

# Package ‘pathfindR’

December 22, 2025

**Type** Package

**Title** Enrichment Analysis Utilizing Active Subnetworks

**Version** 2.7.0

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**Description** Enrichment analysis enables researchers to uncover mechanisms underlying a phenotype. However, conventional methods for enrichment analysis do not take into account protein-protein interaction information, resulting in incomplete conclusions. 'pathfindR' is a tool for enrichment analysis utilizing active subnetworks. The main function identifies active subnetworks in a protein-protein interaction network using a user-provided list of genes and associated p values. It then performs enrichment analyses on the identified subnetworks, identifying enriched terms (i.e. pathways or, more broadly, gene sets) that possibly underlie the phenotype of interest. 'pathfindR' also offers functionalities to cluster the enriched terms and identify representative terms in each cluster, to score the enriched terms per sample and to visualize analysis results. The enrichment, clustering and other methods implemented in 'pathfindR' are described in detail in Ulgen E, Ozisik O, Sezerman OU. 2019. 'pathfindR': An R Package for Comprehensive Identification of Enriched Pathways in Omics Data Through Active Subnetworks. Front. Genet. <doi:10.3389/fgene.2019.00858>.

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**URL** <https://egeulgen.github.io/pathfindR/>,  
<https://github.com/egeulgen/pathfindR>

**BugReports** <https://github.com/egeulgen/pathfindR/issues>

**Encoding** UTF-8

**SystemRequirements** Java (>= 8.0)

**Imports** DBI, AnnotationDbi, doParallel, foreach, rmarkdown, ggplot2, ggraph, ggupset, fpc, ggkegg (>= 1.4.0), grDevices, httr, igraph, R.utils, msigdb (>= 24.1.0), knitr

**Depends** R (>= 4.3.0), pathfindR.data (>= 2.0)

**Suggests** org.Hs.eg.db, testthat (>= 2.3.2), covr, mockery

**RoxygenNote** 7.3.3

**VignetteBuilder** knitr

**NeedsCompilation** no

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**Repository** CRAN

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## Contents

|                                         |    |
|-----------------------------------------|----|
| active_snw_enrichment_wrapper . . . . . | 3  |
| active_snw_search . . . . .             | 5  |
| annotate_term_genes . . . . .           | 7  |
| check_java_version . . . . .            | 8  |
| cluster_enriched_terms . . . . .        | 9  |
| cluster_graph_vis . . . . .             | 10 |
| color_kegg_pathway . . . . .            | 11 |
| combined_results_graph . . . . .        | 12 |
| combine_pathfindR_results . . . . .     | 13 |
| configure_output_dir . . . . .          | 14 |
| create_HTML_report . . . . .            | 15 |
| create_kappa_matrix . . . . .           | 15 |
| enrichment . . . . .                    | 16 |
| enrichment_analyses . . . . .           | 17 |
| enrichment_chart . . . . .              | 19 |
| fetch_gene_set . . . . .                | 20 |
| fetch_java_version . . . . .            | 21 |
| filterActiveSnws . . . . .              | 21 |
| fuzzy_term_clustering . . . . .         | 22 |
| get_biogrid_pin . . . . .               | 23 |
| get_gene_sets_list . . . . .            | 24 |
| get_kegg_gsets . . . . .                | 25 |
| get_mgsigdb_gsets . . . . .             | 26 |
| get_pin_file . . . . .                  | 27 |
| get_reactome_gsets . . . . .            | 27 |
| gset_list_from_gmt . . . . .            | 28 |
| hierarchical_term_clustering . . . . .  | 28 |
| hyperg_test . . . . .                   | 30 |
| input_processing . . . . .              | 31 |
| input_testing . . . . .                 | 32 |
| isColor . . . . .                       | 33 |
| pathfindR . . . . .                     | 33 |
| plot_scores . . . . .                   | 34 |
| process_pin . . . . .                   | 35 |
| return_pin_path . . . . .               | 36 |
| run_pathfindR . . . . .                 | 36 |

*active\_snw\_enrichment\_wrapper* 3

|                                        |    |
|----------------------------------------|----|
| safe_get_content . . . . .             | 39 |
| score_terms . . . . .                  | 40 |
| single_iter_wrapper . . . . .          | 42 |
| summarize_enrichment_results . . . . . | 44 |
| term_gene_graph . . . . .              | 45 |
| term_gene_heatmap . . . . .            | 46 |
| UpSet_plot . . . . .                   | 48 |
| visualize_active_subnetworks . . . . . | 49 |
| visualize_KEGG_diagram . . . . .       | 51 |
| visualize_terms . . . . .              | 52 |
| visualize_term_interactions . . . . .  | 53 |

**Index** 55

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active\_snw\_enrichment\_wrapper  
*Wrapper for Active Subnetwork Search + Enrichment over Single/Multiple Iteration(s)*

---

## Description

Wrapper for Active Subnetwork Search + Enrichment over Single/Multiple Iteration(s)

## Usage

```
active_snw_enrichment_wrapper(  
  input_processed,  
  pin_path,  
  gset_list,  
  enrichment_threshold,  
  list_active_snw_genes,  
  adj_method = "bonferroni",  
  search_method = "GR",  
  disable_parallel = FALSE,  
  use_all_positives = FALSE,  
  iterations = 10,  
  n_processes = NULL,  
  score_quan_thr = 0.8,  
  sig_gene_thr = 0.02,  
  saTemp0 = 1,  
  saTemp1 = 0.01,  
  saIter = 10000,  
  gaPop = 400,  
  gaIter = 200,  
  gaThread = 5,  
  gaCrossover = 1,  
  gaMut = 0,  
  grMaxDepth = 1,  
)
```

```

    grSearchDepth = 1,
    grOverlap = 0.5,
    grSubNum = 1000,
    silent_option = TRUE
)

```

## Arguments

|                       |                                                                                                                                                                                                                                        |
|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| input_processed       | processed input data frame                                                                                                                                                                                                             |
| pin_path              | path/to/PIN/file                                                                                                                                                                                                                       |
| gset_list             | list for gene sets                                                                                                                                                                                                                     |
| enrichment_threshold  | adjusted-p value threshold used when filtering enrichment results (default = 0.05)                                                                                                                                                     |
| list_active_snw_genes | boolean value indicating whether or not to report the non-significant active sub-network genes for the active subnetwork which was enriched for the given term with the lowest p value (default = FALSE)                               |
| adj_method            | correction method to be used for adjusting p-values. (default = 'bonferroni')                                                                                                                                                          |
| search_method         | algorithm to use when performing active subnetwork search. Options are greedy search (GR), simulated annealing (SA) or genetic algorithm (GA) for the search (default = 'GR').                                                         |
| disable_parallel      | boolean to indicate whether to disable parallel runs via foreach (default = FALSE)                                                                                                                                                     |
| use_all_positives     | if TRUE: in GA, adds an individual with all positive nodes. In SA, initializes candidate solution with all positive nodes. (default = FALSE)                                                                                           |
| iterations            | number of iterations for active subnetwork search and enrichment analyses (Default = 10)                                                                                                                                               |
| n_processes           | optional argument for specifying the number of processes used by foreach. If not specified, the function determines this automatically (Default == NULL. Gets set to 1 for Genetic Algorithm)                                          |
| score_quan_thr        | active subnetwork score quantile threshold. Must be between 0 and 1 or set to -1 for not filtering. (Default = 0.8)                                                                                                                    |
| sig_gene_thr          | threshold for the minimum proportion of significant genes in the subnetwork (Default = 0.02) If the number of genes to use as threshold is calculated to be < 2 (e.g. 50 signif. genes x 0.01 = 0.5), the threshold number is set to 2 |
| saTemp0               | Initial temperature for SA (default = 1.0)                                                                                                                                                                                             |
| saTemp1               | Final temperature for SA (default = 0.01)                                                                                                                                                                                              |
| saIter                | Iteration number for SA (default = 10000)                                                                                                                                                                                              |
| gaPop                 | Population size for GA (default = 400)                                                                                                                                                                                                 |
| gaIter                | Iteration number for GA (default = 200)                                                                                                                                                                                                |

|               |                                                                                                                                                                                                                                                                                 |
|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| gaThread      | Number of threads to be used in GA (default = 5)                                                                                                                                                                                                                                |
| gaCrossover   | Applies crossover with the given probability in GA (default = 1, i.e. always perform crossover)                                                                                                                                                                                 |
| gaMut         | For GA, applies mutation with given mutation rate (default = 0, i.e. mutation off)                                                                                                                                                                                              |
| grMaxDepth    | Sets max depth in greedy search, 0 for no limit (default = 1)                                                                                                                                                                                                                   |
| grSearchDepth | Search depth in greedy search (default = 1)                                                                                                                                                                                                                                     |
| grOverlap     | Overlap threshold for results of greedy search (default = 0.5)                                                                                                                                                                                                                  |
| grSubNum      | Number of subnetworks to be presented in the results (default = 1000)                                                                                                                                                                                                           |
| silent_option | boolean value indicating whether to print the messages to the console (FALSE) or not (TRUE, this will print to a temp. file) during active subnetwork search (default = TRUE). This option was added because during parallel runs, the console messages get disorderly printed. |

### Value

Data frame of combined pathfindR enrichment results

---

|                   |                                         |
|-------------------|-----------------------------------------|
| active_snw_search | <i>Perform Active Subnetwork Search</i> |
|-------------------|-----------------------------------------|

---

### Description

Perform Active Subnetwork Search

### Usage

```
active_snw_search(
  input_for_search,
  pin_name_path = "Biogrid",
  snws_file = "active_snws",
  dir_for_parallel_run = NULL,
  score_quan_thr = 0.8,
  sig_gene_thr = 0.02,
  search_method = "GR",
  seedForRandom = 1234,
  silent_option = TRUE,
  use_all_positives = FALSE,
  geneInitProbs = 0.1,
  saTemp0 = 1,
  saTemp1 = 0.01,
  saIter = 10000,
  gaPop = 400,
  gaIter = 10000,
  gaThread = 5,
```

```

    gaCrossover = 1,
    gaMut = 0,
    grMaxDepth = 1,
    grSearchDepth = 1,
    grOverlap = 0.5,
    grSubNum = 1000
)

```

## Arguments

|                      |                                                                                                                                                                                                                                                                                 |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| input_for_search     | input the input data that active subnetwork search uses. The input must be a data frame containing at least these 2 columns:<br><b>GENE</b> Gene Symbol<br><b>P_VALUE</b> p value obtained through a test, e.g. differential expression/methylation                             |
| pin_name_path        | Name of the chosen PIN or absolute/path/to/PIN.sif. If PIN name, must be one of c('Biogrid', 'STRING', 'GeneMania', 'IntAct', 'KEGG', 'mmu_STRING'). If path/to/PIN.sif, the file must comply with the PIN specifications. (Default = 'Biogrid')                                |
| snws_file            | name for active subnetwork search output data <b>without file extension</b> (default = 'active_snws')                                                                                                                                                                           |
| dir_for_parallel_run | (previously created) directory for a parallel run iteration. Used in the wrapper function (see ?run_pathfindR) (Default = NULL)                                                                                                                                                 |
| score_quan_thr       | active subnetwork score quantile threshold. Must be between 0 and 1 or set to -1 for not filtering. (Default = 0.8)                                                                                                                                                             |
| sig_gene_thr         | threshold for the minimum proportion of significant genes in the subnetwork (Default = 0.02) If the number of genes to use as threshold is calculated to be < 2 (e.g. 50 signif. genes x 0.01 = 0.5), the threshold number is set to 2                                          |
| search_method        | algorithm to use when performing active subnetwork search. Options are greedy search (GR), simulated annealing (SA) or genetic algorithm (GA) for the search (default = 'GR').                                                                                                  |
| seedForRandom        | seed for reproducibility while running the java modules (applies for GR and SA)                                                                                                                                                                                                 |
| silent_option        | boolean value indicating whether to print the messages to the console (FALSE) or not (TRUE, this will print to a temp. file) during active subnetwork search (default = TRUE). This option was added because during parallel runs, the console messages get disorderly printed. |
| use_all_positives    | if TRUE: in GA, adds an individual with all positive nodes. In SA, initializes candidate solution with all positive nodes. (default = FALSE)                                                                                                                                    |
| geneInitProbs        | For SA and GA, probability of adding a gene in initial solution (default = 0.1)                                                                                                                                                                                                 |
| saTemp0              | Initial temperature for SA (default = 1.0)                                                                                                                                                                                                                                      |
| saTemp1              | Final temperature for SA (default = 0.01)                                                                                                                                                                                                                                       |
| saIter               | Iteration number for SA (default = 10000)                                                                                                                                                                                                                                       |

|               |                                                                                                 |
|---------------|-------------------------------------------------------------------------------------------------|
| gaPop         | Population size for GA (default = 400)                                                          |
| gaIter        | Iteration number for GA (default = 200)                                                         |
| gaThread      | Number of threads to be used in GA (default = 5)                                                |
| gaCrossover   | Applies crossover with the given probability in GA (default = 1, i.e. always perform crossover) |
| gaMut         | For GA, applies mutation with given mutation rate (default = 0, i.e. mutation off)              |
| grMaxDepth    | Sets max depth in greedy search, 0 for no limit (default = 1)                                   |
| grSearchDepth | Search depth in greedy search (default = 1)                                                     |
| grOverlap     | Overlap threshold for results of greedy search (default = 0.5)                                  |
| grSubNum      | Number of subnetworks to be presented in the results (default = 1000)                           |

### Value

A list of genes in every identified active subnetwork that has a score greater than the ‘score\_quan\_thr’th quantile and that has at least ‘sig\_gene\_thr’ affected genes.

### Examples

```
processed_df <- example_pathfindR_input[1:15, -2]
colnames(processed_df) <- c('GENE', 'P_VALUE')
GR_snws <- active_snw_search(
  input_for_search = processed_df,
  pin_name_path = 'KEGG',
  search_method = 'GR',
  score_quan_thr = 0.8
)
# clean-up
unlink('active_snw_search', recursive = TRUE)
```

---

annotate\_term\_genes      *Annotate the Affected Genes in the Provided Enriched Terms*

---

### Description

Function to annotate the involved affected (input) genes in each term.

### Usage

```
annotate_term_genes(
  result_df,
  input_processed,
  genes_by_term = pathfindR.data::kegg_genes
)
```

**Arguments**

**result\_df** data frame of enrichment results. The only must-have column is 'ID'.  
**input\_processed** input data processed via [input\\_processing](#)  
**genes\_by\_term** List that contains genes for each gene set. Names of this list are gene set IDs (default = kegg\_genes)

**Value**

The original data frame with two additional columns:

**Up\_regulated** the up-regulated genes in the input involved in the given term's gene set, comma-separated

**Down\_regulated** the down-regulated genes in the input involved in the given term's gene set, comma-separated

**Examples**

```
example_gene_data <- example_pathfindR_input
colnames(example_gene_data) <- c('GENE', 'CHANGE', 'P_VALUE')

annotated_result <- annotate_term_genes(
  result_df = example_pathfindR_output,
  input_processed = example_gene_data
)
```

---

|                    |                           |
|--------------------|---------------------------|
| check_java_version | <i>Check Java Version</i> |
|--------------------|---------------------------|

---

**Description**

Check Java Version

**Usage**

```
check_java_version(version = NULL)
```

**Arguments**

**version** character vector containing the output of 'java -version'. If NULL, result of [fetch\\_java\\_version](#) is used (default = NULL)

**Details**

this function was adapted from the CRAN package sparklyr

**Value**

only parses and checks whether the java version is  $\geq 1.8$

---

cluster\_enriched\_terms

*Cluster Enriched Terms*


---

## Description

Cluster Enriched Terms

## Usage

```
cluster_enriched_terms(
  enrichment_res,
  method = "hierarchical",
  plot_clusters_graph = TRUE,
  use_description = FALSE,
  use_active_snw_genes = FALSE,
  ...
)
```

## Arguments

|                      |                                                                                                                                                                                                                                                                            |
|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| enrichment_res       | data frame of pathfindR enrichment results. Must-have columns are 'Term_Description' (if use_description = TRUE) or 'ID' (if use_description = FALSE), 'Down_regulated', and 'Up_regulated'. If use_active_snw_genes = TRUE, 'non_Signif_Snw_Genes' must also be provided. |
| method               | Either 'hierarchical' or 'fuzzy'. Details of clustering are provided in the corresponding functions <a href="#">hierarchical_term_clustering</a> , and <a href="#">fuzzy_term_clustering</a>                                                                               |
| plot_clusters_graph  | boolean value indicate whether or not to plot the graph diagram of clustering results (default = TRUE)                                                                                                                                                                     |
| use_description      | Boolean argument to indicate whether term descriptions (in the 'Term_Description' column) should be used. (default = FALSE)                                                                                                                                                |
| use_active_snw_genes | boolean to indicate whether or not to use non-input active subnetwork genes in the calculation of kappa statistics (default = FALSE, i.e. only use affected genes)                                                                                                         |
| ...                  | additional arguments for <a href="#">hierarchical_term_clustering</a> , <a href="#">fuzzy_term_clustering</a> and <a href="#">cluster_graph_vis</a> . See documentation of these functions for more details.                                                               |

## Value

a data frame of clustering results. For 'hierarchical', the cluster assignments (Cluster) and whether the term is representative of its cluster (Status) is added as columns. For 'fuzzy', terms that are in multiple clusters are provided for each cluster. The cluster assignments (Cluster) and whether the term is representative of its cluster (Status) is added as columns.

**See Also**

See [hierarchical\\_term\\_clustering](#) for hierarchical clustering of enriched terms. See [fuzzy\\_term\\_clustering](#) for fuzzy clustering of enriched terms. See [cluster\\_graph\\_vis](#) for graph visualization of clustering.

**Examples**

```
example_clustered <- cluster_enriched_terms(
  example_pathfindR_output[1:3, ],
  plot_clusters_graph = FALSE
)
example_clustered <- cluster_enriched_terms(
  example_pathfindR_output[1:3, ],
  method = 'fuzzy', plot_clusters_graph = FALSE
)
```

---

cluster\_graph\_vis

*Graph Visualization of Clustered Enriched Terms*


---

**Description**

Graph Visualization of Clustered Enriched Terms

**Usage**

```
cluster_graph_vis(
  clu_obj,
  kappa_mat,
  enrichment_res,
  kappa_threshold = 0.35,
  use_description = FALSE,
  vertex.label.cex = 0.7,
  vertex.size.scaling = 2.5
)
```

**Arguments**

|                 |                                                                                                                                                                                                                                                                            |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| clu_obj         | clustering result (either a matrix obtained via <a href="#">hierarchical_term_clustering</a> or <a href="#">fuzzy_term_clustering</a> ‘fuzzy_term_clustering’ or a vector obtained via ‘hierarchical_term_clustering’)                                                     |
| kappa_mat       | matrix of kappa statistics (output of <a href="#">create_kappa_matrix</a> )                                                                                                                                                                                                |
| enrichment_res  | data frame of pathfindR enrichment results. Must-have columns are ‘Term_Description’ (if use_description = TRUE) or ‘ID’ (if use_description = FALSE), ‘Down_regulated’, and ‘Up_regulated’. If use_active_snn_genes = TRUE, ‘non_Signif_Snn_Genes’ must also be provided. |
| kappa_threshold | threshold for kappa statistics, defining strong relation (default = 0.35)                                                                                                                                                                                                  |

```

use_description      Boolean argument to indicate whether term descriptions (in the 'Term_Description'
                      column) should be used. (default = FALSE)

vertex.label.cex     font size for vertex labels; it is interpreted as a multiplication factor of some
                      device-dependent base font size (default = 0.7)

vertex.size.scaling   scaling factor for the node size (default = 2.5)

```

### Value

Plots a graph diagram of clustering results. Each node is an enriched term from 'enrichment\_res'. Size of node corresponds to  $-\log(\text{lowest\_p})$ . Thickness of the edges between nodes correspond to the kappa statistic between the two terms. Color of each node corresponds to distinct clusters. For fuzzy clustering, if a term is in multiple clusters, multiple colors are utilized.

### Examples

```

## Not run:
cluster_graph_vis(clu_obj, kappa_mat, enrichment_res)

## End(Not run)

```

---

|                    |                               |
|--------------------|-------------------------------|
| color_kegg_pathway | <i>Color hsa KEGG pathway</i> |
|--------------------|-------------------------------|

---

### Description

Color hsa KEGG pathway

### Usage

```

color_kegg_pathway(
  pw_id,
  change_vec,
  scale_vals = TRUE,
  node_cols = NULL,
  legend.position = "top"
)

```

### Arguments

|            |                                                            |
|------------|------------------------------------------------------------|
| pw_id      | hsa KEGG pathway id (e.g. hsa05012)                        |
| change_vec | vector of change values, names should be hsa KEGG gene ids |
| scale_vals | should change values be scaled? (default = TRUE)           |

`node_cols` low, middle and high color values for coloring the pathway nodes (default = NULL). If `node_cols=NULL`, the low, middle and high color are set as 'green', 'gray' and 'red'. If all change values are 1e6 (in case no changes are supplied, this dummy value is assigned by `input_processing`), only one color ('#F38F18' if NULL) is used.

`legend.position` the default position of legends ("none", "left", "right", "bottom", "top", "inside")

### Value

a ggplot object containing the colored KEGG pathway diagram visualization

### Examples

```
## Not run:
pw_id <- 'hsa00010'
change_vec <- c(-2, 4, 6)
names(change_vec) <- c('hsa:2821', 'hsa:226', 'hsa:229')
result <- pathfindR::color_kegg_pathway(pw_id, change_vec)

## End(Not run)
```

---

combined\_results\_graph

*Combined Results Graph*

---

### Description

Combined Results Graph

### Usage

```
combined_results_graph(
  combined_df,
  selected_terms = "common",
  use_description = FALSE,
  layout = "stress",
  node_size = "num_genes"
)
```

### Arguments

`combined_df` Data frame of combined pathfindR enrichment results

`selected_terms` the vector of selected terms for creating the graph (either IDs or term descriptions). If set to 'common', all of the common terms are used. (default = 'common')

|                 |                                                                                                                                                                            |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| use_description | Boolean argument to indicate whether term descriptions (in the 'Term_Description' column) should be used. (default = FALSE)                                                |
| layout          | The type of layout to create (see <a href="#">ggraph</a> for details. Default = 'stress')                                                                                  |
| node_size       | Argument to indicate whether to use number of significant genes ('num_genes') or the -log10(lowest p value) ('p_val') for adjusting the node sizes (default = 'num_genes') |

**Value**

a [ggraph](#) object containing the combined term-gene graph. Each node corresponds to an enriched term (orange if common, different shades of blue otherwise), an up-regulated gene (green), a down-regulated gene (red) or a conflicting (i.e. up in one analysis, down in the other or vice versa) gene (gray). An edge between a term and a gene indicates that the given term involves the gene. Size of a term node is proportional to either the number of genes (if node\_size = 'num\_genes') or the -log10(lowest p value) (if node\_size = 'p\_val').

**Examples**

```
combined_results <- combine_pathfindR_results(
  example_pathfindR_output,
  example_comparison_output,
  plot_common = FALSE
)
g <- combined_results_graph(combined_results, selected_terms = sample(combined_results$ID, 3))
```

---

|                           |                                    |
|---------------------------|------------------------------------|
| combine_pathfindR_results | <i>Combine 2 pathfindR Results</i> |
|---------------------------|------------------------------------|

---

**Description**

Combine 2 pathfindR Results

**Usage**

```
combine_pathfindR_results(result_A, result_B, plot_common = TRUE)
```

**Arguments**

|             |                                                                                                   |
|-------------|---------------------------------------------------------------------------------------------------|
| result_A    | data frame of first pathfindR enrichment results                                                  |
| result_B    | data frame of second pathfindR enrichment results                                                 |
| plot_common | boolean to indicate whether or not to plot the term-gene graph of the common terms (default=TRUE) |

**Value**

Data frame of combined pathfindR enrichment results. Columns are:

**ID** ID of the enriched term

**Term\_Description** Description of the enriched term

**Fold\_Enrichment\_A** Fold enrichment value for the enriched term (Calculated using ONLY the input genes)

**occurrence\_A** the number of iterations that the given term was found to enriched over all iterations

**lowest\_p\_A** the lowest adjusted-p value of the given term over all iterations

**highest\_p\_A** the highest adjusted-p value of the given term over all iterations

**Up\_regulated\_A** the up-regulated genes in the input involved in the given term's gene set, comma-separated

**Down\_regulated\_A** the down-regulated genes in the input involved in the given term's gene set, comma-separated

**Fold\_Enrichment\_B** Fold enrichment value for the enriched term (Calculated using ONLY the input genes)

**occurrence\_B** the number of iterations that the given term was found to enriched over all iterations

**lowest\_p\_B** the lowest adjusted-p value of the given term over all iterations

**highest\_p\_B** the highest adjusted-p value of the given term over all iterations

**Up\_regulated\_B** the up-regulated genes in the input involved in the given term's gene set, comma-separated

**Down\_regulated\_B** the down-regulated genes in the input involved in the given term's gene set, comma-separated

**combined\_p** the combined p value (via Fisher's method)

**status** whether the term is found in both analyses ('common'), found only in the first ('A only') or found only in the second ('B only')

By default, the function also displays the term-gene graph of the common terms

**Examples**

```
combined_results <- combine_pathfindR_results(example_pathfindR_output, example_comparison_output)
```

---

|                      |                                        |
|----------------------|----------------------------------------|
| configure_output_dir | <i>Configure Output Directory Name</i> |
|----------------------|----------------------------------------|

---

**Description**

Configure Output Directory Name

**Usage**

```
configure_output_dir(output_dir = NULL)
```

**Arguments**

output\_dir      the directory to be created where the output and intermediate files are saved  
(default = NULL, a temporary directory is used)

**Value**

/path/to/output/dir

---

create\_HTML\_report      *Create HTML Report of pathfindR Results*

---

**Description**

Create HTML Report of pathfindR Results

**Usage**

```
create_HTML_report(input, input_processed, final_res, dir_for_report)
```

**Arguments**

input              the input data that pathfindR uses. The input must be a data frame with three columns:

1. Gene Symbol (Gene Symbol)
2. Change value, e.g. log(fold change) (OPTIONAL)
3. p value, e.g. adjusted p value associated with differential expression

input\_processed      processed input data frame

final\_res            final pathfindR result data frame

dir\_for\_report      directory to render the report in

---

create\_kappa\_matrix      *Create Kappa Statistics Matrix*

---

**Description**

Create Kappa Statistics Matrix

**Usage**

```
create_kappa_matrix(
  enrichment_res,
  use_description = FALSE,
  use_active_snw_genes = FALSE
)
```

Arguments

- enrichment\_res data frame of pathfindR enrichment results. Must-have columns are 'Term\_Description' (if use\_description = TRUE) or 'ID' (if use\_description = FALSE), 'Down\_regulated', and 'Up\_regulated'. If use\_active\_snw\_genes = TRUE, 'non\_Signif\_Snw\_Genes' must also be provided.
- use\_description Boolean argument to indicate whether term descriptions (in the 'Term\_Description' column) should be used. (default = FALSE)
- use\_active\_snw\_genes boolean to indicate whether or not to use non-input active subnetwork genes in the calculation of kappa statistics (default = FALSE, i.e. only use affected genes)

Value

a matrix of kappa statistics between each term in the enrichment results.

Examples

```
sub_df <- example_pathfindR_output[1:3, ]
create_kappa_matrix(sub_df)
```

---

|            |                                                          |
|------------|----------------------------------------------------------|
| enrichment | <i>Perform Enrichment Analysis for a Single Gene Set</i> |
|------------|----------------------------------------------------------|

---

Description

Perform Enrichment Analysis for a Single Gene Set

Usage

```
enrichment(
  input_genes,
  genes_by_term = pathfindR.data::kegg_genes,
  term_descriptions = pathfindR.data::kegg_descriptions,
  adj_method = "bonferroni",
  enrichment_threshold = 0.05,
  sig_genes_vec,
  background_genes
)
```

Arguments

- input\_genes The set of gene symbols to be used for enrichment analysis. In the scope of this package, these are genes that were identified for an active subnetwork
- genes\_by\_term List that contains genes for each gene set. Names of this list are gene set IDs (default = kegg\_genes)

`term_descriptions` Vector that contains term descriptions for the gene sets. Names of this vector are gene set IDs (default = `kegg_descriptions`)

`adj_method` correction method to be used for adjusting p-values. (default = 'bonferroni')

`enrichment_threshold` adjusted-p value threshold used when filtering enrichment results (default = 0.05)

`sig_genes_vec` vector of significant gene symbols. In the scope of this package, these are the input genes that were used for active subnetwork search

`background_genes` vector of background genes. In the scope of this package, the background genes are taken as all genes in the PIN (see [enrichment\\_analyses](#))

**Value**

A data frame that contains enrichment results

**See Also**

[p.adjust](#) for adjustment of p values. See [run\\_pathfindR](#) for the wrapper function of the pathfindR workflow. [hyperg\\_test](#) for the details on hypergeometric distribution-based hypothesis testing.

**Examples**

```
enrichment(
  input_genes = c('PER1', 'PER2', 'CRY1', 'CREB1'),
  sig_genes_vec = 'PER1',
  background_genes = unlist(pathfindR.data::kegg_genes)
)
```

---

`enrichment_analyses`     *Perform Enrichment Analyses on the Input Subnetworks*

---

**Description**

Perform Enrichment Analyses on the Input Subnetworks

**Usage**

```
enrichment_analyses(
  snws,
  sig_genes_vec,
  pin_name_path = "Biogrid",
  genes_by_term = pathfindR.data::kegg_genes,
  term_descriptions = pathfindR.data::kegg_descriptions,
  adj_method = "bonferroni",
  enrichment_threshold = 0.05,
  list_active_snw_genes = FALSE
)
```

**Arguments**

|                                    |                                                                                                                                                                                                                                                                |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>snws</code>                  | a list of subnetwork genes (i.e., vectors of genes for each subnetwork)                                                                                                                                                                                        |
| <code>sig_genes_vec</code>         | vector of significant gene symbols. In the scope of this package, these are the input genes that were used for active subnetwork search                                                                                                                        |
| <code>pin_name_path</code>         | Name of the chosen PIN or absolute/path/to/PIN.sif. If PIN name, must be one of <code>c('Biogrid', 'STRING', 'GeneMania', 'IntAct', 'KEGG', 'mmu_STRING')</code> . If path/to/PIN.sif, the file must comply with the PIN specifications. (Default = 'Biogrid') |
| <code>genes_by_term</code>         | List that contains genes for each gene set. Names of this list are gene set IDs (default = <code>kegg_genes</code> )                                                                                                                                           |
| <code>term_descriptions</code>     | Vector that contains term descriptions for the gene sets. Names of this vector are gene set IDs (default = <code>kegg_descriptions</code> )                                                                                                                    |
| <code>adj_method</code>            | correction method to be used for adjusting p-values. (default = 'bonferroni')                                                                                                                                                                                  |
| <code>enrichment_threshold</code>  | adjusted-p value threshold used when filtering enrichment results (default = 0.05)                                                                                                                                                                             |
| <code>list_active_snw_genes</code> | boolean value indicating whether or not to report the non-significant active subnetwork genes for the active subnetwork which was enriched for the given term with the lowest p value (default = FALSE)                                                        |

**Value**

a dataframe of combined enrichment results. Columns are:

**ID** ID of the enriched term

**Term\_Description** Description of the enriched term

**Fold\_Enrichment** Fold enrichment value for the enriched term

**p\_value** p value of enrichment

**adj\_p** adjusted p value of enrichment

**support** the support (proportion of active subnetworks leading to enrichment over all subnetworks) for the gene set

**non\_Signif\_Snw\_Genes (OPTIONAL)** the non-significant active subnetwork genes, comma-separated

**See Also**

[enrichment](#) for the enrichment analysis for a single gene set

**Examples**

```
enr_res <- enrichment_analyses(
  snws = example_active_snws[1:2],
  sig_genes_vec = example_pathfindR_input$Gene.symbol[1:25],
  pin_name_path = 'KEGG'
)
```

---

|                  |                                           |
|------------------|-------------------------------------------|
| enrichment_chart | Create Bubble Chart of Enrichment Results |
|------------------|-------------------------------------------|

---

## Description

This function is used to create a ggplot2 bubble chart displaying the enrichment results.

## Usage

```
enrichment_chart(
  result_df,
  top_terms = 10,
  plot_by_cluster = FALSE,
  num_bubbles = 4,
  even_breaks = TRUE
)
```

## Arguments

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| result_df       | a data frame that must contain the following columns:<br><br><b>Term_Description</b> Description of the enriched term<br><b>Fold_Enrichment</b> Fold enrichment value for the enriched term<br><b>lowest_p</b> the lowest adjusted-p value of the given term over all iterations<br><b>Up_regulated</b> the up-regulated genes in the input involved in the given term's gene set, comma-separated<br><b>Down_regulated</b> the down-regulated genes in the input involved in the given term's gene set, comma-separated<br><b>Cluster(OPTIONAL)</b> the cluster to which the enriched term is assigned |
| top_terms       | number of top terms (according to the 'lowest_p' column) to plot (default = 10). If plot_by_cluster = TRUE, selects the top top_terms terms per each cluster. Set top_terms = NULL to plot for all terms. If the total number of terms is less than top_terms, all terms are plotted.                                                                                                                                                                                                                                                                                                                   |
| plot_by_cluster | boolean value indicating whether or not to group the enriched terms by cluster (works if result_df contains a 'Cluster' column).                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| num_bubbles     | number of sizes displayed in the legend # genes (Default = 4)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| even_breaks     | whether or not to set even breaks for the number of sizes displayed in the legend # genes. If TRUE (default), sets equal breaks and the number of displayed bubbles may be different than the number set by num_bubbles. If the exact number set by num_bubbles is required, set this argument to FALSE                                                                                                                                                                                                                                                                                                 |

Value

a `ggplot2` object containing the bubble chart. The x-axis corresponds to fold enrichment values while the y-axis indicates the enriched terms. Size of the bubble indicates the number of significant genes in the given enriched term. Color indicates the  $-\log_{10}(\text{lowest-p})$  value. The closer the color is to red, the more significant the enrichment is. Optionally, if 'Cluster' is a column of `result_df` and `plot_by_cluster == TRUE`, the enriched terms are grouped by clusters.

Examples

```
g <- enrichment_chart(example_pathfindR_output)
```

---

|                |                               |
|----------------|-------------------------------|
| fetch_gene_set | <i>Fetch Gene Set Objects</i> |
|----------------|-------------------------------|

---

Description

Function for obtaining the gene sets per term and the term descriptions to be used for enrichment analysis.

Usage

```
fetch_gene_set(  
  gene_sets = "KEGG",  
  min_gset_size = 10,  
  max_gset_size = 300,  
  custom_genes = NULL,  
  custom_descriptions = NULL  
)
```

Arguments

|                     |                                                                                                                                                                                                                                                                                                                                |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| gene_sets           | Name of the gene sets to be used for enrichment analysis. Available gene sets are 'KEGG', 'Reactome', 'BioCarta', 'GO-All', 'GO-BP', 'GO-CC', 'GO-MF', 'cell_markers', 'mmu_KEGG' or 'Custom'. If 'Custom', the arguments <code>custom_genes</code> and <code>custom_descriptions</code> must be specified. (Default = 'KEGG') |
| min_gset_size       | minimum number of genes a term must contain (default = 10)                                                                                                                                                                                                                                                                     |
| max_gset_size       | maximum number of genes a term must contain (default = 300)                                                                                                                                                                                                                                                                    |
| custom_genes        | a list containing the genes involved in each custom term. Each element is a vector of gene symbols located in the given custom term. Names should correspond to the IDs of the custom terms.                                                                                                                                   |
| custom_descriptions | A vector containing the descriptions for each custom term. Names of the vector should correspond to the IDs of the custom terms.                                                                                                                                                                                               |

**Value**

a list containing 2 elements

**genes\_by\_term** list of vectors of genes contained in each term

**term\_descriptions** vector of descriptions per each term

**Examples**

```
KEGG_gset <- fetch_gene_set()
GO_MF_gset <- fetch_gene_set('GO-MF', min_gset_size = 20, max_gset_size = 100)
```

---

|                    |                            |
|--------------------|----------------------------|
| fetch_java_version | <i>Obtain Java Version</i> |
|--------------------|----------------------------|

---

**Description**

Obtain Java Version

**Usage**

```
fetch_java_version()
```

**Details**

this function was adapted from the CRAN package sparklyr

**Value**

character vector containing the output of 'java -version'

---

|                  |                                                                              |
|------------------|------------------------------------------------------------------------------|
| filterActiveSnws | <i>Parse Active Subnetwork Search Output File and Filter the Subnetworks</i> |
|------------------|------------------------------------------------------------------------------|

---

**Description**

Parse Active Subnetwork Search Output File and Filter the Subnetworks

**Usage**

```
filterActiveSnws(
  active_snw_path,
  sig_genes_vec,
  score_quan_thr = 0.8,
  sig_gene_thr = 0.02
)
```

**Arguments**

|                              |                                                                                                                                                                                                                                        |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>active_snw_path</code> | path to the output of an Active Subnetwork Search                                                                                                                                                                                      |
| <code>sig_genes_vec</code>   | vector of significant gene symbols. In the scope of this package, these are the input genes that were used for active subnetwork search                                                                                                |
| <code>score_quan_thr</code>  | active subnetwork score quantile threshold. Must be between 0 and 1 or set to -1 for not filtering. (Default = 0.8)                                                                                                                    |
| <code>sig_gene_thr</code>    | threshold for the minimum proportion of significant genes in the subnetwork (Default = 0.02) If the number of genes to use as threshold is calculated to be < 2 (e.g. 50 signif. genes x 0.01 = 0.5), the threshold number is set to 2 |

**Value**

A list containing subnetworks: a list of of genes in every active subnetwork that has a score greater than the `score_quan_thr` quantile and that contains at least `sig_gene_thr` of significant genes and scores the score of each filtered active subnetwork

**See Also**

See [run\\_pathfindR](#) for the wrapper function of the pathfindR enrichment workflow

**Examples**

```
path2snw_list <- system.file(
  'extdata/resultActiveSubnetworkSearch.txt',
  package = 'pathfindR'
)
filtered <- filterActiveSnws(
  active_snw_path = path2snw_list,
  sig_genes_vec = example_pathfindR_input$Gene.symbol
)
```

---

fuzzy\_term\_clustering *Heuristic Fuzzy Multiple-linkage Partitioning of Enriched Terms*

---

**Description**

Heuristic Fuzzy Multiple-linkage Partitioning of Enriched Terms

**Usage**

```
fuzzy_term_clustering(
  kappa_mat,
  enrichment_res,
  kappa_threshold = 0.35,
  use_description = FALSE
)
```

**Arguments**

|                 |                                                                                                                                                                                                                                                                            |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| kappa_mat       | matrix of kappa statistics (output of <a href="#">create_kappa_matrix</a> )                                                                                                                                                                                                |
| enrichment_res  | data frame of pathfindR enrichment results. Must-have columns are 'Term_Description' (if use_description = TRUE) or 'ID' (if use_description = FALSE), 'Down_regulated', and 'Up_regulated'. If use_active_snw_genes = TRUE, 'non_Signif_Snw_Genes' must also be provided. |
| kappa_threshold | threshold for kappa statistics, defining strong relation (default = 0.35)                                                                                                                                                                                                  |
| use_description | Boolean argument to indicate whether term descriptions (in the 'Term_Description' column) should be used. (default = FALSE)                                                                                                                                                |

**Details**

The fuzzy clustering algorithm was implemented based on: Huang DW, Sherman BT, Tan Q, et al. The DAVID Gene Functional Classification Tool: a novel biological module-centric algorithm to functionally analyze large gene lists. *Genome Biol.* 2007;8(9):R183.

**Value**

a boolean matrix of cluster assignments. Each row corresponds to an enriched term, each column corresponds to a cluster.

**Examples**

```
## Not run:
fuzzy_term_clustering(kappa_mat, enrichment_res)
fuzzy_term_clustering(kappa_mat, enrichment_res, kappa_threshold = 0.45)

## End(Not run)
```

---

|                 |                                                                        |
|-----------------|------------------------------------------------------------------------|
| get_biogrid_pin | <i>Retrieve the Requested Release of Organism-specific BioGRID PIN</i> |
|-----------------|------------------------------------------------------------------------|

---

**Description**

Retrieve the Requested Release of Organism-specific BioGRID PIN

**Usage**

```
get_biogrid_pin(org = "Homo_sapiens", path2pin, release = "latest")
```

**Arguments**

|          |                                                                                                                                                                                                                                                                                                                                        |
|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| org      | organism name. BioGRID naming requires underscores for spaces so 'Homo sapiens' becomes 'Homo_sapiens', 'Mus musculus' becomes 'Mus_musculus' etc. See <a href="https://wiki.thebiogrid.org/doku.php/statistics">https://wiki.thebiogrid.org/doku.php/statistics</a> for a full list of available organisms (default = 'Homo_sapiens') |
| path2pin | the path of the file to save the PIN data. By default, the PIN data is saved in a temporary file                                                                                                                                                                                                                                       |
| release  | the requested BioGRID release (default = 'latest')                                                                                                                                                                                                                                                                                     |

**Value**

the path of the file in which the PIN data was saved. If path2pin was not supplied by the user, the PIN data is saved in a temporary file

---

|                    |                                                  |
|--------------------|--------------------------------------------------|
| get_gene_sets_list | <i>Retrieve Organism-specific Gene Sets List</i> |
|--------------------|--------------------------------------------------|

---

**Description**

Retrieve Organism-specific Gene Sets List

**Usage**

```
get_gene_sets_list(
  source = "KEGG",
  org_code = "hsa",
  species = "Homo sapiens",
  db_species = "HS",
  collection,
  subcollection = NULL
)
```

**Arguments**

|               |                                                                                                                                                                                                                                      |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| source        | As of this version, either 'KEGG', 'Reactome' or 'MSigDB' (default = 'KEGG')                                                                                                                                                         |
| org_code      | (Used for 'KEGG' only) KEGG organism code for the selected organism. For a full list of all available organisms, see <a href="https://www.genome.jp/kegg/catalog/org_list.html">https://www.genome.jp/kegg/catalog/org_list.html</a> |
| species       | species name for output genes, such as Homo sapiens, Mus musculus, etc. See <a href="#">msigdb_species</a> for all the species available in the msigdb package.                                                                      |
| db_species    | Species abbreviation for the human or mouse databases ("HS" or "MM").                                                                                                                                                                |
| collection    | collection. e.g., H, C1. (default = NULL, i.e. list all gene sets in collection). See <a href="#">msigdb_collections</a> for all available options the msigdb package.                                                               |
| subcollection | sub-collection, such as CGP, BP, etc. (default = NULL, i.e. list all gene sets in collection). See <a href="#">msigdb_collections</a> for all available options the msigdb package.                                                  |

**Value**

A list containing 2 elements:

- gene\_sets - A list containing the genes involved in each gene set
- descriptions - A named vector containing the descriptions for each gene set

. For 'KEGG' and 'MSigDB', it is possible to choose a specific organism. For a full list of all available KEGG organisms, see [https://www.genome.jp/kegg/catalog/org\\_list.html](https://www.genome.jp/kegg/catalog/org_list.html). See [msigdb\\_r\\_species](#) for all the species available in the msigdb\_r package used for obtaining 'MSigDB' gene sets. For Reactome, there is only one collection of pathway gene sets.

---

|                |                                                          |
|----------------|----------------------------------------------------------|
| get_kegg_gsets | <i>Retrieve Organism-specific KEGG Pathway Gene Sets</i> |
|----------------|----------------------------------------------------------|

---

**Description**

Retrieve Organism-specific KEGG Pathway Gene Sets

**Usage**

```
get_kegg_gsets(org_code = "hsa")
```

**Arguments**

|          |                                                                                                                                                                                                               |
|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| org_code | KEGG organism code for the selected organism. For a full list of all available organisms, see <a href="https://www.genome.jp/kegg/catalog/org_list.html">https://www.genome.jp/kegg/catalog/org_list.html</a> |
|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**Value**

list containing 2 elements:

- gene\_sets - A list containing KEGG IDs for the genes involved in each KEGG pathway
- descriptions - A named vector containing the descriptions for each KEGG pathway

get\_mgsigdb\_gsets

*Retrieve Organism-specific MSigDB Gene Sets***Description**

Retrieve Organism-specific MSigDB Gene Sets

**Usage**

```
get_mgsigdb_gsets(
  species = "Homo sapiens",
  db_species = "HS",
  collection = NULL,
  subcollection = NULL
)
```

**Arguments**

|               |                                                                                                                                                                                     |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| species       | species name for output genes, such as Homo sapiens, Mus musculus, etc. See <a href="#">msigdb_species</a> for all the species available in the msigdb package.                     |
| db_species    | Species abbreviation for the human or mouse databases ("HS" or "MM").                                                                                                               |
| collection    | collection. e.g., H, C1. (default = NULL, i.e. list all gene sets in collection). See <a href="#">msigdb_collections</a> for all available options the msigdb package.              |
| subcollection | sub-collection, such as CGP, BP, etc. (default = NULL, i.e. list all gene sets in collection). See <a href="#">msigdb_collections</a> for all available options the msigdb package. |

**Details**

this function utilizes the function [msigdb](#) from the msigdb package to retrieve the 'Molecular Signatures Database' (MSigDB) gene sets (Subramanian et al. 2005 <doi:10.1073/pnas.0506580102>, Liberzon et al. 2015 <doi:10.1016/j.cels.2015.12.004>). Available collections are: H: hallmark gene sets, C1: positional gene sets, C2: curated gene sets, C3: motif gene sets, C4: computational gene sets, C5: GO gene sets, C6: oncogenic signatures and C7: immunologic signatures

**Value**

Retrieves the MSigDB gene sets and returns a list containing 2 elements:

- gene\_sets - A list containing the genes involved in each of the selected MSigDB gene sets
- descriptions - A named vector containing the descriptions for each selected MSigDB gene set

---

|              |                                            |
|--------------|--------------------------------------------|
| get_pin_file | <i>Retrieve Organism-specific PIN data</i> |
|--------------|--------------------------------------------|

---

**Description**

Retrieve Organism-specific PIN data

**Usage**

```
get_pin_file(source = "BioGRID", org = "Homo_sapiens", path2pin, ...)
```

**Arguments**

|          |                                                                                                                                                                                                                                                                                                                                        |
|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| source   | As of this version, this function is implemented to get data from 'BioGRID' only. This argument (and this wrapper function) was implemented for future utility                                                                                                                                                                         |
| org      | organism name. BioGRID naming requires underscores for spaces so 'Homo sapiens' becomes 'Homo_sapiens', 'Mus musculus' becomes 'Mus_musculus' etc. See <a href="https://wiki.thebiogrid.org/doku.php/statistics">https://wiki.thebiogrid.org/doku.php/statistics</a> for a full list of available organisms (default = 'Homo_sapiens') |
| path2pin | the path of the file to save the PIN data. By default, the PIN data is saved in a temporary file                                                                                                                                                                                                                                       |
| ...      | additional arguments for <a href="#">get_biogrid_pin</a>                                                                                                                                                                                                                                                                               |

**Value**

the path of the file in which the PIN data was saved. If path2pin was not supplied by the user, the PIN data is saved in a temporary file

**Examples**

```
## Not run:
pin_path <- get_pin_file()

## End(Not run)
```

---

|                    |                                            |
|--------------------|--------------------------------------------|
| get_reactome_gsets | <i>Retrieve Reactome Pathway Gene Sets</i> |
|--------------------|--------------------------------------------|

---

**Description**

Retrieve Reactome Pathway Gene Sets

**Usage**

```
get_reactome_gsets()
```

**Value**

Gets the latest Reactome pathways gene sets in gmt format. Parses the gmt file and returns a list containing 2 elements:

- gene\_sets - A list containing the genes involved in each Reactome pathway
- descriptions - A named vector containing the descriptions for each Reactome pathway

---

|                    |                                                |
|--------------------|------------------------------------------------|
| gset_list_from_gmt | <i>Retrieve Gene Sets from GMT-format File</i> |
|--------------------|------------------------------------------------|

---

**Description**

Retrieve Gene Sets from GMT-format File

**Usage**

```
gset_list_from_gmt(path2gmt, descriptions_idx = 2)
```

**Arguments**

|                  |                                      |
|------------------|--------------------------------------|
| path2gmt         | path to the gmt file                 |
| descriptions_idx | index for descriptions (default = 2) |

**Value**

list containing 2 elements:

- gene\_sets - A list containing the genes involved in each gene set
- descriptions - A named vector containing the descriptions for each gene set

---

|                              |                                                  |
|------------------------------|--------------------------------------------------|
| hierarchical_term_clustering | <i>Hierarchical Clustering of Enriched Terms</i> |
|------------------------------|--------------------------------------------------|

---

**Description**

Hierarchical Clustering of Enriched Terms

**Usage**

```

hierarchical_term_clustering(
  kappa_mat,
  enrichment_res,
  num_clusters = NULL,
  use_description = FALSE,
  clu_method = "average",
  plot_hmap = FALSE,
  plot_dend = TRUE
)

```

**Arguments**

|                 |                                                                                                                                                                                                                                                                            |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| kappa_mat       | matrix of kappa statistics (output of <a href="#">create_kappa_matrix</a> )                                                                                                                                                                                                |
| enrichment_res  | data frame of pathfindR enrichment results. Must-have columns are 'Term_Description' (if use_description = TRUE) or 'ID' (if use_description = FALSE), 'Down_regulated', and 'Up_regulated'. If use_active_snw_genes = TRUE, 'non_Signif_Snw_Genes' must also be provided. |
| num_clusters    | number of clusters to be formed (default = NULL). If NULL, the optimal number of clusters is determined as the number which yields the highest average silhouette width.                                                                                                   |
| use_description | Boolean argument to indicate whether term descriptions (in the 'Term_Description' column) should be used. (default = FALSE)                                                                                                                                                |
| clu_method      | the agglomeration method to be used (default = 'average', see <a href="#">hclust</a> )                                                                                                                                                                                     |
| plot_hmap       | boolean to indicate whether to plot the kappa statistics clustering heatmap or not (default = FALSE)                                                                                                                                                                       |
| plot_dend       | boolean to indicate whether to plot the clustering dendrogram partitioned into the optimal number of clusters (default = TRUE)                                                                                                                                             |

**Details**

The function initially performs hierarchical clustering of the enriched terms in enrichment\_res using the kappa statistics (defining the distance as 1 - kappa\_statistic). Next, the clustering dendrogram is cut into k = 2, 3, ..., n - 1 clusters (where n is the number of terms). The optimal number of clusters is determined as the k value which yields the highest average silhouette width. (if num\_clusters not specified)

**Value**

a vector of clusters for each enriched term in the enrichment results.

**Examples**

```

## Not run:
hierarchical_term_clustering(kappa_mat, enrichment_res)
hierarchical_term_clustering(kappa_mat, enrichment_res, method = 'complete')

```

```
## End(Not run)
```

---

hyperg\_test

*Hypergeometric Distribution-based Hypothesis Testing*

---

## Description

Hypergeometric Distribution-based Hypothesis Testing

## Usage

```
hyperg_test(term_genes, chosen_genes, background_genes)
```

## Arguments

|                  |                                                                            |
|------------------|----------------------------------------------------------------------------|
| term_genes       | vector of genes in the selected term gene set                              |
| chosen_genes     | vector containing the set of input genes                                   |
| background_genes | vector of background genes (i.e. universal set of genes in the experiment) |

## Details

To determine whether the chosen\_genes are enriched (compared to a background pool of genes) in the term\_genes, the hypergeometric distribution is assumed and the appropriate p value (the value under the right tail) is calculated and returned.

## Value

the p-value as determined using the hypergeometric distribution.

## Examples

```
hyperg_test(letters[1:5], letters[2:5], letters)
hyperg_test(letters[1:5], letters[2:10], letters)
hyperg_test(letters[1:5], letters[2:13], letters)
```

---

|                  |                      |
|------------------|----------------------|
| input_processing | <i>Process Input</i> |
|------------------|----------------------|

---

## Description

Process Input

## Usage

```
input_processing(
  input,
  p_val_threshold = 0.05,
  pin_name_path = "Biogrid",
  convert2alias = TRUE
)
```

## Arguments

|                 |                                                                                                                                                                                                                                                                                                                     |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| input           | the input data that pathfindR uses. The input must be a data frame with three columns: <ol style="list-style-type: none"> <li>1. Gene Symbol (Gene Symbol)</li> <li>2. Change value, e.g. log(fold change) (OPTIONAL)</li> <li>3. p value, e.g. adjusted p value associated with differential expression</li> </ol> |
| p_val_threshold | the p value threshold to use when filtering the input data frame. Must a numeric value between 0 and 1. (default = 0.05)                                                                                                                                                                                            |
| pin_name_path   | Name of the chosen PIN or absolute/path/to/PIN.sif. If PIN name, must be one of c('Biogrid', 'STRING', 'GeneMania', 'IntAct', 'KEGG', 'mmu_STRING'). If path/to/PIN.sif, the file must comply with the PIN specifications. (Default = 'Biogrid')                                                                    |
| convert2alias   | boolean to indicate whether or not to convert gene symbols in the input that are not found in the PIN to an alias symbol found in the PIN (default = TRUE)<br>IMPORTANT NOTE: the conversion uses human gene symbols/alias symbols.                                                                                 |

## Value

This function first filters the input so that all p values are less than or equal to the threshold. Next, gene symbols that are not found in the PIN are identified. If aliases of these gene symbols are found in the PIN, the symbols are converted to the corresponding aliases. The resulting data frame containing the original gene symbols, the updated symbols, change values and p values is then returned.

## See Also

See [run\\_pathfindR](#) for the wrapper function of the pathfindR workflow

Examples

```
processed_df <- input_processing(  
  input = example_pathfindR_input[1:5, ],  
  pin_name_path = 'KEGG'  
)  
processed_df <- input_processing(  
  input = example_pathfindR_input[1:5, ],  
  pin_name_path = 'KEGG',  
  convert2alias = FALSE  
)
```

---

|               |                      |
|---------------|----------------------|
| input_testing | <i>Input Testing</i> |
|---------------|----------------------|

---

Description

Input Testing

Usage

```
input_testing(input, p_val_threshold = 0.05)
```

Arguments

|                 |                                                                                                                                                                                                                                                                                              |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| input           | the input data that pathfindR uses. The input must be a data frame with three columns:<br><div><div>1. Gene Symbol (Gene Symbol)</div><div>2. Change value, e.g. log(fold change) (OPTIONAL)</div><div>3. p value, e.g. adjusted p value associated with differential expression</div></div> |
| p_val_threshold | the p value threshold to use when filtering the input data frame. Must a numeric value between 0 and 1. (default = 0.05)                                                                                                                                                                     |

Value

Only checks if the input and the threshold follows the required specifications.

See Also

See [run\\_pathfindR](#) for the wrapper function of the pathfindR workflow

Examples

```
input_testing(example_pathfindR_input, 0.05)
```

---

|         |                                        |
|---------|----------------------------------------|
| isColor | <i>Check if value is a valid color</i> |
|---------|----------------------------------------|

---

**Description**

Check if value is a valid color

**Usage**

```
isColor(x)
```

**Arguments**

|   |       |
|---|-------|
| x | value |
|---|-------|

**Value**

TRUE if x is a valid color, otherwise FALSE

---

|           |                                                                                   |
|-----------|-----------------------------------------------------------------------------------|
| pathfindR | <i>pathfindR: A package for Enrichment Analysis Utilizing Active Sub-networks</i> |
|-----------|-----------------------------------------------------------------------------------|

---

**Description**

pathfindR is a tool for active-subnetwork-oriented gene set enrichment analysis. The main aim of the package is to identify active subnetworks in a protein-protein interaction network using a user-provided list of genes and associated p values then performing enrichment analyses on the identified subnetworks, discovering enriched terms (i.e. pathways, gene ontology, TF target gene sets etc.) that possibly underlie the phenotype of interest.

**Details**

For analysis on non-Homo sapiens organisms, pathfindR offers utility functions for obtaining organism-specific PIN data and organism-specific gene sets data.

pathfindR also offers functionalities to cluster the enriched terms and identify representative terms in each cluster, to score the enriched terms per sample and to visualize analysis results.

**Author(s)**

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Authors:

- Ozan Ozisik <ozanytu@gmail.com> ([ORCID](#))

**See Also**

See [run\\_pathfindR](#) for details on the pathfindR active-subnetwork-oriented enrichment analysis  
 See [cluster\\_enriched\\_terms](#) for details on methods of enriched terms clustering to define clusters of biologically-related terms  
 See [score\\_terms](#) for details on agglomerated score calculation for enriched terms to investigate how a gene set is altered in a given sample (or in cases vs. controls)  
 See [term\\_gene\\_heatmap](#) for details on visualization of the heatmap of enriched terms by involved genes  
 See [term\\_gene\\_graph](#) for details on visualizing terms and term-related genes as a graph to determine the degree of overlap between the enriched terms by identifying shared and/or distinct significant genes  
 See [UpSet\\_plot](#) for details on creating an UpSet plot of the enriched terms. See [get\\_pin\\_file](#) for obtaining organism-specific PIN data and [get\\_gene\\_sets\\_list](#) for obtaining organism-specific gene sets data

plot\_scores

*Plot the Heatmap of Score Matrix of Enriched Terms per Sample***Description**

Plot the Heatmap of Score Matrix of Enriched Terms per Sample

**Usage**

```
plot_scores(
  score_matrix,
  cases = NULL,
  label_samples = TRUE,
  case_title = "Case",
  control_title = "Control",
  low = "green",
  mid = "black",
  high = "red"
)
```

**Arguments**

|               |                                                                                                      |
|---------------|------------------------------------------------------------------------------------------------------|
| score_matrix  | Matrix of agglomerated enriched term scores per sample. Columns are samples, rows are enriched terms |
| cases         | (Optional) A vector of sample names that are cases in the case/control experiment. (default = NULL)  |
| label_samples | Boolean value to indicate whether or not to label the samples in the heatmap plot (default = TRUE)   |
| case_title    | Naming of the 'Case' group (as in cases) (default = 'Case')                                          |
| control_title | Naming of the 'Control' group (default = 'Control')                                                  |
| low           | a string indicating the color of 'low' values in the coloring gradient (default = 'green')           |

|      |                                                                                            |
|------|--------------------------------------------------------------------------------------------|
| mid  | a string indicating the color of 'mid' values in the coloring gradient (default = 'black') |
| high | a string indicating the color of 'high' values in the coloring gradient (default = 'red')  |

**Value**

A 'ggplot2' object containing the heatmap plot. x-axis indicates the samples. y-axis indicates the enriched terms. 'Score' indicates the score of the term in a given sample. If cases are provided, the plot is divided into 2 facets, named by case\_title and control\_title.

**Examples**

```
score_matrix <- score_terms(  
  example_pathfindR_output,  
  example_experiment_matrix,  
  plot_hmap = FALSE  
)  
hmap <- plot_scores(score_matrix)
```

---

process\_pin

*Process Data frame of Protein-protein Interactions*

---

**Description**

Process Data frame of Protein-protein Interactions

**Usage**

```
process_pin(pin_df)
```

**Arguments**

|        |                                                                                              |
|--------|----------------------------------------------------------------------------------------------|
| pin_df | data frame of protein-protein interactions with 2 columns: 'Interactor_A' and 'Interactor_B' |
|--------|----------------------------------------------------------------------------------------------|

**Value**

processed PIN data frame (removes self-interactions and duplicated interactions)

---

|                 |                                                                           |
|-----------------|---------------------------------------------------------------------------|
| return_pin_path | <i>Return The Path to Given Protein-Protein Interaction Network (PIN)</i> |
|-----------------|---------------------------------------------------------------------------|

---

### Description

This function returns the absolute path/to/PIN.sif. While the default PINs are 'Biogrid', 'STRING', 'GeneMania', 'IntAct', 'KEGG' and 'mmu\_STRING'. The user can also use any other PIN by specifying the 'path/to/PIN.sif'. All PINs to be used in this package must formatted as SIF files: i.e. have 3 columns with no header, no row names and be tab-separated. Columns 1 and 3 must be interactors' gene symbols, column 2 must be a column with all rows consisting of 'pp'.

### Usage

```
return_pin_path(pin_name_path = "Biogrid")
```

### Arguments

|               |                                                                                                                                                                                                                                                  |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| pin_name_path | Name of the chosen PIN or absolute/path/to/PIN.sif. If PIN name, must be one of c('Biogrid', 'STRING', 'GeneMania', 'IntAct', 'KEGG', 'mmu_STRING'). If path/to/PIN.sif, the file must comply with the PIN specifications. (Default = 'Biogrid') |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

### Value

The absolute path to chosen PIN.

### See Also

See [run\\_pathfindR](#) for the wrapper function of the pathfindR workflow

### Examples

```
## Not run:
pin_path <- return_pin_path('GeneMania')

## End(Not run)
```

---

|               |                                                                                        |
|---------------|----------------------------------------------------------------------------------------|
| run_pathfindR | <i>Wrapper Function for pathfindR - Active-Subnetwork-Oriented Enrichment Workflow</i> |
|---------------|----------------------------------------------------------------------------------------|

---

### Description

run\_pathfindR is the wrapper function for the pathfindR workflow

**Usage**

```
run_pathfindR(
  input,
  gene_sets = "KEGG",
  min_gset_size = 10,
  max_gset_size = 300,
  custom_genes = NULL,
  custom_descriptions = NULL,
  pin_name_path = "Biogrid",
  p_val_threshold = 0.05,
  enrichment_threshold = 0.05,
  convert2alias = TRUE,
  plot_enrichment_chart = TRUE,
  output_dir = NULL,
  list_active_snw_genes = FALSE,
  ...
)
```

**Arguments**

|                      |                                                                                                                                                                                                                                                                                                                     |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| input                | the input data that pathfindR uses. The input must be a data frame with three columns: <ol style="list-style-type: none"> <li>1. Gene Symbol (Gene Symbol)</li> <li>2. Change value, e.g. log(fold change) (OPTIONAL)</li> <li>3. p value, e.g. adjusted p value associated with differential expression</li> </ol> |
| gene_sets            | Name of the gene sets to be used for enrichment analysis. Available gene sets are 'KEGG', 'Reactome', 'BioCarta', 'GO-All', 'GO-BP', 'GO-CC', 'GO-MF', 'cell_markers', 'mmu_KEGG' or 'Custom'. If 'Custom', the arguments custom_genes and custom_descriptions must be specified. (Default = 'KEGG')                |
| min_gset_size        | minimum number of genes a term must contain (default = 10)                                                                                                                                                                                                                                                          |
| max_gset_size        | maximum number of genes a term must contain (default = 300)                                                                                                                                                                                                                                                         |
| custom_genes         | a list containing the genes involved in each custom term. Each element is a vector of gene symbols located in the given custom term. Names should correspond to the IDs of the custom terms.                                                                                                                        |
| custom_descriptions  | A vector containing the descriptions for each custom term. Names of the vector should correspond to the IDs of the custom terms.                                                                                                                                                                                    |
| pin_name_path        | Name of the chosen PIN or absolute/path/to/PIN.sif. If PIN name, must be one of c('Biogrid', 'STRING', 'GeneMania', 'IntAct', 'KEGG', 'mmu_STRING'). If path/to/PIN.sif, the file must comply with the PIN specifications. (Default = 'Biogrid')                                                                    |
| p_val_threshold      | the p value threshold to use when filtering the input data frame. Must a numeric value between 0 and 1. (default = 0.05)                                                                                                                                                                                            |
| enrichment_threshold | adjusted-p value threshold used when filtering enrichment results (default = 0.05)                                                                                                                                                                                                                                  |

|                                    |                                                                                                                                                                                                                                     |
|------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>convert2alias</code>         | boolean to indicate whether or not to convert gene symbols in the input that are not found in the PIN to an alias symbol found in the PIN (default = TRUE)<br>IMPORTANT NOTE: the conversion uses human gene symbols/alias symbols. |
| <code>plot_enrichment_chart</code> | boolean value. If TRUE, a bubble chart displaying the enrichment results is plotted. (default = TRUE)                                                                                                                               |
| <code>output_dir</code>            | the directory to be created where the output and intermediate files are saved (default = NULL, a temporary directory is used)                                                                                                       |
| <code>list_active_snw_genes</code> | boolean value indicating whether or not to report the non-significant active subnetwork genes for the active subnetwork which was enriched for the given term with the lowest p value (default = FALSE)                             |
| <code>...</code>                   | additional arguments for <a href="#">active_snw_enrichment_wrapper</a>                                                                                                                                                              |

## Details

This function takes in a data frame consisting of Gene Symbol, log-fold-change and adjusted-p values. After input testing, any gene symbols that are not in the PIN are converted to alias symbols if the alias is in the PIN. Next, active subnetwork search is performed. Enrichment analysis is performed using the genes in each of the active subnetworks. Terms with adjusted-p values lower than `enrichment_threshold` are discarded. The lowest adjusted-p value (over all subnetworks) for each term is kept. This process of active subnetwork search and enrichment is repeated for a selected number of iterations, which is done in parallel. Over all iterations, the lowest and the highest adjusted-p values, as well as number of occurrences are reported for each enriched term.

## Value

Data frame of pathfindR enrichment results. Columns are:

**ID** ID of the enriched term

**Term\_Description** Description of the enriched term

**Fold\_Enrichment** Fold enrichment value for the enriched term (Calculated using ONLY the input genes)

**occurrence** the number of iterations that the given term was found to enriched over all iterations

**support** the median support (proportion of active subnetworks leading to enrichment within an iteration) over all iterations

**lowest\_p** the lowest adjusted-p value of the given term over all iterations

**highest\_p** the highest adjusted-p value of the given term over all iterations

**non\_Signif\_Snw\_Genes (OPTIONAL)** the non-significant active subnetwork genes, comma-separated

**Up\_regulated** the up-regulated genes (as determined by 'change value' > 0, if the 'change column' was provided) in the input involved in the given term's gene set, comma-separated. If change column not provided, all affected are listed here.

**Down\_regulated** the down-regulated genes (as determined by 'change value' < 0, if the 'change column' was provided) in the input involved in the given term's gene set, comma-separated

The function also creates an HTML report with the pathfindR enrichment results linked to the visualizations of the enriched terms in addition to the table of converted gene symbols. This report can be found in 'output\_dir/results.html' under the current working directory.

By default, a bubble chart of top 10 enrichment results are plotted. The x-axis corresponds to fold enrichment values while the y-axis indicates the enriched terms. Sizes of the bubbles indicate the number of significant genes in the given terms. Color indicates the  $-\log_{10}(\text{lowest-p})$  value; the more red it is, the more significant the enriched term is. See [enrichment\\_chart](#).

### Warning

Especially depending on the protein interaction network, the algorithm and the number of iterations you choose, 'active subnetwork search + enrichment' component of run\_pathfindR may take a long time to finish.

### See Also

[input\\_testing](#) for input testing, [input\\_processing](#) for input processing, [active\\_snw\\_search](#) for active subnetwork search and subnetwork filtering, [enrichment\\_analyses](#) for enrichment analysis (using the active subnetworks), [summarize\\_enrichment\\_results](#) for summarizing the active-subnetwork-oriented enrichment results, [annotate\\_term\\_genes](#) for annotation of affected genes in the given gene sets, [visualize\\_terms](#) for visualization of enriched terms, [enrichment\\_chart](#) for a visual summary of the pathfindR enrichment results, [foreach](#) for details on parallel execution of looping constructs, [cluster\\_enriched\\_terms](#) for clustering the resulting enriched terms and partitioning into clusters.

### Examples

```
## Not run:
run_pathfindR(example_pathfindR_input)

## End(Not run)
```

---

safe\_get\_content

*Safely download and parse web content*

---

### Description

This helper function retrieves content from a given URL using **httr**. It ensures that common issues (e.g. no internet, timeouts, HTTP errors, or parsing errors) are handled gracefully with clear, informative error messages.

### Usage

```
safe_get_content(url, ..., timeout_sec = 10)
```

**Arguments**

`url`                      Character string. The URL of the resource to download.

`...`                      Additional arguments passed to [GET](#).

`timeout_sec`            Numeric. Timeout in seconds for the request (default = 10).

**Details**

This function is intended for use inside package functions. For examples, vignettes, or tests, wrap calls in a connectivity check (e.g. using `http_error(HEAD(url))`) to avoid CRAN failures when the resource is temporarily unavailable.

**Value**

A character string containing the parsed content of the response (UTF-8 encoded). On failure, an error is raised with a clear message.

**Examples**

```
## Not run:
# Retrieve the latest BioGRID release page
result <- safe_get_content("https://downloads.thebiogrid.org/BioGRID/Latest-Release/")

## End(Not run)
```

---

|             |                                                                         |
|-------------|-------------------------------------------------------------------------|
| score_terms | <i>Calculate Agglomerated Scores of Enriched Terms for Each Subject</i> |
|-------------|-------------------------------------------------------------------------|

---

**Description**

Calculate Agglomerated Scores of Enriched Terms for Each Subject

**Usage**

```
score_terms(
  enrichment_table,
  exp_mat,
  cases = NULL,
  use_description = FALSE,
  plot_hmap = TRUE,
  ...
)
```

## Arguments

|                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| enrichment_table | a data frame that must contain the 3 columns below:<br><b>Term_Description</b> Description of the enriched term (necessary if use_description = TRUE)<br><b>ID</b> ID of the enriched term (necessary if use_description = FALSE)<br><b>Up_regulated</b> the up-regulated genes in the input involved in the given term's gene set, comma-separated<br><b>Down_regulated</b> the down-regulated genes in the input involved in the given term's gene set, comma-separated |
| exp_mat          | the experiment (e.g., gene expression/methylation) matrix. Columns are samples and rows are genes. Column names must contain sample names and row names must contain the gene symbols.                                                                                                                                                                                                                                                                                    |
| cases            | (Optional) A vector of sample names that are cases in the case/control experiment. (default = NULL)                                                                                                                                                                                                                                                                                                                                                                       |
| use_description  | Boolean argument to indicate whether term descriptions (in the 'Term_Description' column) should be used. (default = FALSE)                                                                                                                                                                                                                                                                                                                                               |
| plot_hmap        | Boolean value to indicate whether or not to draw the heatmap plot of the scores. (default = TRUE)                                                                                                                                                                                                                                                                                                                                                                         |
| ...              | Additional arguments for <a href="#">plot_scores</a> for aesthetics of the heatmap plot                                                                                                                                                                                                                                                                                                                                                                                   |

## Value

Matrix of agglomerated scores of each enriched term per sample. Columns are samples, rows are enriched terms. Optionally, displays a heatmap of this matrix.

## Conceptual Background

For an experiment matrix (containing expression, methylation, etc. values), the rows of which are genes and the columns of which are samples, we denote:

- E as a matrix of size  $m \times n$
- G as the set of all genes in the experiment  $G = E_{i.}, i \in [1, m]$
- S as the set of all samples in the experiment  $S = E_{.j.}, j \in [1, n]$

We next define the gene score matrix GS (the standardized experiment matrix, also of size  $m \times n$ ) as:

$$GS_{gs} = \frac{E_{gs} - \bar{e}_g}{s_g}$$

where  $g \in G$ ,  $s \in S$ ,  $\bar{e}_g$  is the mean of all values for gene g and  $s_g$  is the standard deviation of all values for gene g.

We next denote T to be a set of terms (where each  $t \in T$  is a set of term-related genes, i.e.,  $t = \{g_x, \dots, g_y\} \subset G$ ) and finally define the agglomerated term scores matrix TS (where rows correspond to genes and columns corresponds to samples s.t. the matrix has size  $|T| \times n$ ) as:

$$TS_{ts} = \frac{1}{|t|} \sum_{g \in t} GS_{gs}, \text{ where } t \in T \text{ and } s \in S.$$

**Examples**

```
score_matrix <- score_terms(
  example_pathfindR_output,
  example_experiment_matrix,
  plot_hmap = FALSE
)
```

---

|                     |                                                                                      |
|---------------------|--------------------------------------------------------------------------------------|
| single_iter_wrapper | <i>Active Subnetwork Search + Enrichment Analysis Wrapper for a Single Iteration</i> |
|---------------------|--------------------------------------------------------------------------------------|

---

**Description**

Active Subnetwork Search + Enrichment Analysis Wrapper for a Single Iteration

**Usage**

```
single_iter_wrapper(
  i = NULL,
  dirs,
  input_processed,
  pin_path,
  score_quan_thr,
  sig_gene_thr,
  search_method,
  silent_option,
  use_all_positives,
  geneInitProbs,
  saTemp0,
  saTemp1,
  saIter,
  gaPop,
  gaIter,
  gaThread,
  gaCrossover,
  gaMut,
  grMaxDepth,
  grSearchDepth,
  grOverlap,
  grSubNum,
  gset_list,
  adj_method,
  enrichment_threshold,
  list_active_snw_genes
)
```

**Arguments**

|                      |                                                                                                                                                                                                                                                                                 |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| i                    | current iteration index (default = NULL)                                                                                                                                                                                                                                        |
| dirs                 | vector of directories for parallel runs                                                                                                                                                                                                                                         |
| input_processed      | processed input data frame                                                                                                                                                                                                                                                      |
| pin_path             | path/to/PIN/file                                                                                                                                                                                                                                                                |
| score_quan_thr       | active subnetwork score quantile threshold. Must be between 0 and 1 or set to -1 for not filtering. (Default = 0.8)                                                                                                                                                             |
| sig_gene_thr         | threshold for the minimum proportion of significant genes in the subnetwork (Default = 0.02) If the number of genes to use as threshold is calculated to be < 2 (e.g. 50 signif. genes x 0.01 = 0.5), the threshold number is set to 2                                          |
| search_method        | algorithm to use when performing active subnetwork search. Options are greedy search (GR), simulated annealing (SA) or genetic algorithm (GA) for the search (default = 'GR').                                                                                                  |
| silent_option        | boolean value indicating whether to print the messages to the console (FALSE) or not (TRUE, this will print to a temp. file) during active subnetwork search (default = TRUE). This option was added because during parallel runs, the console messages get disorderly printed. |
| use_all_positives    | if TRUE: in GA, adds an individual with all positive nodes. In SA, initializes candidate solution with all positive nodes. (default = FALSE)                                                                                                                                    |
| geneInitProbs        | For SA and GA, probability of adding a gene in initial solution (default = 0.1)                                                                                                                                                                                                 |
| saTemp0              | Initial temperature for SA (default = 1.0)                                                                                                                                                                                                                                      |
| saTemp1              | Final temperature for SA (default = 0.01)                                                                                                                                                                                                                                       |
| saIter               | Iteration number for SA (default = 10000)                                                                                                                                                                                                                                       |
| gaPop                | Population size for GA (default = 400)                                                                                                                                                                                                                                          |
| gaIter               | Iteration number for GA (default = 200)                                                                                                                                                                                                                                         |
| gaThread             | Number of threads to be used in GA (default = 5)                                                                                                                                                                                                                                |
| gaCrossover          | Applies crossover with the given probability in GA (default = 1, i.e. always perform crossover)                                                                                                                                                                                 |
| gaMut                | For GA, applies mutation with given mutation rate (default = 0, i.e. mutation off)                                                                                                                                                                                              |
| grMaxDepth           | Sets max depth in greedy search, 0 for no limit (default = 1)                                                                                                                                                                                                                   |
| grSearchDepth        | Search depth in greedy search (default = 1)                                                                                                                                                                                                                                     |
| grOverlap            | Overlap threshold for results of greedy search (default = 0.5)                                                                                                                                                                                                                  |
| grSubNum             | Number of subnetworks to be presented in the results (default = 1000)                                                                                                                                                                                                           |
| gset_list            | list for gene sets                                                                                                                                                                                                                                                              |
| adj_method           | correction method to be used for adjusting p-values. (default = 'bonferroni')                                                                                                                                                                                                   |
| enrichment_threshold | adjusted-p value threshold used when filtering enrichment results (default = 0.05)                                                                                                                                                                                              |

`list_active_snw_genes`

boolean value indicating whether or not to report the non-significant active sub-network genes for the active subnetwork which was enriched for the given term with the lowest p value (default = FALSE)

### Value

Data frame of enrichment results using active subnetwork search results

---

`summarize_enrichment_results`

*Summarize Enrichment Results*

---

### Description

Summarize Enrichment Results

### Usage

```
summarize_enrichment_results(enrichment_res, list_active_snw_genes = FALSE)
```

### Arguments

`enrichment_res` a dataframe of combined enrichment results. Columns are:

**ID** ID of the enriched term

**Term\_Description** Description of the enriched term

**Fold\_Enrichment** Fold enrichment value for the enriched term

**p\_value** p value of enrichment

**adj\_p** adjusted p value of enrichment

**non\_Signif\_Snw\_Genes (OPTIONAL)** the non-significant active subnetwork genes, comma-separated

`list_active_snw_genes`

boolean value indicating whether or not to report the non-significant active sub-network genes for the active subnetwork which was enriched for the given term with the lowest p value (default = FALSE)

### Value

a dataframe of summarized enrichment results (over multiple iterations). Columns are:

**ID** ID of the enriched term

**Term\_Description** Description of the enriched term

**Fold\_Enrichment** Fold enrichment value for the enriched term

**occurrence** the number of iterations that the given term was found to enriched over all iterations

**support** the median support (proportion of active subnetworks leading to enrichment within an iteration) over all iterations

**lowest\_p** the lowest adjusted-p value of the given term over all iterations  
**highest\_p** the highest adjusted-p value of the given term over all iterations  
**non\_Signif\_Snw\_Genes (OPTIONAL)** the non-significant active subnetwork genes, comma-separated

Examples

```
## Not run:  
summarize_enrichment_results(enrichment_res)  
  
## End(Not run)
```

---

|                 |                        |
|-----------------|------------------------|
| term_gene_graph | Create Term-Gene Graph |
|-----------------|------------------------|

---

Description

Create Term-Gene Graph

Usage

```
term_gene_graph(  
  result_df,  
  num_terms = 10,  
  layout = "stress",  
  use_description = FALSE,  
  node_size = "num_genes",  
  node_colors = c("#E5D7BF", "green", "red")  
)
```

Arguments

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| result_df       | A dataframe of pathfindR results that must contain the following columns:<br><b>Term_Description</b> Description of the enriched term (necessary if use_description = TRUE)<br><b>ID</b> ID of the enriched term (necessary if use_description = FALSE)<br><b>lowest_p</b> the lowest adjusted-p value of the given term over all iterations<br><b>Up_regulated</b> the up-regulated genes in the input involved in the given term's gene set, comma-separated<br><b>Down_regulated</b> the down-regulated genes in the input involved in the given term's gene set, comma-separated |
| num_terms       | Number of top enriched terms to use while creating the graph. Set to NULL to use all enriched terms (default = 10, i.e. top 10 terms)                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| layout          | The type of layout to create (see <a href="#">ggraph</a> for details. Default = 'stress')                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| use_description | Boolean argument to indicate whether term descriptions (in the 'Term_Description' column) should be used. (default = FALSE)                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

|             |                                                                                                                                                                            |
|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| node_size   | Argument to indicate whether to use number of significant genes ('num_genes') or the -log10(lowest p value) ('p_val') for adjusting the node sizes (default = 'num_genes') |
| node_colors | vector of 3 colors to be used for coloring nodes (colors for term nodes, up, and down, respectively)                                                                       |

Details

This function (adapted from the Gene-Concept network visualization by the R package `enrichplot`) can be utilized to visualize which input genes are involved in the enriched terms as a graph. The term-gene graph shows the links between genes and biological terms and allows for the investigation of multiple terms to which significant genes are related. The graph also enables determination of the overlap between the enriched terms by identifying shared and distinct significant term-related genes.

Value

a `ggraph` object containing the term-gene graph. Each node corresponds to an enriched term (beige), an up-regulated gene (green) or a down-regulated gene (red). An edge between a term and a gene indicates that the given term involves the gene. Size of a term node is proportional to either the number of genes (if `node_size = 'num_genes'`) or the -log10(lowest p value) (if `node_size = 'p_val'`).

Examples

```
p <- term_gene_graph(example_pathfindR_output)
p <- term_gene_graph(example_pathfindR_output, num_terms = 5)
p <- term_gene_graph(example_pathfindR_output, node_size = 'p_val')
```

---

|                   |                               |
|-------------------|-------------------------------|
| term_gene_heatmap | Create Terms by Genes Heatmap |
|-------------------|-------------------------------|

---

Description

Create Terms by Genes Heatmap

Usage

```
term_gene_heatmap(
  result_df,
  genes_df,
  num_terms = 10,
  use_description = FALSE,
  low = "red",
  mid = "black",
  high = "green",
  legend_title = "change",
```

```

    sort_terms_by_p = FALSE,
    ...
)

```

## Arguments

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| result_df       | <p>A dataframe of pathfindR results that must contain the following columns:</p> <p><b>Term_Description</b> Description of the enriched term (necessary if use_description = TRUE)</p> <p><b>ID</b> ID of the enriched term (necessary if use_description = FALSE)</p> <p><b>lowest_p</b> the highest adjusted-p value of the given term over all iterations</p> <p><b>Up_regulated</b> the up-regulated genes in the input involved in the given term's gene set, comma-separated</p> <p><b>Down_regulated</b> the down-regulated genes in the input involved in the given term's gene set, comma-separated</p> |
| genes_df        | <p>the input data that was used with <a href="#">run_pathfindR</a>. It must be a data frame with 3 columns:</p> <ol style="list-style-type: none"> <li>1. Gene Symbol (Gene Symbol)</li> <li>2. Change value, e.g. log(fold change) (optional)</li> <li>3. p value, e.g. adjusted p value associated with differential expression</li> </ol> <p>The change values in this data frame are used to color the affected genes</p>                                                                                                                                                                                    |
| num_terms       | Number of top enriched terms to use while creating the plot. Set to NULL to use all enriched terms (default = 10)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| use_description | Boolean argument to indicate whether term descriptions (in the 'Term_Description' column) should be used. (default = FALSE)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| low             | a string indicating the color of 'low' values in the coloring gradient (default = 'green')                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| mid             | a string indicating the color of 'mid' values in the coloring gradient (default = 'black')                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| high            | a string indicating the color of 'high' values in the coloring gradient (default = 'red')                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| legend_title    | legend title (default = 'change')                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| sort_terms_by_p | boolean to indicate whether to sort terms by 'lowest_p' (TRUE) or by number of genes (FALSE) (default = FALSE)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| ...             | additional arguments for <a href="#">input_processing</a> (used if genes_df is provided)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

## Value

a ggplot2 object of a heatmap where rows are enriched terms and columns are involved input genes. If genes\_df is provided, colors of the tiles indicate the change values.

## Examples

```
term_gene_heatmap(example_pathfindR_output, num_terms = 3)
```

## UpSet\_plot

*Create UpSet Plot of Enriched Terms***Description**

Create UpSet Plot of Enriched Terms

**Usage**

```
UpSet_plot(
  result_df,
  genes_df,
  num_terms = 10,
  method = "heatmap",
  use_description = FALSE,
  low = "red",
  mid = "black",
  high = "green",
  ...
)
```

**Arguments**

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| result_df       | <p>A dataframe of pathfindR results that must contain the following columns:</p> <p><b>Term_Description</b> Description of the enriched term (necessary if use_description = TRUE)</p> <p><b>ID</b> ID of the enriched term (necessary if use_description = FALSE)</p> <p><b>lowest_p</b> the highest adjusted-p value of the given term over all iterations</p> <p><b>Up_regulated</b> the up-regulated genes in the input involved in the given term's gene set, comma-separated</p> <p><b>Down_regulated</b> the down-regulated genes in the input involved in the given term's gene set, comma-separated</p> |
| genes_df        | <p>the input data that was used with <a href="#">run_pathfindR</a>. It must be a data frame with 3 columns:</p> <ol style="list-style-type: none"> <li>1. Gene Symbol (Gene Symbol)</li> <li>2. Change value, e.g. log(fold change) (optional)</li> <li>3. p value, e.g. adjusted p value associated with differential expression</li> </ol> <p>The change values in this data frame are used to color the affected genes</p>                                                                                                                                                                                    |
| num_terms       | <p>Number of top enriched terms to use while creating the plot. Set to NULL to use all enriched terms (default = 10)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| method          | <p>the option for producing the plot. Options include 'heatmap', 'boxplot' and 'barplot'. (default = 'heatmap')</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| use_description | <p>Boolean argument to indicate whether term descriptions (in the 'Term_Description' column) should be used. (default = FALSE)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

|      |                                                                                                    |
|------|----------------------------------------------------------------------------------------------------|
| low  | a string indicating the color of 'low' values in the coloring gradient (default = 'green')         |
| mid  | a string indicating the color of 'mid' values in the coloring gradient (default = 'black')         |
| high | a string indicating the color of 'high' values in the coloring gradient (default = 'red')          |
| ...  | additional arguments for <code>input_processing</code> (used if <code>genes_df</code> is provided) |

### Value

UpSet plots are plots of the intersections of sets as a matrix. This function creates a ggplot object of an UpSet plot where the x-axis is the UpSet plot of intersections of enriched terms. By default (i.e. `method = 'heatmap'`) the main plot is a heatmap of genes at the corresponding intersections, colored by up/down regulation (if `genes_df` is provided, colored by change values). If `method = 'barplot'`, the main plot is bar plots of the number of genes at the corresponding intersections. Finally, if `method = 'boxplot'` and if `genes_df` is provided, then the main plot displays the boxplots of change values of the genes at the corresponding intersections.

### Examples

```
UpSet_plot(example_pathfindR_output)
```

---

```
visualize_active_subnetworks
```

*Visualize Active Subnetworks*

---

### Description

Visualize Active Subnetworks

### Usage

```
visualize_active_subnetworks(
  active_snw_path,
  genes_df,
  pin_name_path = "Biogrid",
  num_snws,
  layout = "stress",
  score_quan_thr = 0.8,
  sig_gene_thr = 0.02,
  ...
)
```

**Arguments**

|                              |                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>active_snw_path</code> | path to the output of an Active Subnetwork Search                                                                                                                                                                                                                                                                                                                                                                |
| <code>genes_df</code>        | the input data that was used with <a href="#">run_pathfindR</a> . It must be a data frame with 3 columns: <ol style="list-style-type: none"> <li>1. Gene Symbol (Gene Symbol)</li> <li>2. Change value, e.g. log(fold change) (optional)</li> <li>3. p value, e.g. adjusted p value associated with differential expression</li> </ol> The change values in this data frame are used to color the affected genes |
| <code>pin_name_path</code>   | Name of the chosen PIN or absolute/path/to/PIN.sif. If PIN name, must be one of c('Biogrid', 'STRING', 'GeneMania', 'IntAct', 'KEGG', 'mmu_STRING'). If path/to/PIN.sif, the file must comply with the PIN specifications. (Default = 'Biogrid')                                                                                                                                                                 |
| <code>num_snws</code>        | number of top subnetworks to be visualized (leave blank if you want to visualize all subnetworks)                                                                                                                                                                                                                                                                                                                |
| <code>layout</code>          | The type of layout to create (see <a href="#">ggraph</a> for details. Default = 'stress')                                                                                                                                                                                                                                                                                                                        |
| <code>score QUAN_thr</code>  | active subnetwork score quantile threshold. Must be between 0 and 1 or set to -1 for not filtering. (Default = 0.8)                                                                                                                                                                                                                                                                                              |
| <code>sig_gene_thr</code>    | threshold for the minimum proportion of significant genes in the subnetwork (Default = 0.02) If the number of genes to use as threshold is calculated to be < 2 (e.g. 50 signif. genes x 0.01 = 0.5), the threshold number is set to 2                                                                                                                                                                           |
| <code>...</code>             | additional arguments for <a href="#">input_processing</a>                                                                                                                                                                                                                                                                                                                                                        |

**Value**

a list of ggplot objects of graph visualizations of identified active subnetworks. Green nodes are down-regulated genes, reds are up-regulated genes and yellows are non-input genes

**Examples**

```
path2snw_list <- system.file(
  'extdata/resultActiveSubnetworkSearch.txt',
  package = 'pathfindR'
)
# visualize top 2 active subnetworks
g_list <- visualize_active_subnetworks(
  active_snw_path = path2snw_list,
  genes_df = example_pathfindR_input[1:10, ],
  pin_name_path = 'KEGG',
  num_snws = 2
)
```

---

`visualize_KEGG_diagram`*Visualize Human KEGG Pathways*

---

## Description

Visualize Human KEGG Pathways

## Usage

```
visualize_KEGG_diagram(  
  kegg_pw_ids,  
  input_processed,  
  scale_vals = TRUE,  
  node_cols = NULL,  
  legend.position = "top"  
)
```

## Arguments

|                              |                                                                                                                                                                                                                                                                                                                                                                         |
|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>kegg_pw_ids</code>     | KEGG ids of pathways to be colored and visualized                                                                                                                                                                                                                                                                                                                       |
| <code>input_processed</code> | input data processed via <a href="#">input_processing</a>                                                                                                                                                                                                                                                                                                               |
| <code>scale_vals</code>      | should change values be scaled? (default = TRUE)                                                                                                                                                                                                                                                                                                                        |
| <code>node_cols</code>       | low, middle and high color values for coloring the pathway nodes (default = NULL). If <code>node_cols=NULL</code> , the low, middle and high color are set as 'green', 'gray' and 'red'. If all change values are 1e6 (in case no changes are supplied, this dummy value is assigned by <a href="#">input_processing</a> ), only one color ('#F38F18' if NULL) is used. |
| <code>legend.position</code> | the default position of legends ("none", "left", "right", "bottom", "top", "inside")                                                                                                                                                                                                                                                                                    |

## Value

Creates colored visualizations of the enriched human KEGG pathways and returns them as a list of ggplot objects, named by Term ID.

## See Also

See [visualize\\_terms](#) for the wrapper function for creating enriched term diagrams. See [run\\_pathfindR](#) for the wrapper function of the pathfindR enrichment workflow.

## Examples

```
## Not run:
input_processed <- data.frame(
  GENE = c("PKLR", "GPI", "CREB1", "INS"),
  CHANGE = c(1.5, -2, 3, 5)
)
gg_list <- visualize_KEGG_diagram(c("hsa00010", "hsa04911"), input_processed)

## End(Not run)
```

---

visualize\_terms

---

*Create Diagrams for Enriched Terms*


---

## Description

Create Diagrams for Enriched Terms

## Usage

```
visualize_terms(
  result_df,
  input_processed = NULL,
  is_KEGG_result = TRUE,
  pin_name_path = "Biogrid",
  ...
)
```

## Arguments

|                 |                                                                                                                                                                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| result_df       | Data frame of enrichment results. Must-have columns for KEGG human pathway diagrams (is_KEGG_result = TRUE) are: 'ID' and 'Term_Description'. Must-have columns for the rest are: 'Term_Description', 'Up_regulated' and 'Down_regulated'        |
| input_processed | input data processed via <a href="#">input_processing</a> , not necessary when is_KEGG_result = FALSE                                                                                                                                            |
| is_KEGG_result  | boolean to indicate whether KEGG gene sets were used for enrichment analysis or not (default = TRUE)                                                                                                                                             |
| pin_name_path   | Name of the chosen PIN or absolute/path/to/PIN.sif. If PIN name, must be one of c('Biogrid', 'STRING', 'GeneMania', 'IntAct', 'KEGG', 'mmu_STRING'). If path/to/PIN.sif, the file must comply with the PIN specifications. (Default = 'Biogrid') |
| ...             | additional arguments for <a href="#">visualize_KEGG_diagram</a> (used when is_KEGG_result = TRUE) or <a href="#">visualize_term_interactions</a> (used when is_KEGG_result = FALSE)                                                              |

## Details

For `is_KEGG_result = TRUE`, KEGG pathway diagrams are created, affected nodes colored by up/down regulation status. For other gene sets, interactions of affected genes are determined (via a shortest-path algorithm) and are visualized (colored by change status) using `igraph`.

## Value

Depending on the argument `is_KEGG_result`, creates visualization of interactions of genes involved in the list of enriched terms in `result_df`. Returns a list of `ggplot` objects named by Term ID.

## See Also

See [visualize\\_KEGG\\_diagram](#) for the visualization function of KEGG diagrams. See [visualize\\_term\\_interactions](#) for the visualization function that generates diagrams showing the interactions of input genes in the PIN. See [run\\_pathfindR](#) for the wrapper function of the `pathfindR` workflow.

## Examples

```
## Not run:
input_processed <- data.frame(
  GENE = c("PARP1", "NDUFA1", "STX6", "SNAP23"),
  CHANGE = c(1.5, -2, 3, 5)
)
result_df <- example_pathfindR_output[1:2, ]

gg_list <- visualize_terms(result_df, input_processed)
gg_list2 <- visualize_terms(result_df, is_KEGG_result = FALSE, pin_name_path = 'IntAct')

## End(Not run)
```

---

`visualize_term_interactions`*Visualize Interactions of Genes Involved in the Given Enriched Terms*

---

## Description

Visualize Interactions of Genes Involved in the Given Enriched Terms

## Usage

```
visualize_term_interactions(result_df, pin_name_path, show_legend = TRUE)
```

**Arguments**

|                            |                                                                                                                                                                                                                                                  |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>result_df</code>     | Data frame of enrichment results. Must-have columns are: 'Term_Description', 'Up_regulated' and 'Down_regulated'                                                                                                                                 |
| <code>pin_name_path</code> | Name of the chosen PIN or absolute/path/to/PIN.sif. If PIN name, must be one of c('Biogrid', 'STRING', 'GeneMania', 'IntAct', 'KEGG', 'mmu_STRING'). If path/to/PIN.sif, the file must comply with the PIN specifications. (Default = 'Biogrid') |
| <code>show_legend</code>   | Boolean to indicate whether to display the legend (TRUE) or not (FALSE) (default: TRUE)                                                                                                                                                          |

**Details**

The following steps are performed for the visualization of interactions of genes involved for each enriched term:

1. shortest paths between all affected genes are determined (via [igraph](#))
2. the nodes of all shortest paths are merged
3. the PIN is subsetting using the merged nodes (genes)
4. using the PIN subset, the graph showing the interactions is generated
5. the final graph is visualized using [igraph](#), colored by changed status (if provided)

**Value**

list of ggplot objects (named by Term ID) visualizing the interactions of genes involved in the given enriched terms (annotated in the `result_df`) in the PIN used for enrichment analysis (specified by `pin_name_path`).

**See Also**

See [visualize\\_terms](#) for the wrapper function for creating enriched term diagrams. See [run\\_pathfindR](#) for the wrapper function of the pathfindR enrichment workflow.

**Examples**

```
## Not run:
result_df <- example_pathfindR_output[1:2, ]
gg_list <- visualize_term_interactions(result_df, pin_name_path = 'IntAct')

## End(Not run)
```

# Index

active\_snw\_enrichment\_wrapper, [3](#), [38](#)  
active\_snw\_search, [5](#), [39](#)  
annotate\_term\_genes, [7](#), [39](#)  
  
check\_java\_version, [8](#)  
cluster\_enriched\_terms, [9](#), [34](#), [39](#)  
cluster\_graph\_vis, [9](#), [10](#), [10](#)  
color\_kegg\_pathway, [11](#)  
combine\_pathfindR\_results, [13](#)  
combined\_results\_graph, [12](#)  
configure\_output\_dir, [14](#)  
create\_HTML\_report, [15](#)  
create\_kappa\_matrix, [10](#), [15](#), [23](#), [29](#)  
  
enrichment, [16](#), [18](#)  
enrichment\_analyses, [17](#), [17](#), [39](#)  
enrichment\_chart, [19](#), [39](#)  
  
fetch\_gene\_set, [20](#)  
fetch\_java\_version, [8](#), [21](#)  
filterActiveSnws, [21](#)  
foreach, [39](#)  
fuzzy\_term\_clustering, [9](#), [10](#), [22](#)  
  
GET, [40](#)  
get\_biogrid\_pin, [23](#), [27](#)  
get\_gene\_sets\_list, [24](#), [34](#)  
get\_kegg\_gsets, [25](#)  
get\_msigdb\_gsets, [26](#)  
get\_pin\_file, [27](#), [34](#)  
get\_reactome\_gsets, [27](#)  
ggplot2, [20](#)  
ggraph, [13](#), [45](#), [46](#), [50](#)  
gset\_list\_from\_gmt, [28](#)  
  
hclust, [29](#)  
hierarchical\_term\_clustering, [9](#), [10](#), [28](#)  
hyperg\_test, [17](#), [30](#)  
  
igraph, [54](#)  
input\_processing, [8](#), [12](#), [31](#), [39](#), [47](#), [49–52](#)  
  
input\_testing, [32](#), [39](#)  
isColor, [33](#)  
  
msigdb, [26](#)  
msigdb\_collections, [24](#), [26](#)  
msigdb\_species, [24–26](#)  
  
p.adjust, [17](#)  
pathfindR, [33](#)  
pathfindR-package (pathfindR), [33](#)  
plot\_scores, [34](#), [41](#)  
process\_pin, [35](#)  
  
return\_pin\_path, [36](#)  
run\_pathfindR, [17](#), [22](#), [31](#), [32](#), [34](#), [36](#), [36](#), [47](#),  
[48](#), [50](#), [51](#), [53](#), [54](#)  
  
safe\_get\_content, [39](#)  
score\_terms, [34](#), [40](#)  
single\_iter\_wrapper, [42](#)  
summarize\_enrichment\_results, [39](#), [44](#)  
  
term\_gene\_graph, [34](#), [45](#)  
term\_gene\_heatmap, [34](#), [46](#)  
  
UpSet\_plot, [34](#), [48](#)  
  
visualize\_active\_subnetworks, [49](#)  
visualize\_KEGG\_diagram, [51](#), [52](#), [53](#)  
visualize\_term\_interactions, [52](#), [53](#), [53](#)  
visualize\_terms, [39](#), [51](#), [52](#), [54](#)