDs of items (genes for TSEA, drugs for DSEA) overlapping among test and annotation sets.
- setSize: size of the functional category

organism organism information of the annotation system. Currently, limited to 'human', since drug-target annotations are too sparse for other organisms.

`ontology` ontology type of the GO annotation system. If the annotation system is KEGG, it will be 'KEGG'

`drugs` input drug names used for the enrichment test

`targets` target information for the query drugs obtained from the chosen drug-target annotation source.

`GCT object` *An S4 Class to Represent a GCT Object*

Description

The GCT class serves to represent annotated matrices. The `mat` slot contains the numeric matrix data and the `rdesc` and `cdesc` slots contain data frames with annotations about the rows and columns, respectively

Slots

`mat` a numeric matrix

`rid` a character vector of row ids

`cid` a character vector of column ids

`rdesc` a `data.frame` of row descriptors

`rdesc` a `data.frame` of column descriptors

`src` a character indicating the source (usually file path) of the data

See Also

`parse_gctx`

`gctx2h5` *Convert GCTX to HDF5 File*

Description

Read matrix-like data from large gctx file in chunks and write result back to an HDF5 file.

Usage

```
gctx2h5(gctx, cid, new_cid = cid, h5file, by_ncol = 5000, overwrite = TRUE)
```

Arguments

`gctx`	character(1), path to gctx file from LINCS
`cid`	character or integer vector referencing the columns of the matrix to include
`new_cid`	character vector of the same length as cid, assigning new column names to matrix
`h5file`	character(1), path of the hdf5 destination file
`by_ncol`	number of columns to import in each iteration to limit memory usage
`overwrite`	TRUE or FALSE, whether to overwrite or to append to existing 'h5file'

Value

HDF5 file

Examples

```
gctx <- system.file("extdata", "test_sample_n2x12328.gctx",
        package="signatureSearch")
h5file <- tempfile(fileext=".h5")
gctx2h5(gctx, cid=1:2,
        new_cid=c('sirolimus__MCF7__trt_cp', 'vorinostat__SKB__trt_cp'),
        h5file=h5file, overwrite=TRUE)
```

---

gessResult *Constructor for* gessResult-class

Description

This is a helper function to construct a gessResult object. For detail description, please consult the help file of the gessResult-class.

Usage

```
gessResult(result, query, gess_method, refdb)
```

Arguments

result	tibble object containing the GESS results
query	list or a matrix, query signature
gess_method	character(1), name of the GESS method
refdb	character(1), path to the reference database

Value

gessResult object

Examples

```
gr <- gessResult(result=dplyr::tibble(pert=letters[seq_len(10)],
                                      val=seq_len(10)),
                 query=list(up=c("g1","g2"), down=c("g3","g4")),
                 gess_method="LINCS", refdb="path/to/lincs/db")
```

gessResult-class *gessResult object*

Description

The gessResult object organizes Gene Expression Signature Search (GESS) results. This includes the main tabular result of a GESS, its query signature, the name of the chosen GESS method and the path to the reference database.

Slots

result tibble object containing the search results for each perturbagen (e.g. drugs) in the reference database ranked by their signature similarity to the query. The result table can be extracted via the result accessor function.

Descriptions of the columns common among the tabular results of the individual GESS methods are given below. Note, the columns specific to each GESS method are described in their help files.

- pert: character, name of perturbagen (e.g. drug) in the reference database
- cell: character, acronym of cell type
- type: character, perturbation type. In the CMAP/LINCS databases provided by signatureSearchData, the perturbation types are currently treatments with drug-like compounds (trt_cp). If required, users can build custom signature database with other types of perturbagens (e.g., gene knockdown or over-expression events) with the provided build_custom_db function.
- trend: character, up or down when the reference signature is positively or negatively connected with the query signature, respectively.
- N_upset: integer, number of genes in the query up set
- N_downset: integer, number of genes in the query down set
- t_gn_sym: character, symbol of the gene encoding the corresponding drug target protein

query query signature

gess_method name of the GESS method

refdb path to the reference database

gess_cmap *CMAP Search Method*

Description

Implements the original Gene Expression Signature Search (GESS) from Lamb et al (2006) known as Connectivity Map (CMap). The method uses as query the two label sets of the most up- and down-regulated genes from a genome-wide expression experiment, while the reference database is composed of rank transformed expression profiles (e.g. ranks of LFC or z-scores).

Usage

```
gess_cmap(qSig, chunk_size = 5000, ref_trts = NULL, workers = 1)
```

Arguments

qSig	qSig object defining the query signature including the GESS method (should be 'CMAP') and the path to the reference database. For details see help of qSig and qSig-class.
chunk_size	number of database entries to process per iteration to limit memory usage of search.
ref_trts	character vector. If users want to search against a subset of the reference database, they could set ref_trts as a character vector representing column names (treatments) of the subsetted refdb.
workers	integer(1) number of workers for searching the reference database parallelly, default is 1.

Details

Lamb et al. (2006) introduced the gene expression-based search method known as Connectivity Map (CMap) where a GES database is searched with a query GES for similar entries. Specifically, this GESS method uses as query the two label sets of the most up- and down-regulated genes from a genome-wide expression experiment, while the reference database is composed of rank transformed expression profiles (e.g.ranks of LFC or z-scores). The actual GESS algorithm is based on a vectorized rank difference calculation. The resulting Connectivity Score expresses to what degree the query up/down gene sets are enriched on the top and bottom of the database entries, respectively. The search results are a list of perturbagens such as drugs that induce similar or opposing GESs as the query. Similar GESs suggest similar physiological effects of the corresponding perturbagens. Although several variants of the CMAP algorithm are available in other software packages including Bioconductor, the implementation provided by signatureSearch follows the original description of the authors as closely as possible.

Value

gessResult object, the result table contains the search results for each perturbagen in the reference database ranked by their signature similarity to the query.

Column description

Descriptions of the columns specific to the CMAP method are given below. Note, the additional columns, those that are common among the GESS methods, are described in the help file of the gessResult object.

- raw_score: bi-directional enrichment score (Kolmogorov-Smirnov statistic) of up and down set in the query siganture
- scaled_score: raw_score scaled to valules from 1 to -1 by dividing the positive and negative scores with the maxmum positive score and the absolute value of the minimum negative score, respectively.

References

For detailed description of the CMap method, please refer to: Lamb, J., Crawford, E. D., Peck, D., Modell, J. W., Blat, I. C., Wrobel, M. J., Golub, T. R. (2006). The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. Science, 313 (5795), 1929-1935. URL: https://doi.org/10.1126/science.1132939

See Also

qSig, gessResult, gess

Examples

```
db_path <- system.file("extdata", "sample_db.h5",
                       package = "signatureSearch")
# qsig_cmap <- qSig(query = list(
#                   upset=c("230", "5357", "2015", "2542", "1759"),
#                   downset=c("22864", "9338", "54793", "10384", "27000")),
#                   gess_method = "CMAP", refdb = db_path)
# cmap <- gess_cmap(qSig=qsig_cmap, chunk_size=5000)
# result(cmap)
```

---

gess_cor *Correlation-based Search Method*

Description

Correlation-based similarity metrics, such as Spearman or Pearson coefficients, can be used as Gene Expression Signature Search (GESS) methods. As non-set-based methods, they require quantitative gene expression values for both the query and the database entries, such as normalized intensities or read counts from microarrays or RNA-Seq experiments, respectively.

Usage

```
gess_cor(
  qSig,
  method = "spearman",
  chunk_size = 5000,
  ref_trts = NULL,
  workers = 1
)
```

Arguments

qSig	qSig object defining the query signature including the GESS method (should be 'Cor') and the path to the reference database. For details see help of qSig and qSig-class.
method	One of 'spearman' (default), 'kendall', or 'pearson', indicating which correlation coefficient to use.
chunk_size	number of database entries to process per iteration to limit memory usage of search.
ref_trts	character vector. If users want to search against a subset of the reference database, they could set ref_trts as a character vector representing column names (treatments) of the subsetted refdb.
workers	integer(1) number of workers for searching the reference database parallelly, default is 1.

Details

For correlation searches to work, it is important that both the query and reference database contain the same type of gene identifiers. The expected data structure of the query is a matrix with a single numeric column and the gene labels (e.g. Entrez Gene IDs) in the row name slot. For convenience, the correlation-based searches can either be performed with the full set of genes represented in the database or a subset of them. The latter can be useful to focus the computation for the correlation values on certain genes of interest such as a DEG set or the genes in a pathway of interest. For comparing the performance of different GESS methods, it can also be advantageous to subset the genes used for a correlation-based search to same set used in a set-based search, such as the up/down DEGs used in a LINCS GESS. This way the search results of correlation- and set-based methods can be more comparable because both are provided with equivalent information content.

Value

`gessResult` object, the result table contains the search results for each perturbagen in the reference database ranked by their signature similarity to the query.

Column description

Descriptions of the columns specific to the corrleation-based GESS method are given below. Note, the additional columns, those that are common among the GESS methods, are described in the help file of the `gessResult` object.

- cor_score: Correlation coefficient based on the method defined in the `gess_cor` function.

See Also

`qSig`, `gessResult`, `gess`

Examples

```
db_path <- system.file("extdata", "sample_db.h5",
                       package = "signatureSearch")
# library(SummarizedExperiment); library(HDF5Array)
# sample_db <- SummarizedExperiment(HDF5Array(db_path, name="assay"))
# rownames(sample_db) <- HDF5Array(db_path, name="rownames")
# colnames(sample_db) <- HDF5Array(db_path, name="colnames")
## get "vorinostat__SKB__trt_cp" signature drawn from sample databass
# query_mat <- as.matrix(assay(sample_db[,"vorinostat__SKB__trt_cp"]))
# qsig_sp <- qSig(query = query_mat, gess_method = "Cor", refdb = db_path)
# sp <- gess_cor(qSig=qsig_sp, method="spearman")
# result(sp)
```

---

gess_fisher *Fisher Search Method*

Description

In its iterative form, Fisher's exact test (Upton, 1992) can be used as Gene Expression Signature (GES) Search to scan GES databases for entries that are similar to a query GES.

Usage

```
gess_fisher(
  qSig,
  higher = NULL,
  lower = NULL,
  padj = NULL,
  chunk_size = 5000,
  ref_trts = NULL,
  workers = 1
)
```

Arguments

qSig	qSig object defining the query signature including the GESS method (should be 'Fisher') and the path to the reference database. For details see help of qSig and qSig-class.
higher	The 'upper' threshold. If not 'NULL', genes with a score larger than or equal to 'higher' will be included in the gene set with sign +1. At least one of 'lower' and 'higher' must be specified. higher argument need to be set as 1 if the refdb in qSig is path to the HDF5 file that were converted from the gmt file.
lower	The lower threshold. If not 'NULL', genes with a score smaller than or equal 'lower' will be included in the gene set with sign -1. At least one of 'lower' and 'higher' must be specified. lower argument need to be set as NULL if the refdb in qSig is path to the HDF5 file that were converted from the gmt file.
padj	numeric(1), cutoff of adjusted p-value or false discovery rate (FDR) of defining DEGs that is less than or equal to 'padj'. The 'padj' argument is valid only if the reference HDF5 file contains the p-value matrix stored in the dataset named as 'padj'.
chunk_size	number of database entries to process per iteration to limit memory usage of search.
ref_trts	character vector. If users want to search against a subset of the reference database, they could set ref_trts as a character vector representing column names (treatments) of the subsetted refdb.
workers	integer(1) number of workers for searching the reference database parallelly, default is 1.

Details

When using the Fisher's exact test (Upton, 1992) as GES Search (GESS) method, both the query and the database are composed of gene label sets, such as DEG sets.

Value

gessResult object, the result table contains the search results for each perturbagen in the reference database ranked by their signature similarity to the query.

Column description

Descriptions of the columns specific to the Fisher method are given below. Note, the additional columns, those that are common among the GESS methods, are described in the help file of the `gessResult` object.

- pval: p-value of the Fisher's exact test.
- padj: p-value adjusted for multiple hypothesis testing using R's p.adjust function with the Benjamini & Hochberg (BH) method.
- effect: z-score based on the standard normal distribution.
- LOR: Log Odds Ratio.
- nSet: number of genes in the GES in the reference database (gene sets) after setting the higher and lower cutoff.
- nFound: number of genes in the GESs of the reference database (gene sets) that are also present in the query GES.
- signed: whether gene sets in the reference database have signs, representing up and down regulated genes when computing scores.

References

Graham J. G. Upton. 1992. Fisher's Exact Test. J. R. Stat. Soc. Ser. A Stat. Soc. 155 (3). [Wiley, Royal Statistical Society]: 395-402. URL: http://www.jstor.org/stable/2982890

See Also

`qSig`, `gessResult`, `gess`

Examples

```
db_path <- system.file("extdata", "sample_db.h5",
                       package = "signatureSearch")
# library(SummarizedExperiment); library(HDF5Array)
# sample_db <- SummarizedExperiment(HDF5Array(db_path, name="assay"))
# rownames(sample_db) <- HDF5Array(db_path, name="rownames")
# colnames(sample_db) <- HDF5Array(db_path, name="colnames")
## get "vorinostat__SKB__trt_cp" signature drawn from sample databass
# query_mat <- as.matrix(assay(sample_db[,"vorinostat__SKB__trt_cp"]))
# qsig_fisher <- qSig(query=query_mat, gess_method="Fisher", refdb=db_path)
# fisher <- gess_fisher(qSig=qsig_fisher, higher=1, lower=-1)
# result(fisher)
```

---

gess_gcmap *gCMAP Search Method*

Description

Adapts the Gene Expression Signature Search (GESS) method from the gCMAP package (Sandmann et al. 2014) to make it compatible with the database containers and methods defined by `signatureSearch`. The specific GESS method, called gCMAP, uses as query a rank transformed GES and the reference database is composed of the labels of up and down regulated DEG sets.

Usage

```
gess_gcmap(
  qSig,
  higher = NULL,
  lower = NULL,
  padj = NULL,
  chunk_size = 5000,
  ref_trts = NULL,
  workers = 1
)
```

Arguments

qSig	qSig object defining the query signature including the GESS method (should be 'gCMAP') and the path to the reference database. For details see help of qSig and qSig-class.
higher	The 'upper' threshold. If not 'NULL', genes with a score larger than or equal to 'higher' will be included in the gene set with sign +1. At least one of 'lower' and 'higher' must be specified. higher argument need to be set as 1 if the refdb in qSig is path to the HDF5 file that were converted from the gmt file.
lower	The lower threshold. If not 'NULL', genes with a score smaller than or equal 'lower' will be included in the gene set with sign -1. At least one of 'lower' and 'higher' must be specified. lower argument need to be set as NULL if the refdb in qSig is path to the HDF5 file that were converted from the gmt file.
padj	numeric(1), cutoff of adjusted p-value or false discovery rate (FDR) of defining DEGs that is less than or equal to 'padj'. The 'padj' argument is valid only if the reference HDF5 file contains the p-value matrix stored in the dataset named as 'padj'.
chunk_size	number of database entries to process per iteration to limit memory usage of search.
ref_trts	character vector. If users want to search against a subset of the reference database, they could set ref_trts as a character vector representing column names (treatments) of the subsetted refdb.
workers	integer(1) number of workers for searching the reference database parallelly, default is 1.

Details

The Bioconductor gCMAP (Sandmann et al. 2014) package provides access to a related but not identical implementation of the original CMAP algorithm proposed by Lamb et al. (2006). It uses as query a rank transformed GES and the reference database is composed of the labels of up and down regulated DEG sets. This is the opposite situation of the orignal CMAP method from Lamb et al (2006), where the query is composed of the labels of up and down regulated DEGs and the database contains rank transformed GESs.

Value

gessResult object, the result table contains the search results for each perturbagen in the reference database ranked by their signature similarity to the query.

Column description

Descriptions of the columns specific to the gCMAP method are given below. Note, the additional columns, those that are common among the GESS methods, are described in the help file of the `gessResult` object.

- effect: Scaled bi-directional enrichment score corresponding to the scaled_score under the CMAP result.
- nSet: Number of genes in the reference gene sets after applying the higher and lower cutoff.
- nFound: Number of genes in the reference gene sets that are present in the query signature.
- signed: Whether the gene sets in the reference database have signs, e.g. representing up and down regulated genes when computing scores.

References

Lamb, J., Crawford, E. D., Peck, D., Modell, J. W., Blat, I. C., Wrobel, M. J., Golub, T. R. (2006). The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. Science, 313 (5795), 1929-1935. URL: https://doi.org/10.1126/science.1132939

Sandmann, T., Kummerfeld, S. K., Gentleman, R., & Bourgon, R. (2014). gCMAP: user-friendly connectivity mapping with R. Bioinformatics , 30 (1), 127-128. URL: https://doi.org/10.1093/bioinformatics/btt592

See Also

`qSig`, `gessResult`, `gess`

Examples

```
db_path <- system.file("extdata", "sample_db.h5",
                       package = "signatureSearch")
# library(SummarizedExperiment); library(HDF5Array)
# sample_db <- SummarizedExperiment(HDF5Array(db_path, name="assay"))
# rownames(sample_db) <- HDF5Array(db_path, name="rownames")
# colnames(sample_db) <- HDF5Array(db_path, name="colnames")
## get "vorinostat__SKB__trt_cp" signature drawn from sample databass
# query_mat <- as.matrix(assay(sample_db[,"vorinostat__SKB__trt_cp"]))
# qsig_gcmap <- qSig(query=query_mat, gess_method="gCMAP", refdb=db_path)
# gcmap <- gess_gcmap(qsig_gcmap, higher=1, lower=-1)
# result(gcmap)
```

---

gess_lincs *LINCS Search Method*

Description

Implements the Gene Expression Signature Search (GESS) from Subramanian et al, 2017, here referred to as LINCS. The method uses as query the two label sets of the most up- and down-regulated genes from a genome-wide expression experiment, while the reference database is composed of differential gene expression values (e.g. LFC or z-scores). Note, the related CMAP method uses here ranks instead.

Usage

```
gess_lincs(
  qSig,
  tau = FALSE,
  sortby = "NCS",
  chunk_size = 5000,
  ref_trts = NULL,
  workers = 1
)
```

Arguments

qSig	qSig object defining the query signature including the GESS method (should be 'LINCS') and the path to the reference database. For details see help of qSig and qSig-class.
tau	TRUE or FALSE, whether to compute the tau score. Note, TRUE is only meaningful when the full LINCS database is searched, since accurate Tau score calculation depends on the usage of the exact same database their background values are based on.
sortby	sort the GESS result table based on one of the following statistics: 'WTCS', 'NCS', 'Tau', 'NCSct' or 'NA'
chunk_size	number of database entries to process per iteration to limit memory usage of search.
ref_trts	character vector. If users want to search against a subset of the reference database, they could set ref_trts as a character vector representing column names (treatments) of the subsetted refdb.
workers	integer(1) number of workers for searching the reference database parallelly, default is 1.

Details

Subramanian et al. (2017) introduced a more complex GESS algorithm, here referred to as LINCS. While related to CMAP, there are several important differences among the two approaches. First, LINCS weights the query genes based on the corresponding differential expression scores of the GESs in the reference database (e.g. LFC or z-scores). Thus, the reference database used by LINCS needs to store the actual score values rather than their ranks. Another relevant difference is that the LINCS algorithm uses a bi-directional weighted Kolmogorov-Smirnov enrichment statistic (ES) as similarity metric.

Value

gessResult object, the result table contains the search results for each perturbagen in the reference database ranked by their signature similarity to the query.

Column description

Descriptions of the columns specific to the LINCS method are given below. Note, the additional columns, those that are common among the GESS methods, are described in the help file of the gessResult object.

- WTCS: Weighted Connectivity Score, a bi-directional Enrichment Score for an up/down query set. If the ES values of an up set and a down set are of different signs, then WTCS is (ESup-ESdown)/2, otherwise, it is 0. WTCS values range from -1 to 1. They are positive or negative for signatures that are positively or inversely related, respectively, and close to zero for signatures that are unrelated.
- WTCS_Pval: Nominal p-value of WTCS computed by comparing WTCS against a null distribution of WTCS values obtained from a large number of random queries (e.g. 1000).
- WTCS_FDR: False discovery rate of WTCS_Pval.
- NCS: Normalized Connectivity Score. To make connectivity scores comparable across cell types and perturbation types, the scores are normalized. Given a vector of WTCS values w resulting from a query, the values are normalized within each cell line c and perturbagen type t to obtain NCS by dividing the WTCS value with the signed mean of the WTCS values within the subset of the signatures in the reference database corresponding to c and t.
- Tau: Enrichment score standardized for a given database. The Tau score compares an observed NCS to a large set of NCS values that have been pre-computed for a specific reference database. The query results are scored with Tau as a standardized measure ranging from 100 to -100. A Tau of 90 indicates that only 10 stronger connectivity to the query. This way one can make more meaningful comparisons across query results.

  Note, there are NAs in the Tau score column, the reason is that the number of signatures in *Qref* that match the cell line of signature *r* (the `TauRefSize` column in the GESS result) is less than 500, Tau will be set as NA since it is redeemed as there are not large enough samples for computing meaningful Tau scores.
- TauRefSize: Size of reference perturbations for computing Tau.
- NCSct: NCS summarized across cell types. Given a vector of NCS values for perturbagen p, relative to query q, across all cell lines c in which p was profiled, a cell-summarized connectivity score is obtained using a maximum quantile statistic. It compares the 67 and 33 quantiles of NCSp,c and retains whichever is of higher absolute magnitude.

References

For detailed description of the LINCS method and scores, please refer to: Subramanian, A., Narayan, R., Corsello, S. M., Peck, D. D., Natoli, T. E., Lu, X., Golub, T. R. (2017). A Next Generation Connectivity Map: L1000 Platform and the First 1,000,000 Profiles. Cell, 171 (6), 1437-1452.e17. URL: https://doi.org/10.1016/j.cell.2017.10.049

See Also

qSig, gessResult, gess

Examples

```
db_path <- system.file("extdata", "sample_db.h5",
                       package = "signatureSearch")
#qsig_lincs <- qSig(query = list(
#                   upset=c("230", "5357", "2015", "2542", "1759"),
#                   downset=c("22864", "9338", "54793", "10384", "27000")),
#                   gess_method = "LINCS", refdb = db_path)
#lincs <- gess_lincs(qsig_lincs, sortby="NCS", tau=FALSE)
#result(lincs)
```

gess_res_vis *GESS Result Visualization*

Description

The function allows to summarize the ranking scores of selected perturbagens for GESS results across cell types along with cell type classifications, such as normal and tumor cells. In the resulting plot the perturbagens are drugs (along x-axis) and the ranking scores are LINCS' NCS values (y-axis). For each drug the NCS values are plotted for each cell type as differently colored dots, while their shape indicates the cell type class.

Usage

```
gess_res_vis(gess_tb, drugs, col, cell_group = "all", ...)
```

Arguments

gess_tb	tibble in the 'result' slot of the gessResult object, can be extracted via result accessor function
drugs	character vector of selected drugs
col	character(1), name of the score column in 'gess_tb', e.g., "NCS" if the result table is from LINCS method. Can also be set as "rank", this way it will show the ranks of each drug in different cell types.
cell_group	character(1), one of "all", "normal", or "tumor". If "all", it will show scores of each drug in both tumor and normal cell types. If "normal" or "tumor", it will only show normal or tumor cell types.
...	Other arguments passed on to geom_point

Value

plot visualizing GESS results

References

Subramanian, A., Narayan, R., Corsello, S. M., Peck, D. D., Natoli, T. E., Lu, X., Golub, T. R. (2017). A Next Generation Connectivity Map: L1000 Platform and the First 1,000,000 Profiles. Cell, 171 (6), 1437-1452.e17. URL: https://doi.org/10.1016/j.cell.2017.10.049

Examples

```
gr <- gessResult(result=dplyr::tibble(pert=c("p1", "p1", "p2", "p3"),
                                      cell=c("MCF7", "SKB", "MCF7", "SKB"),
                                      type=rep("trt_cp", 4),
                                      NCS=c(1.2, 1, 0.9, 0.6)),
                 query=list(up="a", down="b"),
                 gess_method="LINCS", refdb="path/to/refdb")
gess_res_vis(result(gr), drugs=c("p1","p2"), col="NCS")
```

getSig *Drawn Query GES from Reference Database*

Description

Functionalities used to draw from reference database (e.g. lincs, lincs_expr) GESs of compound treatment(s) in cell types.

Usage

```
getSig(cmp, cell, refdb)

getDEGSig(
  cmp,
  cell,
  Nup = NULL,
  Ndown = NULL,
  higher = NULL,
  lower = NULL,
  padj = NULL,
  refdb = "lincs"
)

getSPsubSig(cmp, cell, Nup = 150, Ndown = 150)
```

Arguments

cmp	character vector representing a list of compound name available in refdb for getSig function, or character(1) indicating a compound name (e.g. vorinostat) for other functions
cell	character(1) or character vector of the same length as cmp argument. It indicates cell type that the compound treated in
refdb	character(1), one of "lincs", "lincs_expr", "cmap", "cmap_expr", or path to the HDF5 file built from build_custom_db function
Nup	integer(1). Number of most up-regulated genes to be subsetted
Ndown	integer(1). Number of most down-regulated genes to be subsetted
higher	numeric(1), the upper threshold of defining DEGs. At least one of 'lower' and 'higher' must be specified. If Nup or Ndown arguments are defined, it will be ignored.
lower	numeric(1), the lower threshold of defining DEGs. At least one of 'lower' and 'higher' must be specified. If Nup or Ndown arguments are defined, it will be ignored.
padj	numeric(1), cutoff of adjusted p-value or false discovery rate (FDR) of defining DEGs if the reference HDF5 database contains the p-value matrix stored in the dataset named as 'padj'. If Nup or Ndown arguments are defined, it will be ignored.

Details

The GES could be genome-wide differential expression profiles (e.g. log2 fold changes or z-scores) or normalized gene expression intensity values depending on the data type of `refdb` or n top up/down regulated DEGs

Value

matrix representing genome-wide GES of the query compound(s) in cell

a list of up- and down-regulated gene label sets

a numeric matrix with one column representing gene expression values drawn from `lincs_expr` db of the most up- and down-regulated genes. The genes were subsetted according to z-scores drawn from `lincs` db.

Examples

```
refdb <- system.file("extdata", "sample_db.h5", package = "signatureSearch")
vor_sig <- getSig("vorinostat", "SKB", refdb=refdb)
vor_degsig <- getDEGSig(cmp="vorinostat", cell="SKB", Nup=150, Ndown=150,
                        refdb=refdb)
all_expr <- as.matrix(runif(1000, 0, 10), ncol=1)
rownames(all_expr) <- paste0('g', sprintf("%04d", 1:1000))
colnames(all_expr) <- "drug__cell__trt_cp"
de_prof <- as.matrix(rnorm(1000, 0, 3), ncol=1)
rownames(de_prof) <- paste0('g', sprintf("%04d", 1:1000))
colnames(de_prof) <- "drug__cell__trt_cp"
## getSPsubSig internally uses deprof2subexpr function
## sub_expr <- deprof2subexpr(all_expr, de_prof, Nup=150, Ndown=150)
```

`get_targets` *Target Gene/Protein IDs for Query Drugs*

Description

This function returns for a set of query drug names/ids the corresponding target gene/protein ids. The required drug-target annotations are from DrugBank, CLUE and STITCH. An SQLite database storing these drug-target interactions based on the above three annotation resources is available in the `signatureSearchData` package.

Usage

```
get_targets(drugs, database = "all", verbose = FALSE)
```

Arguments

`drugs`	character vector of drug names
`database`	drug-target annotation resource; one of 'DrugBank', 'CLUE', 'STITCH' or 'all'. If 'all', the targets from DrugBank, CLUE and STITCH databases will be combined.
`verbose`	TRUE or FALSE, whether to print messages

Value

data.frame, one column contains the query drug names and the other target gene symbols.

See Also

dtlink_db_clue_sti

Examples

```
data(drugs10)
dt <- get_targets(drugs10)
```

---

gmt2h5 *Convert GMT to HDF5 File*

Description

Read gene sets from large gmt file in batches, convert the gene sets to 01 matrix and write the result to an HDF5 file.

Usage

```
gmt2h5(gmtfile, dest_h5, by_nset = 5000, overwrite = FALSE)
```

Arguments

gmtfile	character(1), path to gmt file containing gene sets
dest_h5	character(1), path of the hdf5 destination file
by_nset	number of gene sets to import in each iteration to limit memory usage
overwrite	TRUE or FALSE, whether to overwrite or to append to existing 'h5file'

Value

HDF5 file

Examples

```
gmt <- system.file("extdata", "test_gene_sets_n4.gmt",
        package="signatureSearch")
h5file <- tempfile(fileext=".h5")
gmt2h5(gmtfile=gmt, dest_h5=h5file, overwrite=TRUE)
```

gseGO2 *Modified GSEA with GO Terms*

Description

This modified Gene Set Enrichment Analysis (GSEA) of GO terms supports gene test sets with large numbers of zeros.

Usage

```
gseGO2(
  geneList,
  ont = "BP",
  OrgDb,
  keyType = "SYMBOL",
  exponent = 1,
  nproc = 1,
  nPerm = 1000,
  minGSSize = 2,
  maxGSSize = 500,
  pvalueCutoff = 0.05,
  pAdjustMethod = "BH",
  verbose = TRUE
)
```

Arguments

geneList	named numeric vector with gene SYMBOLs in the name slot decreasingly ranked by scores in the data slot.
ont	one of "BP", "MF", "CC" or "ALL"
OrgDb	OrgDb, e.g., "org.Hs.eg.db".
keyType	keytype of gene
exponent	weight of each step
nproc	if not equal to zero, sets BPPARAM to use nproc workers (default = 1)
nPerm	permutation numbers
minGSSize	integer, minimum size of each gene set in annotation system
maxGSSize	integer, maximum size of each gene set in annotation system
pvalueCutoff	pvalue cutoff
pAdjustMethod	pvalue adjustment method
verbose	print message or not

Value

feaResult object

Examples

```
data(targetList)
# gsego <- gseGO2(geneList=targetList, ont="MF", OrgDb="org.Hs.eg.db",
#                 pvalueCutoff=1)
# head(gsego)
```

---

gseKEGG2 *Modified GSEA with KEGG*

Description

This modified Gene Set Enrichment Analysis (GSEA) of KEGG pathways supports gene test sets with large numbers of zeros.

Usage

```
gseKEGG2(
  geneList,
  organism = "hsa",
  keyType = "kegg",
  exponent = 1,
  nproc = 1,
  nPerm = 1000,
  minGSSize = 10,
  maxGSSize = 500,
  pvalueCutoff = 0.05,
  pAdjustMethod = "BH",
  verbose = TRUE
)
```

Arguments

geneList	named numeric vector with gene ids in the name slot decreasingly ranked by scores in the data slot.
organism	supported organism listed in URL: http://www.genome.jp/kegg/catalog/org_list.html
keyType	one of "kegg", 'ncbi-geneid', 'ncib-proteinid' and 'uniprot'
exponent	weight of each step
nproc	if not equal to zero, sets BPPARAM to use nproc workers (default = 1)
nPerm	permutation numbers
minGSSize	integer, minimum size of each gene set in annotation system
maxGSSize	integer, maximum size of each gene set in annotation system
pvalueCutoff	pvalue cutoff
pAdjustMethod	pvalue adjustment method
verbose	print message or not

Value

feaResult object

Examples

```
# Gene Entrez id should be used for KEGG enrichment
data(geneList, package="DOSE")
#geneList[100:length(geneList)]=0
#gsekk <- gseKEGG2(geneList=geneList, pvalueCutoff = 1)
#head(gsekk)
```

---

head *Return the First Part of an Object*

Description

Return the first part of the result table in the gessResult, and feaResult objects

Usage

```
## S4 method for signature 'gessResult'
head(x, n = 6L, ...)

## S4 method for signature 'feaResult'
head(x, n = 6L, ...)
```

Arguments

x	an object
n	a single integer. If positive or zero, size for the resulting object is the number of rows for a data frame. If negative, all but the n last number of rows of x.
...	arguments to be passed to or from other methods

Value

data.frame

Examples

```
gr <- gessResult(result=dplyr::tibble(pert=letters[seq_len(10)],
                                      val=seq_len(10)),
                 query=list(up=c("g1","g2"), down=c("g3","g4")),
                 gess_method="LINCS", refdb="path/to/lincs/db")
head(gr)
fr <- feaResult(result=dplyr::tibble(id=letters[seq_len(10)],
                                     val=seq_len(10)),
                organism="human", ontology="MF", drugs=c("d1", "d2"),
                targets=c("t1","t2"))
head(fr)
```

lincs_expr_inst_info *Instance Information of LINCS Expression Database*

Description

It is a tibble of 3 columns containing compound treatment information of GEP instances in the LINCS expression database. The columns contain the compound name, cell type and perturbation type (all of them are compound treatment, trt_cp).

Usage

```
lincs_expr_inst_info
```

Format

A `tibble` object with 38,824 rows and 3 columns.

Examples

```
# Load object
data(lincs_expr_inst_info)
head(lincs_expr_inst_info)
```

lincs_sig_info *LINCS Signature Information*

Description

It is a tibble of 3 columns containing treatment information of GESs in the LINCS database. The columns contain the perturbation name, cell type and perturbation type (all of them are compound treatment, trt_cp).

Usage

```
lincs_sig_info
```

Format

A `tibble` object with 45,956 rows and 3 columns.

Examples

```
# Load object
data(lincs_sig_info)
head(lincs_sig_info)
```

mabsGO *MeanAbs Enrichment Analysis for GO*

Description

MeanAbs enrichment analysis with GO terms.

Usage

```
mabsGO(
  geneList,
  ont = "BP",
  OrgDb,
  keyType = "SYMBOL",
  nPerm = 1000,
  minGSSize = 5,
  maxGSSize = 500,
  pvalueCutoff = 0.05,
  pAdjustMethod = "BH"
)
```

Arguments

geneList	named numeric vector with gene SYMBOLs in the name slot decreasingly ranked by scores in the data slot.
ont	one of "BP", "MF", "CC" or "ALL"
OrgDb	OrgDb
keyType	keytype of gene
nPerm	permutation numbers
minGSSize	integer, minimum size of each gene set in annotation system
maxGSSize	integer, maximum size of each gene set in annotation system
pvalueCutoff	pvalue cutoff
pAdjustMethod	pvalue adjustment method

Value

feaResult object

Author(s)

Yuzhu Duan

Examples

```
data(targetList)
#mg <- mabsGO(geneList=targetList, ont="MF", OrgDb="org.Hs.eg.db",
#             pvalueCutoff=1)
#head(mg)
```

mabsKEGG *MeanAbs Enrichment Analysis for KEGG*

Description

MeanAbs enrichment analysis with KEGG pathways.

Usage

```
mabsKEGG(
  geneList,
  organism = "hsa",
  keyType = "kegg",
  nPerm = 1000,
  minGSSize = 5,
  maxGSSize = 500,
  pvalueCutoff = 0.05,
  pAdjustMethod = "BH"
)
```

Arguments

geneList	named numeric vector with gene/target ids in the name slot decreasingly ranked by scores in the data slot.
organism	supported organism listed in URL: http://www.genome.jp/kegg/catalog/org_list.html
keyType	one of 'kegg', 'ncbi-geneid', 'ncib-proteinid' and 'uniprot'
nPerm	permutation numbers
minGSSize	integer, minimum size of each gene set in annotation system
maxGSSize	integer, maximum size of each gene set in annotation system
pvalueCutoff	pvalue cutoff
pAdjustMethod	pvalue adjustment method

Value

feaResult object

Examples

```
# Gene Entrez id should be used for KEGG enrichment
data(geneList, package="DOSE")
#geneList[100:length(geneList)]=0
#mk <- mabsKEGG(geneList=geneList, pvalueCutoff = 1)
#head(mk)
```

matrix2h5 *Write Matrix to HDF5 file*

Description

Function writes matrix object to an HDF5 file.

Usage

```
matrix2h5(matrix, h5file, name = "assay", overwrite = TRUE)
```

Arguments

matrix	matrix to be written to HDF5 file, row and column name slots need to be populated
h5file	character(1), path to the hdf5 destination file
name	The name of the dataset in the HDF5 file. The default is write the score matrix (e.g. z-score, logFC) to the 'assay' dataset, users could also write the adjusted p-value or FDR matrix to the 'padj' dataset by setting the name as 'padj'.
overwrite	TRUE or FALSE, whether to overwrite or append matrix to an existing 'h5file'

Value

HDF5 file containing exported matrix

Examples

```
mat <- matrix(rnorm(12), nrow=3, dimnames=list(
             paste0("r",1:3), paste0("c",1:4)))
h5file <- tempfile(fileext=".h5")
matrix2h5(matrix=mat, h5file=h5file, overwrite=TRUE)
```

moa_conn *Summarize GESS Results on MOA Level*

Description

Function summarizes GESS results on Mode of Action (MOA) level. It returns a tabular representation of MOA categories ranked by their average signature search similarity to a query signature.

Usage

```
moa_conn(gess_tb, moa_cats = "default", cells = "normal")
```

Arguments

gess_tb	tibble in gessResult object
moa_cats	if set as "default", it uses MOA annotations from the CLUE website (https://clue.io). Users can customize it by providing a 'list' of character vectors containing drug names and MOA categories as list component names.
cells	one of "normal", "cancer" or "all", or a character vector containing cell types of interest. • "all": all cell types in LINCS database; • "normal": normal cell types in LINCS database as one group; • "tumor": tumor cell types in LINCS database as one group;

Details

Column description of the result table:

moa: Mechanism of Action (MOA)

cells: cell type information

mean_rank: mean rank of drugs in corresponding GESS result for each MOA category

n_drug: number of drugs in each MOA category

Value

data.frame

See Also

gessResult

Examples

```
res_moa <- moa_conn(dplyr::tibble(
                    pert=c("vorinostat", "trichostatin-a", "HC-toxin"),
                    cell=rep("SKB",3),
                    pval=c(0.001,0.02,0.05)))
```

---

parse_gctx *Parse GCTX*

Description

Parse a GCTX file into the R workspace as a GCT object

Usage

```
parse_gctx(
  fname,
  rid = NULL,
  cid = NULL,
  set_annot_rownames = FALSE,
  matrix_only = FALSE
)
```

Arguments

fname	character(1), path to the GCTX file on disk
rid	either a vector of character or integer row indices or a path to a grp file containing character row indices. Only these indices will be parsed from the file.
cid	either a vector of character or integer column indices or a path to a grp file containing character column indices. Only these indices will be parsed from the file.
set_annot_rownames	boolean indicating whether to set the rownames on the row/column metadata data.frames. Set this to false if the GCTX file has duplicate row/column ids.
matrix_only	boolean indicating whether to parse only the matrix (ignoring row and column annotations)

Value

gct object

Examples

```
gctx <- system.file("extdata", "test_sample_n2x12328.gctx",
                    package="signatureSearch")
gct <- parse_gctx(gctx)
```

---

qSig *Helper Function to Construct a qSig Object*

Description

It builds a 'qSig' object to store the query signature, reference database and GESS method used for GESS methods

Usage

```
qSig(query, gess_method, refdb)
```

Arguments

query	If 'gess_method' is 'CMAP' or 'LINCS', it should be a list with two character vectors named upset and downset for up- and down-regulated gene labels, respectively. The labels should be gene Entrez IDs if the reference database is a pre-built CMAP or LINCS database. If a custom database is used, the labels need to be of the same type as those in the reference database. If 'gess_method' is 'gCMAP', the query is a matrix with a single column representing gene ranks from a biological state of interest. The corresponding gene labels are stored in the row name slot of the matrix. Instead of ranks one can provide scores (e.g. z-scores). In such a case, the scores will be internally transformed to ranks. If 'gess_method' is 'Fisher', the query is expected to be a list with two character vectors named upset and downset for up- and down-regulated gene labels, respectively (same as for 'CMAP' or 'LINCS' method). Internally, the up/down

gene labels are combined into a single gene set when querying the reference database with the Fisher's exact test. This means the query is performed with an unsigned set. The query can also be a matrix with a single numeric column and the gene labels (e.g. Entrez gene IDs) in the row name slot. The values in this matrix can be z-scores or LFCs. In this case, the actual query gene set is obtained according to upper and lower cutoffs in the `gess_fisher` function set by the user.

If 'gess_method' is 'Cor', the query is a matrix with a single numeric column and the gene labels in the row name slot. The numeric column can contain z-scores, LFCs, (normalized) gene expression intensity values or read counts.

`gess_method` one of 'CMAP', 'LINCS', 'gCMAP', 'Fisher' or 'Cor'

`refdb` character(1), can be one of "cmap", "cmap_expr", "lincs", or "lincs_expr" when using the CMAP/LINCS databases from the affiliated `signatureSearchData` package. With 'cmap' the database contains signatures of LFC scores obtained from DEG analysis routines; with 'cmap_expr' normalized gene expression values; with 'lincs' z-scores obtained from the DEG analysis methods of the LINCS project; and with 'lincs_expr' normalized expression values.

To use a custom signature database, it should be the file path to the HDF5 file generated with the `build_custom_db` function, the HDF5 file needs to have the `.h5` extension.

When the `gess_method` is set as 'gCMAP' or 'Fisher', it could also be the file path to the HDF5 file converted from the gmt file containing gene sets by using `gmt2h5` function. For example, the gmt files could be from the MSigDB https://www.gsea-msigdb.org/gsea/msigdb/index.jsp or GSKB http://ge-lab.org/#/data.

Value

`qSig` object

See Also

`build_custom_db`, `signatureSearchData`, `gmt2h5`

Examples

```
db_path <- system.file("extdata", "sample_db.h5",
                       package = "signatureSearch")
## Load sample_db as `SummarizedExperiment` object
library(SummarizedExperiment); library(HDF5Array)
sample_db <- SummarizedExperiment(HDF5Array(db_path, name="assay"))
rownames(sample_db) <- HDF5Array(db_path, name="rownames")
colnames(sample_db) <- HDF5Array(db_path, name="colnames")
## get "vorinostat__SKB__trt_cp" signature drawn from sample databass
query_mat <- as.matrix(assay(sample_db[,"vorinostat__SKB__trt_cp"]))
query = as.numeric(query_mat); names(query) = rownames(query_mat)
upset <- head(names(query[order(-query)]), 150)
downset <- tail(names(query[order(-query)]), 150)
qsig_lincs <- qSig(query=list(upset=upset, downset=downset),
                   gess_method="LINCS", refdb=db_path)
qsig_gcmap <- qSig(query=query_mat, gess_method="gCMAP", refdb=db_path)
```

qSig-class *Class "qSig"*

Description

S4 object named qSig containing query signature information for Gene Expression Signature (GES) searches. It contains slots for query signature, GESS method and path to the GES reference database.

Slots

query If 'gess_method' is one of 'CMAP' or 'LINCS', this should be a list with two character vectors named upset and downset for up- and down-regulated gene labels (here Entrez IDs), repectively.

If 'gess_method' is 'gCMAP', 'Fisher' or 'Cor', a single column matrix with gene expression values should be assigned. The corresponding gene labels are stored in the row name slot of the matrix. The expected type of gene expression values is explained in the help files of the corresponding GESS methods.

gess_method one of 'CMAP', 'LINCS', 'gCMAP', 'Fisher' or 'Cor'

refdb character(1), can be "cmap", "cmap_expr", "lincs", or "lincs_expr" when using existing CMAP/LINCS databases.

If users want to use a custom signature database, it should be the file path to the HDF5 file generated with the build_custom_db function. Alternatively, source files of the CMAP/LINCS databases can be used as explained in the vignette of the signatureSearchData package.

rand_query_ES *Generate WTCS Null Distribution with Random Queries*

Description

Function computes null distribution of Weighted Connectivity Scores (WTCS) used by the LINCS GESS method for computing nominal P-values.

Usage

```
rand_query_ES(h5file, N_queries = 1000, dest)
```

Arguments

h5file	character(1), path to the HDF5 file representing the reference database
N_queries	number of random queries
dest	path to the output file (e.g. "ES_NULL.txt")

Value

File with path assigned to dest

References

Subramanian, A., Narayan, R., Corsello, S. M., Peck, D. D., Natoli, T. E., Lu, X., Golub, T. R. (2017). A Next Generation Connectivity Map: L1000 Platform and the First 1,000,000 Profiles. Cell, 171 (6), 1437-1452.e17. URL: https://doi.org/10.1016/j.cell.2017.10.049

See Also

gess_lincs

Examples

```
db_path = system.file("extdata", "sample_db.h5", package="signatureSearch")
rand_query_ES(h5file=db_path, N_queries=5, dest="ES_NULL.txt")
unlink("ES_NULL.txt")
```

---

read_gmt *Read in gene set information from .gmt files*

Description

This function reads in and parses information from the MSigDB's .gmt files. Pathway information will be returned as a list of gene sets.

Usage

```
read_gmt(file, start = 1, end = -1)
```

Arguments

file	The .gmt file to be read
start	integer(1), read the gmt file from start line
end	integer(1), read the gmt file to the end line, the default -1 means read to the end

Details

The .gmt format is a tab-delimited list of gene sets, where each line is a separate gene set. The first column must specify the name of the gene set, and the second column is used for a short description (which this function discards). For complete details on the .gmt format, refer to the Broad Institute's Data Format's page http://www.broadinstitute.org/cancer/software/gsea/wiki/index.php/Data_formats.

Value

A list, where each index represents a separate gene set.

Warning

The function does not check that the file is correctly formatted, and may return incorrect or partial gene sets, e.g. if the first two columns are omitted. Please make sure that files are correctly formatted before reading them in using this function.

Examples

```
library(signatureSearch)
# geneSets <- read_gmt("path/to/the/gmt/file")
```

`result` *Method to Extract Result Slots*

Description

Method extracts `tibbles` from `result` slots of `feaResult` and `gessResult` objects. They are generated by the GESS and FEA functions defined by `signatureSearch`, respectively.

Usage

```
result(x)

## S4 method for signature 'feaResult'
result(x)

## S4 method for signature 'gessResult'
result(x)
```

Arguments

x	`gessResult` or `feaResult` object

Value

tibble

Examples

```
fr <- feaResult(result=dplyr::tibble(id=letters[seq_len(10)],
                                     val=seq_len(10)),
                organism="human", ontology="MF", drugs=c("d1", "d2"),
                targets=c("t1","t2"))
result(fr)
gr <- gessResult(result=dplyr::tibble(pert=letters[seq_len(10)],
                                      val=seq_len(10)),
                 query=list(up=c("g1","g2"), down=c("g3","g4")),
                 gess_method="LINCS", refdb="path/to/lincs/db")
result(gr)
```

runWF *Run the Entire GESS/FEA Workflow*

Description

This function runs the entire GESS/FEA workflow when providing the query drug and cell type, as well as selecting the reference database (e.g. 'cmap' or 'lincs'), defining the specific GESS and FEA methods. In this case, the query GES is drawn from the reference database. The N (defined by the 'N_gess_drugs' argument) top ranking hits in the GESS tables were then used for FEA where three different annotation systems were used: GO Molecular Function (GO MF), GO Biological Process (GO BP) and KEGG pathways.

The GESS/FEA results will be stored in a list object in R session. A working environment named by the use case will be created under users current working directory or under other directory defined by users. This environment contains a `results` folder where the GESS/FEA result tables were written to. The working environment also contains a template Rmd vignette as well as a rended HTML report, users could make modifications on the Rmd vignette as they need and re-render it to generate their HTML report.

Usage

```
runWF(
  drug,
  cell,
  refdb,
  gess_method,
  fea_method,
  N_gess_drugs = 100,
  env_dir = ".",
  tau = TRUE,
  Nup = 150,
  Ndown = 150,
  higher = 1,
  lower = -1,
  method = "spearman",
  pvalueCutoff = 1,
  qvalueCutoff = 1,
  minGSSize = 5,
  maxGSSize = 500
)
```

Arguments

`drug`	character(1) representing query drug name (e.g. vorinostat). This query drug should be included in the `refdb`
`cell`	character(1) indicating the cell type that the query drug treated in. Details about cell type options in LINCS database can be found in the `cell_info` table after load the 'signatureSearch' package and running 'data("cell_info")'
`refdb`	character(1), one of "lincs", "lincs_expr", "cmap", "cmap_expr", or path to the HDF5 file built from `build_custom_db` function

gess_method	character(1), one of "LINCS", "CORsub", "CORall", "Fisher", "CMAP", "gCMAP". When gess_method is "CORsub" or "CORall", only "lincs_expr" or "cmap_expr" databases are supported.
fea_method	character(1), one of "dup_hyperG", "mGSEA", "mabs", "hyperG", "GSEA"
N_gess_drugs	number of unique drugs in GESS result used as input of FEA
env_dir	character(1), directory under which the result environment located. The default is users current working directory in R session, can be checked via getwd() command in R
tau	TRUE or FALSE indicating whether to compute Tau scores if gess_method is set as 'LINCS'
Nup	integer(1). Number of most up-regulated genes to be subsetted for GESS query when gess_method is CMAP, LINCS or CORsub
Ndown	integer(1). Number of most down-regulated genes to be subsetted for GESS query when gess_method is CMAP, LINCS or CORsub
higher	numeric(1), it is defined when gess_method argument is 'gCMAP' or 'Fisher' representing the 'upper' threshold of subsetting genes with a score larger than 'higher'
lower	numeric(1), it is defined when gess_method argument is 'gCMAP' or 'Fisher' representing the 'lower' threshold of subsetting genes
method	One of 'spearman' (default), 'kendall', or 'pearson', indicating which correlation coefficient to use
pvalueCutoff	double, p-value cutoff for FEA result
qvalueCutoff	double, qvalue cutoff for FEA result
minGSSize	integer, minimum size of each gene set in annotation system
maxGSSize	integer, maximum size of each gene set in annotation system

Value

list object containing GESS/FEA result tables

Examples

```
drug <- "vorinostat"; cell <- "SKB"
refdb <- system.file("extdata", "sample_db.h5", package="signatureSearch")
env_dir <- tempdir()
wf_list <- runWF(drug, cell, refdb, gess_method="LINCS",
    fea_method="dup_hyperG", N_gess_drugs=10, env_dir=env_dir, tau=FALSE)
```

---

show *show method*

Description

show qSig, gessResult, feaResult objects

Usage

```
## S4 method for signature 'feaResult'
show(object)

show(object)

## S4 method for signature 'qSig'
show(object)
```

Arguments

object	object used for show

Value

message

Examples

```
fr <- feaResult(result=dplyr::tibble(id=letters[seq_len(10)],
                                     val=seq_len(10)),
                organism="human", ontology="MF", drugs=c("d1", "d2"),
                targets=c("t1","t2"))
fr
gr <- gessResult(result=dplyr::tibble(pert=letters[seq_len(10)],
                                  val=seq_len(10)),
                 query=list(up=c("g1","g2"), down=c("g3","g4")),
                 gess_method="LINCS", refdb="path/to/lincs/db")
gr
```

---

sim_score_grp *Summary Scores by Groups of Cell Types*

Description

Function appends two columns (score_column_grp1, score_column_grp2) to GESS result tibble. The appended columns contain summary scores for groups of cell types, such as normal and tumor cells.

Usage

```
sim_score_grp(tib, grp1, grp2, score_column)
```

Arguments

tib	tibble in gessResult object
grp1	character vector, group 1 of cell types, e.g., tumor cell types
grp2	character vector, group 2 of cell types, e.g., normal cell types
score_column	character, column name of similarity scores to be grouped

Value

tibble

Examples

```
gr <- gessResult(result=dplyr::tibble(pert=c("p1", "p1", "p2", "p3"),
                                      cell=c("MCF7", "SKB", "MCF7", "SKB"),
                                      type=rep("trt_cp", 4),
                                      NCS=c(1.2, 1, 0.9, 0.6)),
                 query=list(up="a", down="b"),
                 gess_method="LINCS", refdb="path/to/refdb")
df <- sim_score_grp(result(gr), grp1="SKB", grp2="MCF7", "NCS")
```

---

tail *Return the Last Part of an Object*

Description

Return the last part of the result table in the gessResult, and feaResult objects

Usage

```
## S4 method for signature 'gessResult'
tail(x, n = 6L, ...)

## S4 method for signature 'feaResult'
tail(x, n = 6L, ...)
```

Arguments

x	an object
n	a single integer. If positive or zero, size for the resulting object is the number of rows for a data frame. If negative, all but the n first number of rows of x.
...	arguments to be passed to or from other methods

Value

data.frame

Examples

```
gr <- gessResult(result=dplyr::tibble(pert=letters[seq_len(10)],
                                      val=seq_len(10)),
                 query=list(up=c("g1","g2"), down=c("g3","g4")),
                 gess_method="LINCS", refdb="path/to/lincs/db")
tail(gr)
fr <- feaResult(result=dplyr::tibble(id=letters[seq_len(10)],
                                     val=seq_len(10)),
                organism="human", ontology="MF", drugs=c("d1", "d2"),
                targets=c("t1","t2"))
tail(fr)
```

targetList *Target Sample Data Set*

Description

A named numeric vector with Gene Symbols as names. It is the first 1000 elements from the 'targets' slot of the 'mgsea_res' result object introduced in the vignette of this package. The scores represent the weights of the target genes/proteins in the target set of the selected top 10 drugs.

Usage

```
targetList
```

Format

An object of class `numeric` of length 1000.

Examples

```
# Load object
data(targetList)
head(targetList)
tail(targetList)
```

tarReduce *Show Reduced Targets*

Description

Reduce number of targets for each element of a character vector by replacting the targets that beyond Ntar to '...'.

Usage

```
tarReduce(vec, Ntar = 5)
```

Arguments

vec	character vector, each element composed by a list of targets symbols separated by '; '
Ntar	integer, for each element in the vec, number of targets to show

Value

character vector after reducing

Examples

```
vec <- c("t1; t2; t3; t4; t5; t6", "t7; t8")
vec2 <- tarReduce(vec, Ntar=5)
```

`tsea_dup_hyperG` *Target Set Enrichment Analysis (TSEA) with Hypergeometric Test*

Description

The `tsea_dup_hyperG` function performs Target Set Enrichment Analysis (TSEA) based on a modified hypergeomtric test that supports test sets with duplications. This is achieved by maintaining the frequency information of duplicated items in form of weighting values.

Usage

```
tsea_dup_hyperG(
  drugs,
  universe = "Default",
  type = "GO",
  ont = "MF",
  pAdjustMethod = "BH",
  pvalueCutoff = 0.05,
  qvalueCutoff = 0.05,
  minGSSize = 5,
  maxGSSize = 500,
  dt_anno = "all"
)
```

Arguments

`drugs`	character vector containing drug identifiers used for functional enrichment testing. This can be the top ranking drugs from a GESS result. Internally, drug test sets are translated to the corresponding target protein test sets based on the drug-target annotations provided under the `dt_anno` argument.
`universe`	character vector defining the universe of genes/proteins. If set as 'Default', it uses all genes/proteins present in the corresponding annotation system (e.g. GO or KEGG). If 'type' is 'GO', it can be assigned a custom vector of gene SYMBOL IDs. If 'type' is 'KEGG', the vector needs to contain Entrez gene IDs.
`type`	one of 'GO' or 'KEGG'
`ont`	character(1). If type is 'GO', assign `ont` (ontology) one of 'BP','MF', 'CC' or 'ALL'. If type is 'KEGG', `ont` is ignored.
`pAdjustMethod`	p-value adjustment method, one of 'holm', 'hochberg', 'hommel', 'bonferroni', 'BH', 'BY', 'fdr'
`pvalueCutoff`	double, p-value cutoff
`qvalueCutoff`	double, qvalue cutoff
`minGSSize`	integer, minimum size of each gene set in annotation system
`maxGSSize`	integer, maximum size of each gene set in annotation system
`dt_anno`	drug-target annotation source. Currently, one of 'DrugBank', 'CLUE', 'STITCH' or 'all'. If 'dt_anno' is 'all', the targets from the DrugBank, CLUE and STITCH databases will be combined. Usually, it is recommended to set the 'dt_anno' to 'all' since it provides the most complete drug-target annotations. Choosing a single annotation source results in sparser drug-target annotations (particularly CLUE), and thus less complete enrichment results.

Details

The classical hypergeometric test assumes uniqueness in its test sets. To maintain the duplication information in the test sets used for TSEA, the values of the total number of genes/proteins in the test set and the number of genes/proteins in the test set annotated at a functional category are adjusted by maintating their frequency information in the test set rather than counting each entry only once. Removing duplications in TSEA would be inappropriate since it would erase one of the most important pieces of information of this approach.

Value

`feaResult` object, the result table contains the enriched functional categories (e.g. GO terms or KEGG pathways) ranked by the corresponding enrichment statistic.

Column description

The TSEA results (including `tsea_dup_hyperG`) stored in the `feaResult` object can be returned with the `result` method in tabular format, here `tibble`. The columns of this `tibble` are described below.

- GeneRatio: ratio of genes in the test set that are annotated at a specific GO node or KEGG pathway
- BgRatio: ratio of background genes that are annotated at a specific GO node or KEGG pathway
- pvalue: raw p-value of enrichment test

Additional columns are described under the 'result' slot of the `feaResult` object.

See Also

`feaResult`, `fea`

Examples

```
data(drugs10)
## GO annotation system
#dup_hyperG_res <- tsea_dup_hyperG(drugs = drugs, universe = "Default",
#                                  type = "GO", ont="MF", pvalueCutoff=0.05,
#                                  pAdjustMethod="BH", qvalueCutoff = 0.1,
#                                  minGSSize = 10, maxGSSize = 500)
#result(dup_hyperG_res)
## KEGG annotation system
#dup_hyperG_k_res <- tsea_dup_hyperG(drugs = drugs10, universe = "Default",
#                                    type = "KEGG", pvalueCutoff=0.1,
#                                    pAdjustMethod="BH", qvalueCutoff = 0.2,
#                                    minGSSize = 10, maxGSSize = 500)
#result(dup_hyperG_k_res)
```

`tsea_mabs` *Target Set Enrichment Analysis (TSEA) with meanAbs*

Description

The meanAbs (mabs) method is a simple but effective functional enrichment statistic (Fang et al., 2012). As required for TSEA, it supports query label sets (here for target proteins/genes) with duplications by transforming them to score ranked label lists and then calculating mean absolute scores of labels in label set S.

Usage

```
tsea_mabs(
  drugs,
  type = "GO",
  ont = "MF",
  nPerm = 1000,
  pAdjustMethod = "BH",
  pvalueCutoff = 0.05,
  minGSSize = 5,
  maxGSSize = 500,
  dt_anno = "all"
)
```

Arguments

`drugs`	character vector containing drug identifiers used for functional enrichment testing. This can be the top ranking drugs from a GESS result. Internally, drug test sets are translated to the corresponding target protein test sets based on the drug-target annotations provided under the `dt_anno` argument.
`type`	one of 'GO' or 'KEGG'
`ont`	character(1). If type is 'GO', assign `ont` (ontology) one of 'BP','MF', 'CC' or 'ALL'. If type is 'KEGG', `ont` is ignored.
`nPerm`	integer, permutation number used to calculate p-values
`pAdjustMethod`	p-value adjustment method, one of 'holm', 'hochberg', 'hommel', 'bonferroni', 'BH', 'BY', 'fdr'
`pvalueCutoff`	double, p-value cutoff
`minGSSize`	integer, minimum size of each gene set in annotation system
`maxGSSize`	integer, maximum size of each gene set in annotation system
`dt_anno`	drug-target annotation source. Currently, one of 'DrugBank', 'CLUE', 'STITCH' or 'all'. If 'dt_anno' is 'all', the targets from the DrugBank, CLUE and STITCH databases will be combined. Usually, it is recommended to set the 'dt_anno' to 'all' since it provides the most complete drug-target annotations. Choosing a single annotation source results in sparser drug-target annotations (particularly CLUE), and thus less complete enrichment results.

Details

The input for the mabs method is L_tar, the same as for mGSEA. In this enrichment statistic, $mabs(S)$, of a label (e.g. gene/protein) set S is calculated as mean absolute scores of the labels in S. In order to adjust for size variations in label set S, 1000 random permutations of L_tar are performed to determine $mabs(S, pi)$. Subsequently, $mabs(S)$ is normalized by subtracting the median of the $mabs(S, pi)$ and then dividing by the standard deviation of $mabs(S, pi)$ yielding the normalized scores $Nmabs(S)$. Finally, the portion of $mabs(S, pi)$ that is greater than $mabs(S)$ is used as nominal p-value (Fang et al., 2012). The resulting nominal p-values are adjusted for multiple hypothesis testing using the Benjamini-Hochberg method.

Value

`feaResult` object, the result table contains the enriched functional categories (e.g. GO terms or KEGG pathways) ranked by the corresponding enrichment statistic.

Column description

The TSEA results (including `tsea_mabs`) stored in the `feaResult` object can be returned with the `result` method in tabular format, here `tibble`. The columns in this `tibble` specific to the `mabs` method are described below.

- mabs: given a scored ranked gene list L, $mabs(S)$ represents the mean absolute scores of the genes in set S.
- Nmabs: $mabs(S)$ normalized

Additional columns are described under the 'result' slot of the `feaResult` object.

References

Fang, Z., Tian, W., & Ji, H. (2012). A network-based gene-weighting approach for pathway analysis. Cell Research, 22(3), 565-580. URL: https://doi.org/10.1038/cr.2011.149

See Also

`feaResult`, `fea`, `tsea_mGSEA`

Examples

```
data(drugs10)
## GO annotation system
#mabs_res <- tsea_mabs(drugs=drugs10, type="GO", ont="MF", nPerm=1000,
#                      pvalueCutoff=0.05, minGSSize=5)
#result(mabs_res)
## KEGG annotation system
#mabs_k_res <- tsea_mabs(drugs=drugs10, type="KEGG", nPerm=1000,
#                        pvalueCutoff=0.05, minGSSize=5)
#result(mabs_k_res)
```

`tsea_mGSEA` *Target Set Enrichment Analysis (TSEA) with mGSEA Algorithm*

Description

The `tsea_mGSEA` function performs a Modified Gene Set Enrichment Analysis (mGSEA) that supports test sets (e.g. genes or protein IDs) with duplications. The duplication support is achieved by a weighting method for duplicated items, where the weighting is proportional to the frequency of the items in the test set.

Usage

```
tsea_mGSEA(
  drugs,
  type = "GO",
  ont = "MF",
  nPerm = 1000,
  exponent = 1,
  pAdjustMethod = "BH",
  pvalueCutoff = 0.05,
  minGSSize = 5,
  maxGSSize = 500,
  verbose = FALSE,
  dt_anno = "all"
)
```

Arguments

`drugs`	character vector containing drug identifiers used for functional enrichment testing. This can be the top ranking drugs from a GESS result. Internally, drug test sets are translated to the corresponding target protein test sets based on the drug-target annotations provided under the `dt_anno` argument.
`type`	one of 'GO' or 'KEGG'
`ont`	character(1). If type is 'GO', assign `ont` (ontology) one of 'BP','MF', 'CC' or 'ALL'. If type is 'KEGG', `ont` is ignored.
`nPerm`	integer defining the number of permutation iterations for calculating p-values
`exponent`	integer value used as exponent in GSEA algorithm. It defines the weight of the items in the item set S.
`pAdjustMethod`	p-value adjustment method, one of 'holm', 'hochberg', 'hommel', 'bonferroni', 'BH', 'BY', 'fdr'
`pvalueCutoff`	double, p-value cutoff
`minGSSize`	integer, minimum size of each gene set in annotation system
`maxGSSize`	integer, maximum size of each gene set in annotation system
`verbose`	TRUE or FALSE, print message or not
`dt_anno`	drug-target annotation source. Currently, one of 'DrugBank', 'CLUE', 'STITCH' or 'all'. If 'dt_anno' is 'all', the targets from the DrugBank, CLUE and STITCH databases will be combined. Usually, it is recommended to set the 'dt_anno' to 'all' since it provides the most complete drug-target annotations. Choosing a single annotation source results in sparser drug-target annotations (particularly CLUE), and thus less complete enrichment results.

Details

The original GSEA method proposed by Subramanian et at., 2005 uses predefined gene sets S defined by functional annotation systems such as GO and KEGG. The goal is to determine whether the genes in S are randomly distributed throughout a ranked test gene list L (e.g. all genes ranked by log2 fold changes) or enriched at the top or bottom of the test list. This is expressed by an Enrichment Score (ES) reflecting the degree to which a set S is overrepresented at the extremes of L.

For TSEA, the query is a target protein set where duplicated entries need to be maintained. To perform GSEA with duplication support, here referred to as mGSEA, the target set is transformed to a score ranked target list L_tar of all targets provided by the corresponding annotation system. For each target in the query target set, its frequency is divided by the number of targets in the target set, which is the weight of that target. For targets present in the annotation system but absent in the target set, their scores are set to 0. Thus, every target in the annotation system will be assigned a score and then sorted decreasingly to obtain L_tar.

In case of TSEA, the original GSEA method cannot be used directly since a large portion of zeros exists in L_tar. If the scores of the genes in set S are all zeros, N_R (sum of scores of genes in set S) will be zero, which cannot be used as the denominator. In this case, ES is set to -1. If only some genes in set S have scores of zeros then N_R is set to a larger number to decrease the weight of the genes in S that have non-zero scores.

The reason for this modification is that if only one gene in gene set S has a non-zero score and this gene ranks high in L_tar, the weight of this gene will be 1 resulting in an $ES(S)$ close to 1. Thus, the original GSEA method will score the gene set S as significantly enriched. However, this is undesirable because in this example only one gene is shared among the target set and the gene set S. Therefore, giving small weights to genes in S that have zero scores could decrease the weight of the genes in S that have non-zero scores, thereby decreasing the false positive rate. To favor truly enriched GO terms and KEGG pathways (gene set S) at the top of L_tar, only gene sets with positive ES are selected.

Value

`feaResult` object, the result table contains the enriched functional categories (e.g. GO terms or KEGG pathways) ranked by the corresponding enrichment statistic.

Column description

The TSEA results (including `tsea_mGSEA`) stored in the `feaResult` object can be returned with the `result` method in tabular format, here `tibble`. The columns of this `tibble` are described below.

- enrichmentScore: ES from the GSEA algorithm (Subramanian et al., 2005). The score is calculated by walking down the gene list L, increasing a running-sum statistic when we encounter a gene in S and decreasing when it is not. The magnitude of the increment depends on the gene scores. The ES is the maximum deviation from zero encountered in the random walk. It corresponds to a weighted Kolmogorov-Smirnov-like statistic.
- NES: Normalized enrichment score. The positive and negative enrichment scores are normalized separately by permutating the composition of the gene list L nPerm times, and dividing the enrichment score by the mean of the permutation ES with the same sign.
- pvalue: The nominal p-value of the ES is calculated using a permutation test. Specifically, the composition of the gene list L is permuted and the ES of the gene set is recomputed for the permutated data generating a null distribution for the ES. The p-value of the observed ES is then calculated relative to this null distribution.

- leadingEdge: Genes in the gene set S (functional category) that appear in the ranked list L at, or before, the point where the running sum reaches its maximum deviation from zero. It can be interpreted as the core of a gene set that accounts for the enrichment signal.
- ledge_rank: Ranks of genes in 'leadingEdge' in gene list L.

Additional columns are described under the 'result' slot of the feaResult object.

References

GSEA algorithm: Subramanian, A., Tamayo, P., Mootha, V. K., Mukherjee, S., Ebert, B. L., Gillette, M. A., Mesirov, J. P. (2005). Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. Proceedings of the National Academy of Sciences of the United States of America, 102(43), 15545-15550. URL: https://doi.org/10.1073/pnas.0506580102

See Also

feaResult, fea

Examples

```
data(drugs10)
## GO annotation system
#mgsea_res <- tsea_mGSEA(drugs=drugs10, type="GO", ont="MF", exponent=1,
#                        nPerm=1000, pvalueCutoff=1, minGSSize=5)
#result(mgsea_res)
#mgsea_k_res <- tsea_mGSEA(drugs=drugs10, type="KEGG", exponent=1,
#                          nPerm=100, pvalueCutoff=1, minGSSize=5)
#result(mgsea_k_res)
```

---

vec_char_redu *Reduce Number of Character*

Description

Reduce number of characters for each element of a character vector by replacting the part that beyond Nchar (e.g. 50) character to '...'.

Usage

```
vec_char_redu(vec, Nchar = 50)
```

Arguments

vec	character vector to be reduced
Nchar	integer, for each element in the vec, number of characters to remain

Value

character vector after reducing

Examples

```
vec <- c(strrep('a', 60), strrep('b', 30))
vec2 <- vec_char_redu(vec, Nchar=50)
```

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