Package 'dce'

October 14, 2021

Type Package

Title Pathway Enrichment Based on Differential Causal Effects

Version 1.0.0

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

BugReports https://github.com/cbg-ethz/dce/issues

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

License GPL-3

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LazyData true

Depends R (>= 4.1)

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R topics documented:

`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

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 = "glm2",
  solver_args = list(method = glm.dce.fit),
  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 = "glm2",
  solver_args = list(method = glm.dce.fit),
  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 = "glm2",
  solver_args = list(method = glm.dce.fit),
  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 = "glm2",
  solver_args = list(method = glm.dce.fit),
  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, "test" for the selfcontained test of package 'CombinePValue' or any method from package 'metap', e.g., "meanp" 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

```
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)
```

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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, "test" for the selfcontained test of package 'CombinePValue' or any method from package 'metap', e.g., "meanp" 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

```
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

```
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

```
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

```
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

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

get_pathways *Easy pathway network access*

Description

Easy pathway network access

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
)
```

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")))
```

get_prediction_counts *Compute true positive/... counts*

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

```
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

```
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, ...)
```

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
`...`	additional arguments for function 'fun'

Value

matrix of p-values

Examples

```
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

```
## 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",
  show_edge_labels = FALSE,
  visualize_edge_weights = TRUE,
  use_symlog = FALSE,
  highlighted_nodes = c(),
  legend_title = "edge weight",
  value_matrix = NULL,
  ...
)
```

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
node_color	Which color to plot nodes in
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
...	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

Value

graph with only genes as nodes

Examples

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

`resample_edge_weights` *Resample network edge weights*

Description

Takes a graph and modifies edge weights.

Usage

```
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

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

---

rlm_dce *costum rlm function*

Description

costum rlm function

Usage

```
rlm_dce(...)
```

Arguments

...	see ?MASS::rlm

---

simulate_data *Simulate data*

Description

Generate data for given DAG.

Usage

```
simulate_data(
  graph,
  n = 100,
  dist_mean = 1000,
  dist_dispersion = 100,
  link = negative.binomial.special()$linkfun,
  pop_size = 0,
  latent = 0
)
```

```
## S4 method for signature 'igraph'
simulate_data(
  graph,
  n = 100,
  dist_mean = 1000,
  dist_dispersion = 100,
  link = negative.binomial.special()$linkfun,
  pop_size = 0,
  latent = 0
)

## S4 method for signature 'graphNEL'
simulate_data(
  graph,
  n = 100,
  dist_mean = 1000,
  dist_dispersion = 100,
  link = negative.binomial.special()$linkfun,
  pop_size = 0,
  latent = 0
)

## S4 method for signature 'matrix'
simulate_data(
  graph,
  n = 100,
  dist_mean = 1000,
  dist_dispersion = 100,
  link = negative.binomial.special()$linkfun,
  pop_size = 0,
  latent = 0
)
```

Arguments

graph	Graph to simulate on
n	Number of samples
dist_mean	distribution mean as numeric
dist_dispersion	distribution dispersion (actually dispersion^-1) as a scalar
link	special link function for the negative binomial distribution
pop_size	numeric for the population size, e.g., pop_size=1000 adds 1000-n random genes not in the graph
latent	number of latent variables

Value

graph

Examples

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

`summary.rlm_dce` *summary for rlm_dce*

Description

summary for rlm_dce

Usage

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

Arguments

`object`	object of class 'rlm_dce'
`...`	see ?MASS::summary.rlm

`topologically_ordering` *Topological ordering*

Description

Order rows/columns of a adjacency matrix topologically

Usage

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

Arguments

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

Value

topologically ordered matrix

Examples

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

`trueEffects` *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

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

Arguments

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

Value

matrix of causal effects

Author(s)

Martin Pirkl

Examples

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

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