Package ‘dce’

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**Type** Package

**Title** Pathway Enrichment Based on Differential Causal Effects

**Version** 1.10.0

**Description** Compute differential causal effects (dce) on (biological) networks.

Given observational samples from a control experiment and non-control (e.g., cancer) for two genes A and B, we can compute differential causal effects with a (generalized) linear regression.

If the causal effect of gene A on gene B in the control samples is different from the causal effect in the non-control samples the dce will differ from zero.

We regularize the dce computation by the inclusion of prior network information from pathway databases such as KEGG.

**URL** [https://github.com/cbg-ethz/dce](https://github.com/cbg-ethz/dce)

**BugReports** [https://github.com/cbg-ethz/dce/issues](https://github.com/cbg-ethz/dce/issues)

**biocViews** Software, StatisticalMethod, GraphAndNetwork, Regression, GeneExpression, DifferentialExpression, NetworkEnrichment, Network, KEGG

**License** GPL-3

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**VignetteBuilder** knitr

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**Imports** stats, methods, assertthat, graph, pcalg, purrr, tidyverse, Matrix, ggraph, tidygraph, ggplot2, rlang, expm, MASS, edgeR, epiNEM, igraph, metap, mnem, naturalsort, ppcor, glm2, graphite, reshape2, dplyr, magrittr, glue, Rgraphviz, harmonicmeanp, org.Hs.eg.db, logger, shadowtext
git_url https://git.bioconductor.org/packages/dce

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as.data.frame.dce  
Dce to data frame

Description
Turn dce object into data frame

Usage
## S3 method for class 'dce'
as.data.frame(x, row.names = NULL, optional = FALSE, ...)

Arguments
x           dce object
row.names   optional character vector of rownames
optional    logical; allow optional arguments
...         additional arguments

Value
data frame containing the dce output

Examples
dag <- create_random_DAG(30, 0.2)
X_wt <- simulate_data(dag)
dag_mt <- resample_edge_weights(dag)
X_mt <- simulate_data(dag_mt)
dce_list <- dce(dag, X_wt, X_mt)

as_adjmat  
graph to adjacency

Description
From graphNEL with 0 edge weights to proper adjacency matrix

Usage
as_adjmat(g)

Arguments
g         graphNEL object
create_random_DAG

Value

graph as adjacency matrix

Examples

dag <- create_random_DAG(30, 0.2)
adj <- as_adjmat(dag)

create_random_DAG Create random DAG (topologically ordered)

Description

Creates a DAG according to given parameters.

Usage

create_random_DAG(
  node_num,
  prob,
  eff_min = -1,
  eff_max = 1,
  node_labels = paste0("n", as.character(seq_len(node_num))),
  max_par = 3
)

Arguments

node_num Number of nodes
prob Probability of creating an edge
eff_min Lower bound for edge weights
eff_max Upper bound for edge weights
node_labels Node labels
max_par Maximal number of parents

Value

graph

Author(s)

Martin Pirkl

Examples

dag <- create_random_DAG(30, 0.2)
dce

Differential Causal Effects - main function

Description

Main function to compute differential causal effects and the pathway enrichment

Usage

dce(
  graph,
  df_expr_wt,
  df_expr_mt,
  solver = "lm",
  solver_args = list(),
  adjustment_type = "parents",
  effect_type = "total",
  p_method = "hmp",
  test = "wald",
  lib_size = FALSE,
  deconfounding = FALSE,
  conservative = FALSE,
  log_level = logger::INFO
)

## S4 method for signature 'igraph'

dce(
  graph,
  df_expr_wt,
  df_expr_mt,
  solver = "lm",
  solver_args = list(),
  adjustment_type = "parents",
  effect_type = "total",
  p_method = "hmp",
  test = "wald",
  lib_size = FALSE,
  deconfounding = FALSE,
  conservative = FALSE,
  log_level = logger::INFO
)

## S4 method for signature 'graphNEL'

dce(
  graph,
  df_expr_wt,
  df_expr_mt,
solver = "lm",
solver_args = list(),
adjustment_type = "parents",
effect_type = "total",
p_method = "hmp",
test = "wald",
lib_size = FALSE,
deconfounding = FALSE,
conservative = FALSE,
log_level = logger::INFO
)

## S4 method for signature 'matrix'
dce(
  graph,
  df_expr_wt,
  df_expr_mt,
  solver = "lm",
  solver_args = list(),
  adjustment_type = "parents",
  effect_type = "total",
  p_method = "hmp",
  test = "wald",
  lib_size = FALSE,
  deconfounding = FALSE,
  conservative = FALSE,
  log_level = logger::INFO
)

Arguments

graph valid object defining a directed acyclic graph
df_expr_wt data frame with wild type expression values
df_expr_mt data from with mutation type expression values
solver character with name of solver function
solver_args additional arguments for the solver function. please adress this argument, if you use your own solver function. the default argument works with glm functions in the packages MASS, stats and glm2
adjustment_type character string for the method to define the adjustment set Z for the regression
effect_type method of computing causal effects
p_method character string. "mean", "sum" for standard summary functions, "hmp" for harmonic mean or any method from package 'metap'. e.g., "meunp" or "sump".
test either "wald" for testing significance with the wald test or "lr" for using a likelihood ratio test. Alternatively, "vcovHC" can improve results for zero-inflated date, i.e., from single cell RNAseq experiments.
library size either a numeric vector of the same length as the sum of wild type and mutant samples or a logical. If TRUE, it is recommended that both data sets include not only the genes included in the graph but all genes available in the original data set.

deconfounding indicates whether adjustment against latent confounding is used. If FALSE, no adjustment is used, if TRUE it adjusts for confounding by automatically estimating the number of latent confounders. The estimated number of latent confounders can be chosen manually by setting this variable to some number.

conservative logical; if TRUE, does not use the indicator variable for the variables in the adjustment set

log_level Control verbosity (logger::INFO, logger::DEBUG, ...)

Value

diff of matrices with dces and corresponding p-value

Examples

dag <- create_random_DAG(30, 0.2)
X.wt <- simulate_data(dag)
dag.mt <- resample_edge_weights(dag)
X.mt <- simulate_data(dag)
dce(dag,X.wt,X.mt)

dce_nb

Differential Causal Effects for negative binomial data

Description

Shortcut for the main function to analyse negative binomial data

Usage

dce_nb(
graph,
df_expr_wt,
df_expr_mt,
solver_args = list(method = "glm.dce.nb.fit", link = "identity"),
adjustment_type = "parents",
effect_type = "total",
p_method = "hmp",
test = "wald",
lib_size = FALSE,
deconfounding = FALSE,
conservative = FALSE,
log_level = logger::INFO
)

Arguments

- **graph**: valid object defining a directed acyclic graph
- **df_expr_wt**: data frame with wild type expression values
- **df_expr_mt**: data from with mutation type expression values
- **solver_args**: additional arguments for the solver function
- **adjustment_type**: character string for the method to define the adjustment set Z for the regression
- **effect_type**: method of computing causal effects
- **p_method**: character string. "mean", "sum" for standard summary functions, "hmp" for harmonic mean or any method from package 'metap', e.g., "meant" or "sump".
- **test**: either "wald" for testing significance with the wald test or "lr" for using a likelihood ratio test
- **lib_size**: either a numeric vector of the same length as the sum of wild type and mutant samples or a logical. If TRUE, it is recommended that both data sets include not only the genes included in the graph but all genes available in the original data set.
- **deconfounding**: indicates whether adjustment against latent confounding is used. If FALSE, no adjustment is used, if TRUE it adjusts for confounding by automatically estimating the number of latent confounders. The estimated number of latent confounders can be chosen manually by setting this variable to some number.
- **conservative**: logical; if TRUE, does not use the indicator variable for the variables in the adjustment set
- **log_level**: Control verbosity (logger::INFO, logger::DEBUG, ...)

Value

list of matrices with dces and corresponding p-value

Examples

```r
dag <- create_random_DAG(30, 0.2)
X.wt <- simulate_data(dag)
dag.mt <- resample_edge_weights(dag)
X.mt <- simulate_data(dag)
dce_nb(dag, X.wt, X.mt)
```

---

**df_pathway_statistics**  
Biological pathway information.

Description

A dataset containing pathway statistics.
Usage

df_pathway_statistics

Format

A data frame with pathway statistics

- **database**: Pathway database
- **pathway_id**: Internal ID of pathway
- **pathway_name**: Canonical name of pathway
- **node_num**: Number of nodes in pathway
- **edge_num**: Number of edges in pathway

estimate_latent_count: *Estimate number of latent confounders Compute the true casual effects of a simulated dag*

Description

This function takes a DAG with edgeweights as input and computes the causal effects of all nodes on all direct and indirect children in the DAG. Alternatively see pcalg::causalEffect for pairwise computation.

Usage

```r
estimate_latent_count(X1, X2, method = "auto")
```

Arguments

- **X1**: data matrix corresponding to the first condition
- **X2**: data matrix corresponding to the second condition
- **method**: a string indicating the method used for estimating the number of latent variables

Value

estimated number of latent variables

Author(s)

Domagoj Ćevid

Examples

```r
graph1 <- create_random_DAG(node_num = 100, prob = .1)
graph2 <- resample_edge_weights(graph1, tp=0.15)
X1 <- simulate_data(graph1, n=200, latent = 3)
X2 <- simulate_data(graph2, n=200, latent = 3)
estimate_latent_count(X1, X2)
```
**g2dag**

*Graph to DAG*

**Description**

Converts a general graph to a dag with minimum distance to the original graph. The general idea is to transitively close the graph to detect cycles and remove them based on the rule "the more outgoing edges a node has, the more likely it is that incoming edges from a cycle will be deleted, and vice versa. However, this is too rigorous and deletes too many edges, which do not lead to a cycle. These edges are added back in the final step.

**Usage**

```r
g2dag(g, tc = FALSE)
```

**Arguments**

- `g` graph as adjacency matrix
- `tc` if TRUE computes the transitive closure

**Value**

dag as adjacency matrix

**Author(s)**

Ken Adams

**Examples**

```r
g <- matrix(c(1,0,1,0, 1,1,0,0, 0,1,1,0, 1,1,0,1), 4, 4)ownames(g) <- colnames(g) <- LETTERS[seq_len(4)]
dag <- g2dag(g)
```

---

**get_pathways**

*Easy pathway network access*

**Description**

Easy pathway network access
get_pathway_info

Usage

get_pathways(
    query_species = "hsapiens",
    database_list = NULL,
    remove_empty_pathways = TRUE,
    pathway_list = NULL
)

Arguments

query_species For which species
database_list Which databases to query. Query all if ‘NULL’.
remove_empty_pathways Discard pathways without nodes
pathway_list List mapping database name to vector of pathway names to download

Value

list of pathways

Examples

pathways <- get_pathways(
    pathway_list = list(kegg = c("Protein processing in endoplasmic reticulum")
)
plot_network(as(pathways[[1]]$graph, "matrix"))

get_pathway_info

Dataframe containing meta-information of pathways in database

Description

Dataframe containing meta-information of pathways in database

Usage

get_pathway_info(
    query_species = "hsapiens",
    database_list = NULL,
    include_network_statistics = FALSE
)
get_prediction_counts

Arguments

query_species  For which species

database_list  Which databases to query. Query all if ‘NULL’.

include_network_statistics  Compute some useful statistics per pathway. Takes longer!

Value

data frame with pathway meta information

Examples

head(get_pathway_info(database_list = c("kegg")))

Description

Useful for performance evaluations

Usage

get_prediction_counts(truth, inferred, cutoff = 0.5)

Arguments

truth  Ground truth

inferred  Computed results

cutoff  Threshold for classification

Value

data.frame

Author(s)

Hans Wurst

Examples

get_prediction_counts(c(1,0), c(1,1))
### graph2df

**Graph to data frame**

**Description**
Convert graph object to dataframe with source and target columns

**Usage**
```
graph2df(graph)
```

**Arguments**
- `graph` Network

**Value**
data frame

**Examples**
```r
dag <- create_random_DAG(30, 0.2)
graph2df(dag)
```

### graph_union

**Graph union**

**Description**
Create union of multiple graphs

**Usage**
```
graph_union(graph_list)
```

**Arguments**
- `graph_list` List of graphs

**Value**
graph union

**Examples**
```r
dag <- create_random_DAG(30, 0.2)
dag2 <- create_random_DAG(30, 0.2)
graph_union(list(g1=dag, g2=dag2))```
**pcor**  
*Partial correlation*

**Description**
Robust partial correlation of column variables of a numeric matrix

**Usage**
```
pcor(x, g = NULL, adjustment_type = "parents", ...)
```

**Arguments**
- `x`: matrix
- `g`: related graph as adjacency matrix (optional)
- `adjustment_type`: character string for the method to define the adjustment set Z for the regression
- `...`: additional arguments for function `cor`

**Value**
matrix of partial correlations

**Examples**
```
x <- matrix(rnorm(100), 10, 10)
pcor(x)
```

---

**permutation_test**  
*Permutation test for (partial) correlation on non-Gaussian data*

**Description**
Computes the significance of (partial) correlation based on permutations of the observations

**Usage**
```
permutation_test(x, y, iter = 1000, fun = pcor, mode = 1, ...)
```
Arguments

- **x**: wild type data set
- **y**: mutant data set
- **iter**: number of iterations (permutations)
- **fun**: function to compute the statistic, e.g., cor or pcor
- **mode**: either 1 for a function that takes a single data set and produces an output of class matrix, and 2, if the function takes two data sets
- **...**: additional arguments for function ‘fun’

Value

matrix of p-values

Examples

```r
x <- matrix(rnorm(100),10,10)
y <- matrix(rnorm(100),10,10)
permutation_test(x,y,iter=10)
```

---

plot.dce

*Plot dce object*

Description

This function takes a differential causal effects object and plots the dag with the dces

Usage

```r
## S3 method for class 'dce'
plot(x, ...)
```

Arguments

- **x**: dce object
- **...**: Parameters passed to dce::plot_network

Value

plot of dag and dces

Author(s)

Martin Pirkl, Kim Philipp Jablonski
Examples

dag <- create_random_DAG(30, 0.2)
X.wt <- simulate_data(dag)
dag.mt <- resample_edge_weights(dag)
X.mt <- simulate_data(dag)
dce.list <- dce(dag,X.wt,X.mt)
plot(dce.list)

plot_network

Plot network adjacency matrix

Description

Generic function which plots any adjacency matrix (assumes DAG)

Usage

plot_network(
adja_matrix,
nodename_map = NULL,
edgescale_limits = NULL,
nodesize = 17,
labelsize = 3,
node_color = "white",
node_border_size = 0.5,
arrow_size = 0.05,
scale_edge_width_max = 1,
show_edge_labels = FALSE,
visualize_edge_weights = TRUE,
use_symlog = FALSE,
highlighted_nodes = c(),
legend_title = "edge weight",
value_matrix = NULL,
shadowtext = FALSE,
...)

Arguments

adja_matrix Adjacency matrix of network
nodename_map node names
edgescale_limits Limits for scale_edge_color_gradient2 (should contain 0). Useful to make plot comparable to others
nodesize Node sizes
labelsize Node label sizes
propagate_gene_edges

node_color Which color to plot nodes in
node_border_size Thickness of node's border stroke
arrow_size Size of edge arrows
scale_edge_width_max Max range for 'scale_edge_width'
show_edge_labels Whether to show edge labels (DCEs)
visualize_edge_weights Whether to change edge color/width/alpha relative to edge weight
use_symlog Scale edge colors using dce::symlog
highlighted_nodes List of nodes to highlight
legend_title Title of edge weight legend
value_matrix Optional matrix of edge weights if different from adjacency matrix
shadowtext Draw white outline around node labels
... additional parameters

Value
plot of dag and dces

Author(s)
Martin Pirkl, Kim Philipp Jablonski

Examples
adj <- matrix(c(0,0,0,1,0,0,0,1,0),3,3)
plot_network(adj)

propagate_gene_edges Remove non-gene nodes from pathway and reconnect nodes

Description
Remove non-gene nodes from pathway and reconnect nodes

Usage
propagate_gene_edges(graph)

Arguments
graph Biological pathway
**resample_edge_weights**

**Value**

graph with only genes as nodes

**Examples**

```r
dag <- create_random_DAG(30, 0.2)
propagate_gene_edges(dag)
```

---

**Description**

Takes a graph and modifies edge weights.

**Usage**

```r
resample_edge_weights(g, tp = 0.5, mineff = 1, maxeff = 2, method = "unif")
```

**Arguments**

- `g` original graph
- `tp` fraction of edge weights which will be modified
- `mineff` minimal differential effect size
- `maxeff` maximum effect effect size or standard deviation, if method is "gauss"
- `method` method for drawing the differential for the causal effects. Can be "unif", "exp" or "gauss".

**Value**

graph with new edge weights

**Author(s)**

Martin Pirkl

**Examples**

```r
graph.wt <- as(matrix(c(0,0,0,1,0,0,0,1,0), 3), "graphNEL")
graph.mt <- resample_edge_weights(graph.wt)
```
Description

costum rlm function

Usage

rlm_dce(...)
dist_fun = rnbinom,
dist_args = list(mu = 1000, size = 100),
child_fun = rpois,
child_args = list(),
child_dep = "lambda",
link_fun = negative.binomial.special()$linkfun,
link_args = list(offset = 1),
pop_size = 0,
latent = 0,
latent_fun = "unif"
)

## S4 method for signature 'graphNEL'
simulate_data(
  graph,
  n = 100,
  dist_fun = rnbinom,
  dist_args = list(mu = 1000, size = 100),
  child_fun = rpois,
  child_args = list(),
  child_dep = "lambda",
  link_fun = negative.binomial.special()$linkfun,
  link_args = list(offset = 1),
  pop_size = 0,
  latent = 0,
  latent_fun = "unif"
)

## S4 method for signature 'matrix'
simulate_data(
  graph,
  n = 100,
  dist_fun = rnbinom,
  dist_args = list(mu = 1000, size = 100),
  child_fun = rpois,
  child_args = list(),
  child_dep = "lambda",
  link_fun = negative.binomial.special()$linkfun,
  link_args = list(offset = 1),
  pop_size = 0,
  latent = 0,
  latent_fun = "unif"
)

**Arguments**

- **graph**: Graph to simulate on
- **n**: Number of samples
**Value**

graph

**Examples**

dag <- create_random_DAG(30, 0.2)
X <- simulate_data(dag)

```r

summary.rlm_dce

summary for rlm_dce

```

**Description**

summary for rlm_dce

**Usage**

```r

## S3 method for class 'rlm_dce'
summary(object, ...)

```

**Arguments**

object object of class 'rlm_dce'

... see ?MASS::summary.rlm

---

dist_fun
dist_args
child_fun
child_args
child_dep
link_fun
link_args
pop_size
latent
latent_fun
summary for rlm_dce

```r

```
topologically_ordering

*Description*

Order rows/columns of a adjacency matrix topologically

*Usage*

```r
topologically_ordering(adja_mat, alt = FALSE)
```

*Arguments*

- `adja_mat`: Adjacency matrix of network
- `alt`: Use igraph implementation

*Value*

topologically ordered matrix

*Examples*

```r
adj <- matrix(c(0,1,0,0,0,1,0,0,0),3,3)
topologically_ordering(adj)
```

**trueEffects**

*Compute the true causal effects of a simulated dag*

*Description*

This function takes a DAG with edgeweights as input and computes the causal effects of all nodes on all direct and indirect children in the DAG. Alternatively see pcalg::causalEffect for pairwise computation.

*Usage*

```r
trueEffects(g, partial = FALSE)
```

*Arguments*

- `g`: graphNEL object
- `partial`: if FALSE computes the total causal effects and not just the partial edge effects
**trueEffects**

**Value**

matrix of causal effects

**Author(s)**

Martin Pirkl

**Examples**

```r
graph.wt <- as(matrix(c(0,0,0,1,0,0,0,1,0), 3), "graphNEL")
trueEffects(graph.wt)
```
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