

# Package ‘dce’

May 17, 2024

**Type** Package

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

**Version** 1.12.0

**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

**Encoding** UTF-8

**LazyData** true

**Depends** R (>= 4.1)

**Suggests** knitr, rmarkdown, testthat (>= 2.1.0), BiocStyle, formatR, cowplot, ggplotify, dagitty, lmtest, sandwich, devtools, curatedTCGADData, TCGAutils, SummarizedExperiment, RcppParallel, docopt, CARNIVAL

**VignetteBuilder** knitr

**RoxygenNote** 7.1.2

**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>

**git\_branch** RELEASE\_3\_19

**git\_last\_commit** 28e0453

**git\_last\_commit\_date** 2024-04-30

**Repository** Bioconductor 3.19

**Date/Publication** 2024-05-17

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## Contents

as.data.frame.dce . . . . .	3
as_adjmat . . . . .	3
create_random_DAG . . . . .	4
dce . . . . .	5
dce_nb . . . . .	7
df_pathway_statistics . . . . .	8
estimate_latent_count . . . . .	9
g2dag . . . . .	10
get_pathways . . . . .	10
get_pathway_info . . . . .	11
get_prediction_counts . . . . .	12
graph2df . . . . .	13
graph_union . . . . .	13
pcor . . . . .	14
permutation_test . . . . .	14
plot.dce . . . . .	15
plot_network . . . . .	16
propagate_gene_edges . . . . .	17
resample_edge_weights . . . . .	18
rlm_dce . . . . .	19
simulate_data . . . . .	19
summary.rlm_dce . . . . .	21
topologically_ordering . . . . .	22
trueEffects . . . . .	22

## Index

24

---

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	<i>Create random DAG (topologically ordered)</i>
-------------------	--

---

**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., "meanp" 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 data, i.e., from single cell RNAseq experiments.

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)
```

---

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., "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 Čevič

**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**

<code>g</code>	graph as adjacency matrix
<code>tc</code>	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	<i>Graph to data frame</i>
----------	----------------------------

---

**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	<i>Graph union</i>
-------------	--------------------

---

**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, 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**

```
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,
  labelsizes = 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
labelsizes	Node label sizes



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

**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	<i>costum rlm function</i>
---------	----------------------------

---

**Description**

costum rlm function

**Usage**

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

**Arguments**

... see ?MASS::rlm

---

simulate_data	<i>Simulate data</i>
---------------	----------------------

---

**Description**

Generate data for given DAG. The flexible framework allows for different distributions for source and child nodes. Default distributions are negative binomial (with mean = 100 and 1/dispersion = 100), and poisson, respectively.

**Usage**

```
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 'igraph'
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 '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

dist_fun	distribution function for nodes without parents
dist_args	list of arguments for dist_fun
child_fun	distribution function for nodes with parents
child_args	list of arguments for child_fun
child_dep	link_fun computes an output for the expression of nodes without parents. this output is than used as input for child_fun. child_dep defines the parameter (a a string) of child_fun, which is used for the input. E.g., the link_fun is the identity and the child_fun is rnorm, we usually set child_dep = "mean".
link_fun	special link function for the negative binomial distribution
link_args	list of arguments for link_fun
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
latent_fun	uniform "unif" or exponential "exp" distribution of latent coefficients

**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)
```

# Index

- \* **datasets**
  - df\_pathway\_statistics, 8
- as.data.frame.dce, 3
- as\_adjmat, 3
- create\_random\_DAG, 4
- dce, 5
  - dce, graphNEL-method (dce), 5
  - dce, igraph-method (dce), 5
  - dce, matrix-method (dce), 5
  - dce\_nb, 7
  - df\_pathway\_statistics, 8
- estimate\_latent\_count, 9
- g2dag, 10
- get\_pathway\_info, 11
- get\_pathways, 10
- get\_prediction\_counts, 12
- graph2df, 13
- graph\_union, 13
- pcor, 14
- permutation\_test, 14
- plot.dce, 15
- plot\_network, 16
- propagate\_gene\_edges, 17
- resample\_edge\_weights, 18
- rlm\_dce, 19
- simulate\_data, 19
  - simulate\_data, graphNEL-method (simulate\_data), 19
  - simulate\_data, igraph-method (simulate\_data), 19
  - simulate\_data, matrix-method (simulate\_data), 19
- summary.rlm\_dce, 21
- topologically\_ordering, 22
- trueEffects, 22