Package ‘wppi’

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Type Package
Title Weighting protein-protein interactions
Version 1.10.0
Description Protein-protein interaction data is essential for omics data analysis and modeling. Database knowledge is general, not specific for cell type, physiological condition or any other context determining which connections are functional and contribute to the signaling. Functional annotations such as Gene Ontology and Human Phenotype Ontology might help to evaluate the relevance of interactions. This package predicts functional relevance of protein-protein interactions based on functional annotations such as Human Protein Ontology and Gene Ontology, and prioritizes genes based on network topology, functional scores and a path search algorithm.
License MIT + file LICENSE
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common_neighbors

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common_neighbors  
*Shared neighbors of connected vertices*

**Description**

For each interacting pair of proteins in the PPI network, store the nodes of the common neighbors. This function works for any igraph graph.

**Usage**

```r
common_neighbors(graph_op)
```

**Arguments**

- `graph_op`  Igraph object based on OmniPath PPI interactions from `graph_from_op`. 
count_genes

Value

Data frame (tibble) with igraph vertex IDs of connected pairs of vertices (source and target), a list column with the IDs of their common neighbors, and a column with the number of neighbors.

See Also

graph_from_op

Examples

graph_op <- graph_from_op(wppi_omnipath_data())
genes_interest <- c("ERCC8", "AKT3", "NOL3", "GFI1B", "CDC25A", "TPX2", "SHE")
graph_op_1 <- subgraph_op(graph_op, genes_interest, 1)
shared_neighbors <- common_neighbors(graph_op_1)

---

count_genes | Number of total genes in an ontology database

Description

Number of total genes in an ontology database

Usage

count_genes(data_annot)

Arguments

data_annot | Data frame (tibble) of GO or HPO datasets from wppi_go_data or wppi_hpo_data.

Value

Number of total unique genes in each ontology database.

See Also

• wppi_go_data
• wppi_hpo_data

Examples

go <- wppi_go_data()
count_genes(go)
# [1] 19712
filter_annot_with_network

Filter ontology datasets using PPI network object

Description

Filter ontology datasets using PPI network object

Usage

filter_annot_with_network(data_annot, graph_op)

Arguments

data_annot Data frame (tibble) of GO or HPO datasets from wppi_go_data or wppi_hpo_data.

graph_op Igraph graph object obtained from built OmniPath PPI of genes of interest and x-degree neighbors.

Value

Data frame (tibble) of GO or HPO datasets filtered based on proteins available in the igraph object.

See Also

• wppi_go_data
• wppi_hpo_data
• graph_from_op

Examples

# Get GO database
GO_data <- wppi_go_data()
# Create igraph object based on genes of interest and first neighbors
genes_interest <- c("ERCC8", "AKT3", "NOL3", "GFI1B", "CDC25A", "TPX2", "SHE")
graph_op <- graph_from_op(wppi_omnipath_data())
graph_op_1 <- subgraph_op(graph_op, genes_interest, 1)
# Filter GO data
GO_data_filtered <- filter_annot_with_network(GO_data, graph_op_1)
functional_annot

Functional similarity score based on ontology

Description

Functional similarity between two genes in ontology databases (GO or HPO). Each pair of interacting proteins in the PPI graph network, is quantified the shared annotations between them using the Fisher’s combined probability test (https://doi.org/10.1007/978-1-4612-4380-9_6). This is based on the number of genes annotated in each shared ontology term and the total amount of unique genes available in the ontology database.

Usage

functional_annot(annot, gene_i, gene_j)

Arguments

annot Processed annotation data as provided by process_annot.
gene_i String with the gene symbol in the row of the adjacency matrix.
gene_j String with the gene symbol in the column of the adjacency matrix.

Value

Numeric value with GO/HPO functional similarity between given pair of proteins.

See Also

- process_annot
- weighted_adj

Examples

hpo <- wppi_hpo_data()
hpo <- process_annot(hpo)
hpo_score <- functional_annot(hpo, 'AKT1', 'MTOR')
# [1] 106.9376
**graph_from_op**  
*Igraph object from OmniPath network*

**Description**  
Creation of igraph object from PPI OmniPath database with information regarding proteins and gene symbols.

**Usage**  
```r
graph_from_op(op_data)
```

**Arguments**  
- `op_data`  
  Data frame (tibble) of OmniPath PPI interactions from `wppi_omnipath_data`.

**Value**  
Igraph PPI graph object with vertices defined by UniProt ID and Gene Symbol, and edges based on interactions, for all connections in OmniPath.

**See Also**  
`wppi_omnipath_data`

**Examples**  
```r
graph_op <- graph_from_op(wppi_omnipath_data())
edges_op <- igraph::E(graph_op)
vertices_op <- igraph::V(graph_op)
```

**in_omnipath**  
*Check which genes of interest are or not in OmniPath*

**Description**  
Check which genes of interest are or not in OmniPath

**Usage**  
```r
in_omnipath(graph_op, gene_set, in_network = TRUE)
```
prioritization_genes

Candidate genes prioritization

Description

Ranks candidate genes based on correlation with the given seed genes of interest. For this, the source proteins/genes (i.e. starting nodes) are reduced to the candidate genes and the target proteins/genes (i.e. end nodes) to the given genes of interest. Each candidate gene score is defined by the sum of its correlations towards the known disease-related genes.

Usage

prioritization_genes(
  graph_op,
  prob_matrix,
  genes_interest,
  percentage_genes_ranked = 100
)
prioritization_genes

Arguments

- **graph_op**: Igraph object based on OmniPath PPI interactions from `graph_from_op`.
- **prob_matrix**: Matrix object with correlations/probabilities of the all nodes in the network from `random_walk`.
- **genes_interest**: Character vector with known-disease specific genes.
- **percentage_genes_ranked**: Positive integer (range between 0 and 100) specifying the percentage (network returned in the output. If not specified, the score of all the candidate genes is delivered.

Value

Data frame with the ranked candidate genes based on the functional score inferred from given ontology terms, PPI and Random Walk with Restart parameters.

See Also

- `graph_from_op`
- `weighted_adj`
- `random_walk`
- `score_candidate_genes_from_PPI`

Examples

```r
db <- wppi_data()
GO_data <- db$go
HPO_data <- db$hpo
# Genes of interest
genes_interest <- c("ERCC8", "AKT3", "NOL3", "GFI1B", "CDC25A", "TPX2", "SHE")
# Graph object with PPI
graph_op <- graph_from_op(db$omnipath)
graph_op_1 <- subgraph_op(graph_op, genes_interest, 1)
# Filter ontology data
GO_data_filtered <- filter_annot_with_network(GO_data, graph_op_1)
HPO_data_filtered <- filter_annot_with_network(HPO_data, graph_op_1)
# Weighted adjacency
w_adj <- weighted_adj(graph_op_1, GO_data_filtered, HPO_data_filtered)
# Random Walk with Restart
w_rw <- random_walk(w_adj)
# Ranked candidate genes
scores <- prioritization_genes(graph_op_1, w_rw, genes_interest)
```
process_annot

Processing of ontology annotations

Description

Ontology databases such as Gene Ontology (GO, http://geneontology.org/) and Human Phenotype Ontology (HPO, https://hpo.jax.org/app/) provide important genome and disease functional annotations of genes. These combined allow to build a connection between proteins/genes and phenotype/disease. This function aggregates information in the GO and HPO ontology datasets.

Usage

process_annot(data_annot)

Arguments

data_annot Data frame (tibble) of GO or HPO datasets from wppi_data, wppi_go_data or wppi_hpo_data.

Value

A list of four elements: 1) "term_size" a list which serves as a lookup table for size (number of genes) for each ontology term; 2) "gene_term" a list to look up terms by gene symbol; 3) "annot" the original data frame (data_annot); 4) "total_genes" the number of genes annotated in the ontology dataset.

See Also

- wppi_data
- wppi_go_data
- wppi_hpo_data

Examples

hpo_raw <- wppi_hpo_data()
hpo <- process_annot(hpo_raw)
Description

RWR on the normalized weighted adjacency matrix. The RWR algorithm estimates each protein/gene relevance based on the functional similarity of genes and disease/phenotype, and the topology of the network. This similarity score between nodes measures how closely two proteins/genes are related in a network. Thus, enabling to identify which candidate genes are more related to our given genes of interest.

Usage

random_walk(weighted_adj_matrix, restart_prob = 0.4, threshold = 1e-05)

Arguments

- **weighted_adj_matrix**: Matrix object corresponding to the weighted adjacency from `weighted_adj`.
- **restart_prob**: Positive value between 0 and 1 defining the restart probability parameter used in the RWR algorithm. If not specified, 0.4 is the default value.
- **threshold**: Positive value depicting the threshold parameter in the RWR algorithm. When the error between probabilities is smaller than the threshold defined, the algorithm stops. If not specified, 1e-5 is the default value.

Value

Matrix of correlation/probabilities for the functional similarities for all proteins/genes in the network.

See Also

- `weighted_adj`
- `prioritization_genes`
- `score_candidate_genes_from_PPI`

Examples

db <- wppi_data()
GO_data <- db$go
HPO_data <- db$hpo
# Genes of interest
genes_interest <-
c("ERCC8", "AKT3", "NOL3", "GFI1B", "CDC25A", "TPX2", "SHE")
# Graph object with PPI
graph_op <- graph_from_op(db$omnipath)
graph_op_1 <- subgraph_op(graph_op, genes_interest, 1)
# Filter ontology data
GO_data_filtered <- filter_annot_with_network(GO_data, graph_op_1)
HPO_data_filtered <- filter_annot_with_network(HPO_data, graph_op_1)

# Weighted adjacency
w_adj <- weighted_adj(graph_op_1, GO_data_filtered, HPO_data_filtered)
# Random Walk with Restart
w_rw <- random_walk(w_adj)

---

**Description**

The wppi package implements a prioritization of genes according to their potential relevance in a disease or other experimental or physiological condition. For this it uses a PPI network and functional annotations. A protein-protein interactions (PPI) in the neighborhood of the genes of interest are weighted according to the number of common neighbors of interacting partners and the similarity of their functional annotations. The PPI networks are obtained using the OmniPath (https://omnipathdb.org/) resource and functionality is deduced using the Gene Ontology (GO, http://geneontology.org/) and Human Phenotype Ontology (HPO, https://hpo.jax.org/app/) ontology databases. To score the candidate genes, a Random Walk with Restart algorithm is applied on the weighted network.

**Usage**

```r
score_candidate_genes_from_PPI(
  genes_interest,
  HPO_interest = NULL,
  percentage_output_genes = 100,
  graph_order = 1,
  GO_annot = TRUE,
  GO_slim = NULL,
  GO_aspects = c("C", "F", "P"),
  GO_organism = "human",
  HPO_annot = TRUE,
  restart_prob_rw = 0.4,
  threshold_rw = 1e-05,
  databases = NULL,
  ...
)
```

**Arguments**

- `genes_interest`: Character vector of gene symbols with genes known to be related to the investigated disease or condition.
score_candidate_genes_from_PPI

HPO_interest  Character vector with Human Phenotype Ontology (HPO) annotations of interest from which to construct the functionality (for a list of available annotations see the 'Name' column in the data frame provided by \texttt{wppi.hpo.data}). If not specified, all the annotations available in the HPO database will be used.

percentage_output_genes  Positive integer (range between 0 and 100) specifying the percentage (%) of the total candidate genes in the network returned in the output. If not specified, the score of all the candidate genes is delivered.

graph_order  Integer larger than zero: the neighborhood range counted as steps from the genes of interest. These genes, also called candidate genes, together with the given genes of interest define the Protein-Protein Interaction (PPI) network used in the analysis. If not specified, the first order neighbors are used.

GO_annot  Logical: use the Gene Ontology (GO) annotation database to weight the PPI network. The default is to use it.

GO_slim  Character: use a GO subset (slim). If NULL, the full GO is used. The most often used slim is called "generic". For a list of available slims see \texttt{OmnipathR::go_annot.slim}.

GO_aspects  Character vector with the single letter codes of the gene ontology aspects to use. By default all three aspects are used. The aspects are "C": cellular component, "F": molecular function and "P" biological process.

GO_organism  Character: name of the organism for GO annotations.

HPO_annot  Logical: use the Human Phenotype Ontology (HPO) annotation database to weight the PPI network. The default is to use it.

restart_prob_rw  Numeric: between 0 and 1, defines the restart probability parameter used in the Random Walk with Restart algorithm. The default value is 0.4.

threshold_rw  Numeric: the threshold parameter in the Random Walk with Restart algorithm. When the error between probabilities is smaller than the threshold, the algorithm stops. The default is 1e-5.

databases  Database knowledge as produced by \texttt{wppi.data}.

...  Passed to \texttt{OmnipathR::import_post_translational_interactions}. With these options you can customize the network retrieved from OmniPath.

Details

If you use a GO subset (slim), building it at the first time might take around 20 minutes. The result is saved into the cache so next time loading the data from there is really quick. Gene Ontology annotations are available for a few other organisms apart from human. The currently supported organisms are "chicken", "cow", "dog", "human", "pig" and "uniprot_all". If you disable HPO_annot you can use \texttt{wppi} to score PPI networks other than human.

Value

Data frame with the ranked candidate genes based on the functional score inferred from given ontology terms, PPI and Random Walk with Restart parameters.
See Also

- wppi_data
- weighted_adj
- random_walk
- prioritization_genes

Examples

```r
# example gene set
genes_interest <-
c(c(“ERCC8”, “AKT3”, “NOL3”, “GFI1B”, “CDC25A”, “TPX2”, “SHE”))
# example HPO annotations set
hpo <- wppi_hpo_data()
HPO_interest <- unique(
  dplyr::filter(hpo, grepl(“Diabetes”, .data$Name))$Name
)

# Score 1st-order candidate genes
new_genes_diabetes <-
score_candidate_genes_from_PPI(
  genes_interest = genes_interest,
  HPO_interest = HPO_interest,
  percentage_output_genes = 10,
  graph_order = 1)

new_genes_diabetes
# # A tibble: 30 x 3
# score gene_symbol uniprot
# <dbl> <chr> <chr>
# 1 0.247 KNL1 Q8NG31
# 2 0.247 HTRA2 O43464
# 3 0.247 KAT6A Q92794
# 4 0.247 BABAM1 P12755
# 5 0.247 SKI P12755
# # . with 25 more rows
```

**subgraph_op**

Extract PPI subgraph by genes of interest

**Description**

From the igraph object of a PPI network obtained from OmniPath extracts a subnetwork around the provided genes of interest. The size of the graph is determined by the sub_level parameter, i.e. the maximum number of steps (order) from the genes of interest.

**Usage**

```r
subgraph_op(graph_op, gene_set, sub_level = 1L)
```
Arguments

- **graph_op**: Igraph object based on OmniPath PPI interactions from `graph_from_op`.
- **gene_set**: Character vector of gene symbols. These are the genes of interest, for example known disease specific genes.
- **sub_level**: Integer larger than 0 defining the order of neighborhood (number of steps) from the genes of interest. If not specified, the first-order neighbors are used.

Value

Igraph graph object with PPI network of given genes of interest and their x-order degree neighbors.

Examples

```r
# Subgraphs of first and second order
graph_op <- graph_from_op(wppi_omnipath_data())
genes_interest <- c("ERCC8", "AKT3", "NOL3", "GFI1B", "CDC25A", "TPX2", "SHE")
graph_op_1 <- subgraph_op(graph_op, genes_interest, 1)
graph_op_2 <- subgraph_op(graph_op, genes_interest, 2)
```

**weighted_adj**

*Weighted adjacency matrix*

Description

Converts adjacency to weighted adjacency using network topology information (shared neighbors between connected nodes via `common_neighbors`) integrated with genome and phenotype factors from GO and HPO annotation terms (functionality computed by `functional_annot`). At the end, the weighted adjacency matrix is normalized by column.

Usage

`weighted_adj(graph_op, GO_data, HPO_data)`

Arguments

- **graph_op**: Igraph object based on OmniPath PPI interactions from `graph_from_op`.
- **GO_data**: Data frame with GO annotations as provided by `wppi_go_data`.
- **HPO_data**: Data frame with HPO annotations as provided by `wppi_hpo_data`.

Value

Weighted adjacency matrix based on network topology and functional similarity between interacting proteins/genes based on ontology databases.
See Also

- random_walk
- prioritization_genes
- common_neighbors
- graph_from_op
- subgraph_op
- score_candidate_genes_from_PPI
- wppi_go_data
- wppi_hpo_data

Examples

```r
db <- wppi_data()
GO_data <- db$go
HP0_data <- db$hpo
# Genes of interest
genes_interest <- c(“ERCC8”, “AKT3”, “NOL3”, “GFI1B”, “CDC25A”, “TPX2”, “SHE”)
# Graph object with PPI
graph_op <- graph_from_op(db$omnipath)
graph_op_1 <- subgraph_op(graph_op, genes_interest, 1)
# Filter ontology data
GO_data_filtered <- filter_annot_with_network(GO_data, graph_op_1)
HP0_data_filtered <- filter_annot_with_network(HP0_data, graph_op_1)
# Weighted adjacency
w_adj <- weighted_adj(graph_op_1, GO_data_filtered, HP0_data_filtered)
```

---

**wppi**  
*The wppi package*

**Description**

The wppi package calculates context specific scores for genes in the network neighborhood of genes of interest. The context specificity is ensured by the selection of the genes of interest and potentially by using a more relevant subset of the ontology annotations, e.g. selecting only the diabetes related categories. The PPI network and the functional annotations are obtained automatically from public databases, though it’s possible to use custom databases. The network is limited to a neighborhood of the genes of interest. The ontology annotations are also filtered to the genes in this subnetwork. Then the adjacency matrix is weighted according to the number of common neighbors and the similarity in functional annotations of each pair of interacting proteins. On this weighted adjacency matrix a random walk with restart is performed. The final score for the genes in the neighborhood is the sum of their scores (probabilities to be visited) in the random walk. The method can be fine tuned by setting the neighborhood range, the restart probability of the random walk and the threshold for the random walk.
Author(s)
Ana Galhoz <ana.galhoz@helmholtz-muenchen.de> and Denes Turei <turei.denes@gmail.com>

Examples

# Example with a single call:
genes_interest <-
c("ERCC8", "AKT3", "NOL3", "GFI1B", "CDC25A", "TPX2", "SHE")
scores <- score_candidate_genes_from_PPI(genes_interest)
# The workflow step by step:
db <- wppi_data()
genes_interest <-
c("ERCC8", "AKT3", "NOL3", "GFI1B", "CDC25A", "TPX2", "SHE")
graph_op <- graph_from_op(db$omnipath)
graph_op_1 <- subgraph_op(graph_op, genes_interest, 1)
w_adj <- weighted_adj(graph_op_1, db$go, db$hpo)
w_rw <- random_walk(w_adj)
scores <- prioritization_genes(graph_op_1, w_rw, genes_interest)

wppi_data

Database knowledge for wppi

Description

Retrieves the database knowledge necessary for WPPI directly from the databases. The databases used here are the Human Phenotype Ontology (HPO, https://hpo.jax.org/app/), Gene Ontology (GO, http://geneontology.org/) and OmniPath (https://omnipathdb.org/). The downloads carried out by the OmnipathR package and data required by wppi are extracted from each table.

Usage

wppi_data(
  GO_slim = NULL,
  GO_aspects = c("C", "F", "P"),
  GO_organism = "human",
  ...
)

Arguments

GO_slim Character: use a GO subset (slim). If NULL, the full GO is used. The most often used slim is called "generic". For a list of available slims see OmnipathR::go_annot_slim.

GO_aspects Character vector with the single letter codes of the gene ontology aspects to use. By default all three aspects are used. The aspects are "C": cellular component, "F": molecular function and "P" biological process.
**GO_organism** Character: name of the organism for GO annotations.

Passed to OmnipathR::import_post_translational_interactions. With these options you can customize the network retrieved from OmniPath.

**Details**

If you use a GO subset (slim), building it at the first time might take around 20 minutes. The result is saved into the cache so next time loading the data from there is really quick. Gene Ontology annotations are available for a few other organisms apart from human. The currently supported organisms are "chicken", "cow", "dog", "human", "pig" and "uniprot_all". If you disable HPO_annot you can use wppi to score PPI networks other than human.

**Value**

A list of data frames (tibbles) with database knowledge from HPO, GO and OmniPath.

**See Also**

- wppi_go_data
- wppi_hpo_data
- wppi_omnipath_data

**Examples**

```r
# Download all data
data_wppi <- wppi_data()
# OmniPath
omnipath_data <- data_wppi$omnipath
# HPO
HPO_data <- data_wppi$hpo
# GO
GO_data <- data_wppi$go
```

---

**wppi_go_data**

Retrieves data from Gene Ontology (GO)

**Description**

Gene Ontology (http://geneontology.org/), GO) annotates genes by their function, localization and biological processes.

**Usage**

```r
wppi_go_data(slim = NULL, aspects = c("C", "F", "P"), organism = "human")
```
Arguments

- **slim**: Character: use a GO subset (slim). If **NULL**, the full GO is used. The most often used slim is called "generic". For a list of available slims see `OmnipathR::go_annot_slim`.
- **aspects**: Character vector with the single letter codes of the gene ontology aspects to use. By default all three aspects are used. The aspects are "C": cellular component, "F": molecular function and "P" biological process.
- **organism**: Character: name of the organism for GO annotations.

Details

If you use a GO subset (slim), building it at the first time might take around 20 minutes. The result is saved into the cache so next time loading the data from there is really quick. Gene Ontology annotations are available for a few other organisms apart from human. The currently supported organisms are "chicken", "cow", "dog", "human", "pig" and "uniprot_all". If you disable HPO annot you can use `wppi` to score PPI networks other than human.

Value

A data frame (tibble) with GO annotation data.

See Also

- `wppi_data`

Examples

```r
  go <- wppi_go_data()
```

---

**wppi_hpo_data**

Retrieves data from Human Phenotype Ontology (HPO)

Description

Human Phenotype Ontology ([https://hpo.jax.org/app/](https://hpo.jax.org/app/)), HPO) annotates proteins with phenotypes and diseases.

Usage

```r
  wppi_hpo_data()
```

Value

A data frame (tibble) with HPO data.

See Also

- `wppi_data`
wpipi_omnipath_data

Examples

hpo <- wppi_hpo_data()

---

wpipi_omnipath_data  Protein-protein interaction data from OmniPath

Description

OmniPath ([https://omnipathdb.org/](https://omnipathdb.org/)) integrates protein-protein interactions (PPI) from more than 30 resources. The network created is highly customizable by passing parameters to OmnipathR::import_post_translational_interactions.

Usage

wpipi_omnipath_data(...)

Arguments

...  Passed to OmnipathR::import_post_translational_interactions.

Value

A data frame (tibble) with protein-protein interaction data from OmniPath.

See Also

wpipi_data

Examples

omnipath <- wppi_omnipath_data()
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