

Package ‘PANACEA’

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Title Personalized Network-Based Anti-Cancer Therapy Evaluation

Version 1.1.0

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Description Identification of the most appropriate pharmacotherapy for each patient based on genomic alterations is a major challenge in personalized oncology. 'PANACEA' is a collection of personalized anti-cancer drug prioritization approaches utilizing network methods. The methods utilize personalized ``driverness" scores from 'driveR' to rank drugs, mapping these onto a protein-protein interaction network. The ``distance-based" method scores each drug based on these scores and distances between drugs and genes to rank given drugs. The ``RWR" method propagates these scores via a random-walk with restart framework to rank the drugs. The methods are described in detail in Ulgen E, Ozisik O, Sezerman OU. 2023. PANACEA: network-based methods for pharmacotherapy prioritization in personalized oncology. Bioinformatics <doi:10.1093/bioinformatics/btad022>.

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Encoding UTF-8

RoxygenNote 7.3.3

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

BugReports <https://github.com/egeulgen/PANACEA/issues>

Imports DBI, igraph, reshape2

Suggests org.Hs.eg.db, rmarkdown, knitr, testthat (>= 3.0.0), covr

Config/testthat/edition 3

Depends R (>= 4.0)

LazyData true

LazyDataCompression xz

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NeedsCompilation yes

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add_drugs_as_nodes	<i>Add Drugs as Nodes</i>
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Description

Add Drugs as Nodes

Usage

add_drugs_as_nodes(W_mat, drug_target_interactions, edge_weight = 1000)

Arguments

- | | |
|--------------------------|---|
| W_mat | adjacency matrix for the chosen PIN |
| drug_target_interactions | data frame containing (processed) drugs and target genes |
| edge_weight | edge weight for drug-target gene interaction (default = 1000) |

Value

adjacency matrix with the drugs added as nodes

adj_list2mat	<i>Turn Adjacency List into Adjacency Matrix</i>
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Description

Turn Adjacency List into Adjacency Matrix

Usage

```
adj_list2mat(adj_list)
```

Arguments

adj_list	Adjacency list
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Value

Adjacency matrix

convert2alias	<i>Convert Input Gene Symbols to Alias</i>
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Description

Convert Input Gene Symbols to Alias

Usage

```
convert2alias(input_genes, target_genes)
```

Arguments

input_genes	vector of input genes
target_genes	vector of target genes

Value

vector of converted gene symbols (if any alias in target genes)

DGIdb_interactions_df	<i>DGIdb Interactions Expert-curated Sources</i>
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Description

Data frame containing drug-gene interactions from expert-curated sources (CancerCommons, CGI, ChEMBLInteractions, CIViC, ClarityFoundationBiomarkers, ClarityFoundationClinicalTrial, COSMIC, DoCM, MyCancerGenome, MyCancerGenomeClinicalTrial, TALC, TdgClinicalTrial, TEND) from DGIdb.

Usage

```
DGIdb_interactions_df
```

Format

a data frame containing 11323 rows and 2 variables:

drug_name Drug name

gene_name HGNC gene symbol for the interacting gene

example_driveR_res	<i>Example driveR Result</i>
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Description

Data frame containing 'driveR' results for a lung adenocarcinoma case.

Usage

```
example_driveR_res
```

Format

a data frame containing 106 rows and 3 variables:

gene_symbol HGNC gene symbol

driverness_prob 'driverness' probability

prediction driveR's prediction for whether the gene is a 'driver' or 'non-driver'

example_scores_dist	<i>Example PANACEA "distance-based" Method Result</i>
---------------------	---

Description

Vector containing 'PANACEA' "distance-based" results for a lung adenocarcinoma case. Names are drug names, values are scores

Usage

```
example_scores_dist
```

Format

named vector of 1423 values

example_scores_RWR	<i>Example PANACEA "RWR" Method Result</i>
--------------------	--

Description

Vector containing 'PANACEA' "RWR" results for a lung adenocarcinoma case. Names are drug names, values are scores

Usage

```
example_scores_RWR
```

Format

named vector of 1423 values

Laplacian.norm	<i>Graph Laplacian Normalization</i>
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Description

Graph Laplacian Normalization

Usage

```
Laplacian.norm(W)
```

Arguments

W square symmetric adjacency matrix

Value

normalized adjacency matrix

network_propagation *Network Propagation (Random-walk with Restart)*

Description

Network Propagation (Random-walk with Restart)

Usage

```
network_propagation(prior_vec, W_prime, alpha, max.iter = 1000, eps = 1e-04)
```

Arguments

prior_vec vector of prior knowledge on selected genes (names are gene symbols)

W_prime (Laplacian-normalized, symmetric) adjacency matrix

alpha restart parameter, controlling trade-off between prior information and network smoothing

max.iter maximum allowed number of iterations (default = 1000)

eps epsilon value to assess the L2 norm of the difference between iterations (default = 1e-4)

Details

Implementing RWR following the following publications: Cowen L, Ideker T, Raphael BJ, Sharan R. Network propagation: a universal amplifier of genetic associations. Nat Rev Genet. 2017 Sep;18(9):551–62. Shnaps O, Perry E, Silverbush D, Sharan R. Inference of personalized drug targets via network propagation. Pac Symp Biocomput. 2016;21:156–67.

Value

vector of propagation values

PANACEA	<i>PANACEA: Personalized Network-based Anti-Cancer Therapy Evaluation</i>
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Description

Identification of the most appropriate pharmacotherapy for each patient based on genomic alterations is a major challenge in personalized oncology. PANACEA is a collection of personalized anti-cancer drug prioritization approaches utilizing network methods. The methods utilize personalized "driverness" scores from 'driveR' to rank drugs, mapping these onto a protein-protein interaction network (PIN). The "distance-based" method scores each drug based on these scores and distances between drugs and genes to rank given drugs. The "RWR" method propagates these scores via a random-walk with restart framework to rank the drugs.

Author(s)

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See Also

[score_drugs](#) for the wrapper function for scoring of drugs via network-based methods

process_drug_target_interactions	<i>Process Drug-Target Interactions</i>
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Description

Process Drug-Target Interactions

Usage

```
process_drug_target_interactions(  
  drug_target_interactions,  
  PIN_genes,  
  drug_name_col = "drug_name",  
  target_col = "gene_name"  
)
```

Arguments

- drug_target_interactions data frame containing drugs and target genes
- PIN_genes gene symbols for the chosen PIN
- drug_name_col name of the column containing drug names (default = "drug_name")
- target_col name of the column containing drug targets (default = "converted_target_gene")

Value

processed drug-target interactions. Processing involves converting symbols missing in the PIN, merging drugs that have the same target gene(s)

score_drugs	<i>Scoring of Drugs via Network-based Methods</i>
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Description

Scoring of Drugs via Network-based Methods

Usage

score_drugs(driveR_res, drug_interactions_df, W_mat, method, ...)

Arguments

- driveR_res data frame of driveR results
- drug_interactions_df data frame of drug-gene interactions
- W_mat adjacency matrix for the PIN
- method scoring method (one of 'distance-based' or 'RWR')
- ... additional arguments for [score_drugs_distance_based](#) or [score_drugs_RWR_based](#)

Details

This is the wrapper function for the two proposed methods for personalized scoring of drugs for individual cancer samples via network-based methods. The available methods are 'distance-based' and 'RWR'. For the 'distance-based' method, the score between a gene (g) and drug (d) is formulated as:

$$score(g, d) = driver(g) / (d(g, d) + 1)^2$$

where driver(g) is the driverness probability of gene g, as predicted by 'driveR' and d(g, d) is the distance withing the PIN between gene g and drug d. The final score of the drug d is then the average of the scores between each altered gene and d:

$$score(d) = \Sigma score(g, d) / |genes|$$

For the 'RWR' method, a random-walk with restart framework is used to propagate the driverness probabilities.

By default [DGIdb_interactions_df](#) is used as the drug_interactions_df.

If the W_mat argument is not supplied, the built-in STRNG data [STRING_adj_df](#) is used to generate W_mat.

Value

vector of scores per drug.

Examples

```

toy_data <- data.frame(
  gene_symbol = c("TP53", "EGFR", "KDR", "ATM"),
  driverness_prob = c(0.94, 0.92, 0.84, 0.72)
)
toy_interactions <- DGIdb_interactions_df[1:25, ]
res <- score_drugs(
  driveR_res = toy_data,
  drug_interactions_df = toy_interactions, # leave blank for default
  W_mat = toy_W_mat, # leave blank for default
  method = "distance-based",
  verbose = FALSE
)

```

score_drugs_distance_based

Distance-based Scoring of Drugs

Description

Distance-based Scoring of Drugs

Usage

```

score_drugs_distance_based(
  driveR_res,
  drug_interactions_df,
  W_mat,
  driver_prob_cutoff = 0.05,
  drug_name_col = "drug_name",
  target_col = "gene_name",
  verbose = TRUE
)

```

Arguments

driveR_res	data frame of driveR results
drug_interactions_df	data frame of drug-gene interactions
W_mat	adjacency matrix for the PIN
driver_prob_cutoff	cut-off value for 'driverness_prob' (default = 0.05)
drug_name_col	for 'drug_interactions_df', the column name containing drug names/identifiers
target_col	for 'drug_interactions_df', the column name containing target gene symbols
verbose	boolean to control verbosity (default = TRUE)

Value

vector of scores per drug. Drugs with the same target gene(s) are merged (via [process_drug_target_interactions](#))

Examples

```
toy_data <- data.frame(
  gene_symbol = c("TP53", "EGFR", "KDR", "ATM"),
  driverness_prob = c(0.94, 0.92, 0.84, 0.72)
)
toy_interactions <- DGIdb_interactions_df[1:100, ]
res <- score_drugs_distance_based(
  driveR_res = toy_data,
  drug_interactions_df = toy_interactions,
  W_mat = toy_W_mat, verbose = FALSE
)
```

score_drugs_RWR_based *RWR-based Scoring of Drugs*

Description

RWR-based Scoring of Drugs

Usage

```
score_drugs_RWR_based(
  driveR_res,
  drug_interactions_df,
  W_mat,
  alpha = 0.05,
  max.iter = 1000,
  eps = 1e-04,
  drug_name_col = "drug_name",
  target_col = "gene_name",
  verbose = TRUE
)
```

Arguments

driveR_res	data frame of driveR results
drug_interactions_df	data frame of drug-gene interactions
W_mat	adjacency matrix for the PIN
alpha	restart parameter, controlling trade-off between prior information and network smoothing
max.iter	maximum allowed number of iterations (default = 1000)

eps	epsilon value to assess the L2 norm of the difference between iterations (default = 1e-4)
drug_name_col	for 'drug_interactions_df', the column name containing drug names/identifiers
target_col	for 'drug_interactions_df', the column name containing target gene symbols
verbose	boolean to control verbosity (default = TRUE)

Value

vector of scores per drug. Drugs with the same target gene(s) are merged (via [process_drug_target_interactions](#))

Examples

```
toy_data <- data.frame(
  gene_symbol = c("TP53", "EGFR", "KDR", "ATM"),
  driverness_prob = c(0.94, 0.92, 0.84, 0.72)
)
toy_interactions <- DGIdb_interactions_df[1:100, ]
res <- score_drugs_RWR_based(
  driveR_res = toy_data,
  drug_interactions_df = toy_interactions,
  W_mat = toy_W_mat, verbose = FALSE
)
```

STRING_adj_df	<i>Adjacency List for STRING v11.5 - High Confidence Interactions</i>
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Description

Data frame of adjacency list for STRING v11.5 interactions with combined score > 700 (high confidence)

Usage

```
STRING_adj_df
```

Format

a data frame with 887797 rows and 3 variables:

- protein1** Interactor 1
- protein2** Interactor 2
- value** edge weight(combined score)

toy_W_mat	<i>Toy Adjacency Matrix (for examples)</i>
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Description

Symmetric matrix containing example adjacency data

Usage

toy_W_mat

Format

matrix of 84 rows and 84 columns

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