Package ‘mslp’
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Type Package
Title Predict synthetic lethal partners of tumour mutations
Version 1.4.0

Description An integrated pipeline to predict the potential synthetic lethality partners (SLPs) of tumour mutations, based on gene expression, mutation profiling and cell line genetic screens data. It has built-in support for data from cBioPortal. The primary SLPs correlating with mutations in WT and compensating for the loss of function of mutations are predicted by random forest based methods (GENIE3) and Rank Products, respectively. Genetic screens are employed to identify consensus SLPs leads to reduced cell viability when perturbed.

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**Description**

Identify SLPs compensating for the loss of function of mutations. The up-regulated SLPs are selected via the rank products algorithm, with option calculateProduct = FALSE for a robust results and capacity on large datasets.

**Usage**

```r
comp_slp(
  zscore_data,
  mut_data,
  mutgene = NULL,
  positive_perc = 0.5,
  p_thresh = 0.01,
  ...
)
```

**Arguments**

- `zscore_data` a matrix (genes by patients) reflecting gene expression related to wide type samples. For example, generated from `pp_tcga`.
- `mut_data` a data.table with columns "patientid" and "mut_entrez".
- `mutgene` identify SLPs for specific mutation (gene symbols). If NULL (by default), the intersection genes between zscore_data and mut_data are used.
cons_slp

**positive_perc**  keep genes with positive zscore in at least positive_perc * number of mutation patients.

**p_thresh**  pvalue threshold to filter out results.

...  additional parameters to RankProducts.

**Value**

A data.table with predicted SLPs.

- **mut_entrez**  Entrez ids of mutations.
- **mut_symbol**  Gene symbols of mutations.
- **slp_entrez**  Entrez ids of SLPs.
- **slp_symbol**  Gene symbols of SLPs.
- **pvalue**  p_value from RankProducts.
- **fdr**  "BH" adjusted pvalue via p.adjust.

**Examples**

```r
#- Toy examples, see vignette for more.
#- Add the parallel backend.
require(future)
require(doFuture)
plan(multisession, workers = 2)
data("example_z")
data("example_comp_mut")
res <- comp_slp(example_z, example_comp_mut)
plan(sequential)
```

---

**cons_slp**  Identify consensus SLPs

**Description**

Identify consensus SLPs based on Cohen's Kappa or hypergeometric test.

**Usage**

```r
cons_slp(screen_slp, tumour_slp)
```

**Arguments**

- **screen_slp**  screen hits data annotated with SLPs information, generated by scr_slp.
- **tumour_slp**  the merged SLPs data predicted by corr_slp and comp_slp.
Details
Consensus SLPs are enriched screen hits that are SLPs of same mutations in different cell lines. For each common mutation, the SLPs predicted from human tumour data are used as the total sets. We used either Cohen’s Kappa coefficient on a confusion matrix, or Hypergeometric test, to test the significance of overlapping of screen hits.

Value
A data.table.

- **mut_entrez**: Entrez ids of mutations.
- **mut_symbol**: Gene symbols of mutations.
- **cons_slp_entrez**: Entrez ids of consensus SLPs.
- **cons_slp_symbol**: Gene symbols of Consensus SLPs.
- **cell_1, cell_2**: From which pair of cell lines the consensus SLPs predicted.
- **judgement**: Judgement based on Cohen’s Kappa.
- **kappa_value**: Cohen’s Kappa coefficient.
- **pvalue**: pvalue for Cohen’s Kappa coefficient.
- **fdr**: “BH” adjusted pvalue via *p.adjust*.

References

Examples
```r
#- See the examples in the vignette.
if (FALSE) k_res <- cons_slp(scr_res, merged_res)
```

---

**corr_slp**

*Identify SLPs via correlation*

Description
Identify SLPs of mutations based on co-expression. GENIE3 is employed to find genes highly correlated with mutations in wide type patients.

Usage
```r
corr_slp(
  expr_data, 
  mut_data, 
  mutgene = NULL, 
  im_thresh = 0.001, 
  topgene = 2000,  
  ...  
)
```
est_im

Arguments

- `expr_data`: an expression matrix, genes by patients.
- `mut_data`: a data.table with columns "patientid" and "mut_entrez".
- `mutgene`: identify SLPs for specific mutation (gene symbols). If NULL (by default), the intersection genes between expr_data and mut_data are used.
- `im_thresh`: minimum importance threshold.
- `topgene`: top N genes above the `im_thresh`.
- ... further parameters to genie3.

Value

A data.table with predicted SLPs.

- `mut_entrez`: Entrez ids of mutations.
- `mut_symbol`: Gene symbols of mutations.
- `slp_entrez`: Entrez ids of SLPs.
- `slp_symbol`: Gene symbols of SLPs.
- `fdr`: "BH" adjusted pvalue via `p.adjust`.
- `im`: The importance value returned by genie3.

Examples

```r
# Toy examples, see vignette for more.
require(future)
require(doFuture)
plan(multisession, workers = 2)
data("example_expr")
data("example_corr_mut")
res <- corr_slp(example_expr, example_corr_mut)
plan(sequential)
```

---

est_im

Estimate the importance threshold for GENIE3

Description

Estimate the importance threshold based on repetition GENIE3 results via ROC.

Usage

```r
est_im(permu_data, fdr_thresh = 0.001)
```

Arguments

- `permu_data`: permuted corr_slp results.
- `fdr_thresh`: fdr threshold to selected "TRUE" SLPs.
Details

We first generate a SLPs by repetition matrix from repetition GENIE3 results. SLPs with high im value in repetitions are selected and considered as "TRUE" SLPs via the rank product algorithm. Then for each repetition, we perform receiver operating characteristic curve analysis and select an optimal threshold by "youden" approach. The optimal thresholds are averaged to get the final threshold.

Value

A data.table with mut_entrez (mutation entrez_id) and roc_thresh (estimated im threshold).

Examples

```r
# Toy examples.
require(future)
require(doFuture)
plan(multisession, workers = 2)
data(example_expr)
data(example_corr_mut)
mutgene <- sample(intersect(example_corr_mut$mut_entrez, rownames(example_expr)), 2)
nperm <- 5
res <- lapply(seq_len(nperm), function(x) corr_slp(example_expr, example_corr_mut, mutgene = mutgene))
roc_thresh <- est_im(res)
plan(sequential)
```

---

table(example_compSLP, caption = "SLPs predicted by comp_slp")

Description

SLPs predicted by comp_slp

Usage

data(example_compSLP)

Format

A data.table.
**example_comp_mut**

*Patients mutations to be use in the comp_slp*

**Description**
Mutations and related TCGA ids.

**Usage**
```r
data(example_comp_mut)
```

**Format**
A data.table.

---

**example_corrSLP**

*SLPs predicted by corr_slp*

**Description**
SLPs predicted by corr_slp

**Usage**
```r
data(example_corrSLP)
```

**Format**
A data.table.

---

**example_corr_mut**

*Patients mutations to be use in the corr_slp*

**Description**
Mutations and related TCGA ids.

**Usage**
```r
data(example_corr_mut)
```

**Format**
A data.table.
example_expr  Expression data to be used in comp_slp

Description
Expression matrix, genes by samples.

Usage
data(example_expr)

Format
A matrix.

example_z  Expression data to be used in corr_slp

Description
Z score matrix, genes by samples.

Usage
data(example_z)

Format
A matrix.

genie3  Run GENIE3

Description
Calculate the weight matrix between genes via randomForest, modified from original codes by Huynh-Thu, V.A.
Usage

genie3(  
    expr.matrix,  
    ngene = NULL,  
    K = "sqrt",  
    nb.trees = 1000,  
    input.idx = NULL,  
    importance.measure = "IncNodePurity",  
    trace = FALSE,  
    ...  
)

Arguments

expr.matrix  expression matrix (genes by samples).
ngene  an integer, only up to the first ngene (included) targets (responsible variables).
K  choice of number of input genes randomly, must be one of "sqrt", "all", an integer.
 nb.trees  number of trees in ensemble for each target gene (default 1000).
input.idx  subset of genes used as input genes (default all genes). A vector of indices or gene names is accepted.
importance.measure  type of variable importance measure, "IncNodePurity" or "%IncMSE".
trace  index of currently computed gene is reported (default FALSE).
...

Value

A weighted adjacency matrix of inferred network, element w_ij (row i, column j) gives the importance of the link from regulatory gene i to target gene j.

References


Examples

#- Toy examples.
mtx <- matrix(sample(1000, 100), nrow = 5)
mtx <- rbind(mtx[1, ] * 2 + rnorm(20), mtx)
colnames(mtx) <- paste0("s_", seq_len(ncol(mtx)))
rownames(mtx) <- paste0("g_", seq_len(nrow(mtx)))
res <- genie3(mtx, nb.trees = 100)
### getlink

**Get sorted list of regulatory links in GENIE3 results**

**Description**

Take genie3 output and sort the links.

**Usage**

```r
getlink(weight.matrix, report.max = NULL)
```

**Arguments**

- `weight.matrix`: a weighted adjacency matrix as returned by genie3.
- `report.max`: maximum number of links to report (default all links).

**Value**

A data.table of links with columns "from.gene", "to.gene", "im".

**Examples**

```r
mtx <- matrix(sample(1000, 100), nrow = 5)
mtx <- rbind(mtx[1, ] * 2 + rnorm(20), mtx)
colnames(mtx) <- paste0("s_", seq_len(ncol(mtx)))
rownames(mtx) <- paste0("g_", seq_len(nrow(mtx)))
res <- genie3(mtx, nb.trees = 10)
res_link <- getlink(res)
```

---

### merge_slp

**Merge SLPs**

**Description**

Merge predicted SLPs from comp_slp and corr_slp.

**Usage**

```r
merge_slp(comp_data, corr_data)
```

**Arguments**

- `comp_data`: predicted SLPs from `comp_slp`
- `corr_data`: predicted SLPs from `corr_slp`
Value

A data.table.

mut_entrez  Entrez ids of mutations.
mut_symbol  Gene symbols of mutations.
slp_entrez  Entrez ids of SLPs.
slp_symbol  Gene symbols of SLPs.
pvalue  p_value from RankProducts.
fdr  "BH" adjusted pvalue via p.adjust.
im  The importance value returned by genie3.
dualhit  Whether the slp is identified by corr_slp and comp_slp.

Examples

data("example_z")
data("example_comp_mut")
comp_res <- comp_slp(example_z, example_comp_mut)

data("example_expr")
data("example_corr_mut")
corr_res <- corr_slp(example_expr, example_corr_mut)

res <- merge_slp(comp_res, corr_res)
**Arguments**

- `p_mut` path of mutation data, like "data_mutations_uniprot.txt" provided by cBioPortal.
- `p_cna` path of copy number variation data, like "data_CNA.txt".
- `p_exprs` path of normalized RNAseq expression data, like "data_RNA_Seq_v2_expression_median.txt".
- `p_score` path of zscore data, like "data_RNA_Seq_v2_mRNA_median_Zscores.txt".
- `freq_thresh` threshold to select recurrent mutations.
- `expr_thresh` threshold to remove low expression genes.
- `hyperm_mut_thresh` threshold for hypermutations.

**Details**

It is designed to process the TCGA data provided by cBioPortal. In mutation data, "Missense_Mutation", "Nonsense_Mutation", "Frame_Shift_Del", "Frame_Shift_Ins", "In_Frame_Del", "In_Frame_Ins", "Nonstop_Mutation" are selected for the downstream analysis. In CNA data, genes with GISTIC value equal to -2 are used. Patients with hypermutations are removed. Low expression genes, or genes that are not detected in any patient are filtered out.

**Value**

Return a list of `mut_data`, `expr_data` and `zscore_data`, while `expr_data` and `zscore_data` are matrix (entrez_id by patients), `mut_data` is a data.table with two columns of "patientid" and "mut_entrez".

**References**


**Examples**

```r
#- See vignette for more details.
if (FALSE) {
  P_mut <- "data_mutations_extended.txt"
  P_cna <- "data_CNA.txt"
  P_expr <- "data_RNA_Seq_v2_expression_median.txt"
  P_z <- "data_RNA_Seq_v2_mRNA_median_Zscores.txt"
  res <- pp_tcga(P_mut, P_cna, P_expr, P_z)
  saveRDS(res$mut_data, "mut_data.rds")
  saveRDS(res$expr_data, "expr_data.rds")
  saveRDS(res$zscore_data, "zscore_data.rds")
}
```
Identify SLPs in screen hits

Description

Identify whether screen hits are SLPs of mutations detected in both patients and cell lines, based on predicted SLPs in `corr_slp` and `comp_slp`.

Usage

```r
cscr_slp(cell, screen_data, cell_mut, tumour_slp)
```

Arguments

- `cell` a cell line.
- `screen_data` a data.table of genomic screen results with three columns, "screen_entrez", "screen_symbol" and "cell_line".
- `cell_mut` cell line mutation data.
- `tumour_slp` merged SLPs.

Value

A data.table.

- `cell_line` Name of cell lines.
- `screen_entrez` Entrez ids of hits.
- `screen_symbol` Gene symbols of hits.
- `mut_entrez` Entrez ids of mutations.
- `mut_symbol` Gene symbols of mutations.
- `is_slp` Whether the targeted gene is a SLP.
- `pvalue` p_value from `RankProducts`.
- `fdr` "BH" adjusted pvalue via `p.adjust`.
- `im` The importance value returned by `genie3`.
- `dualhit` Whether the slp is identified by `corr_slp` and `comp_slp`.

Examples

```r
require(future)
require(doFuture)
plan(multisession, workers = 2)
library(magrittr)
library(data.table)
data(example_compSLP)
data(example_corrSLP)
merged_res <- merge_slp(example_compSLP, example_corrSLP)
```
#- Toy hits data.
screen_1 <- merged_res[, .(slp_entrez, slp_symbol)] %>%
  unique %>%
  .[sample(nrow(.), round(.8 * nrow(.)))] %>%
  setnames(c(1, 2), c("screen_entrez", "screen_symbol")) %>%
  [, cell_line := "cell_1"]

screen_2 <- merged_res[, .(slp_entrez, slp_symbol)] %>%
  unique %>%
  .[sample(nrow(.), round(.8 * nrow(.)))] %>%
  setnames(c(1, 2), c("screen_entrez", "screen_symbol")) %>%
  [, cell_line := "cell_2"]

screen_hit <- rbind(screen_1, screen_2)

#- Toy mutations data.
mut_1 <- merged_res[, .(mut_entrez)] %>%
  unique %>%
  .[sample(nrow(.), round(.8 * nrow(.)))] %>%
  [, cell_line := "cell_1"]

mut_2 <- merged_res[, .(mut_entrez)] %>%
  unique %>%
  .[sample(nrow(.), round(.8 * nrow(.)))] %>%
  [, cell_line := "cell_2"]

mut_info <- rbind(mut_1, mut_2)

#- Hits that are identified as SLPs.
scr_res <- lapply(c("cell_1", "cell_2"), scr_slp, screen_hit, mut_info, merged_res)
scr_res[lengths(scr_res) == 0] <- NULL
scr_res <- rbindlist(scr_res)
plan(sequential)
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