Package 'pareg'

August 5, 2022

Title Pathway enrichment using a regularized regression approach

Version 1.1.0

Description Compute pathway enrichment scores while accounting for term-term relations.
This package uses a regularized multiple linear regression to regress differential expression p-values obtained from multi-condition experiments on a pathway membership matrix.
By doing so, it is able to incorporate additional biological knowledge into the enrichment analysis and to estimate pathway enrichment scores more robustly.

URL https://github.com/cbg-ethz/pareg

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

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License GPL-3

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`as.data.frame.pareg` *as.data.frame for an object of class* `pareg`.

Description

Retrieve dataframe with enrichment information.

Usage

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

Arguments

`x`	An object of class `pareg`.
`row.names`	Optional character vector of rownames.
`optional`	Allow optional arguments.
`...`	Additional arguments.

Value

Dataframe containing enrichment score and name for each pathway.

Examples

```
df_genes <- data.frame(
  gene = paste("g", 1:20, sep = ""),
  pvalue = c(
    rbeta(10, .1, 1),
    rbeta(10, 1, 1)
  )
)
df_terms <- rbind(
  data.frame(
    term = "foo",
    gene = paste("g", 1:10, sep = "")
  ),
  data.frame(
    term = "bar",
    gene = paste("g", 11:20, sep = "")
  )
)
fit <- pareg(df_genes, df_terms, max_iterations = 10)
as.data.frame(fit)
```

---

as_dense_sim *Convert matrices.*

Description

Convert sparse similarity matrix from package data to a dense version with 1 on its diagonal. This matrix can then be used by `pareg`.

Usage

```
as_dense_sim(mat_sparse)
```

Arguments

`mat_sparse`	Sparse matrix.

Value

Dense matrix

Examples

```
transform_y(c(0, 0.5, 1))
```

`as_enrichplot_object` *Convert object of class* `pareg` *to class* `enrichResult`.

Description

The resulting object can be passed to any method from the enrichplot package and thus allows for nice visualizations of the enrichment results. Note: term similarities are included if available.

Usage

```
as_enrichplot_object(x, pvalue_threshold = 0.05)
```

Arguments

`x`	An object of class `pareg`.
`pvalue_threshold`	Treshold to select genes for count statistics.

Value

Object of class `enrichResult`.

Examples

```
df_genes <- data.frame(
  gene = paste("g", 1:20, sep = ""),
  pvalue = c(
    rbeta(10, .1, 1),
    rbeta(10, 1, 1)
  )
)
df_terms <- rbind(
  data.frame(
    term = "foo",
    gene = paste("g", 1:10, sep = "")
  ),
  data.frame(
    term = "bar",
    gene = paste("g", 11:20, sep = "")
  )
)
fit <- pareg(df_genes, df_terms, max_iterations = 10)
as_enrichplot_object(fit)
```

compute_term_similarities *Term similarity computation.*

Description

Generate similarity matrix for input terms.

Usage

```
compute_term_similarities(
  df_terms,
  similarity_function = jaccard,
  max_similarity = 1
)
```

Arguments

df_terms	Dataframe storing pathway database.
similarity_function	Function to compute similarity between two sets.
max_similarity	Value to fill diagonal with.

Value

Symmetric matrix of similarity scores.

Examples

```
df_terms <- data.frame(
  term = c("A", "A", "B", "B", "B", "C", "C", "C"),
  gene = c("a", "b", "a", "b", "c", "a", "c", "d")
)
compute_term_similarities(df_terms)
```

create_model_df *Create design matrix.*

Description

Store term membership for each gene.

Usage

```
create_model_df(df_genes, df_terms, pvalue_threshold = 0.05)
```

Arguments

df_genes	Dataframe storing gene names and DE p-values.
df_terms	Dataframe storing pathway database.
pvalue_threshold	P-value threshold to create binary columns ‘pvalue_sig‘ and ‘pvalue_notsig‘.

Value

Dataframe.

Examples

```
df_genes <- data.frame(
  gene = c("g1", "g2"),
  pvalue = c(0.1, 0.2)
)
df_terms <- data.frame(
  term = c("A", "A", "B", "B", "C"),
  gene = c("g1", "g2", "g1", "g2", "g2")
)
create_model_df(df_genes, df_terms)
```

---

cv_edgenet *Find the optimal shrinkage parameters for edgenet*

Description

Finds the optimal regulariztion parameters using cross-validation for edgenet. We use the BOBYQA algorithm to find the optimial regularization parameters in a cross-validation framework.

Usage

```
cv_edgenet(
  X,
  Y,
  G.X = NULL,
  G.Y = NULL,
  lambda = NA_real_,
  psigx = NA_real_,
  psigy = NA_real_,
  thresh = 1e-05,
  maxit = 1e+05,
  learning.rate = 0.01,
  family = gaussian,
  optim.thresh = 0.01,
  optim.maxit = 100,
  lambda_range = seq(0, 2, length.out = 10),
```

```
  psigx_range = seq(0, 500, length.out = 10),
  psigy_range = seq(0, 500, length.out = 10),
  nfolds = 2,
  cv_method = c("grid_search", "optim")
)

## S4 method for signature 'matrix,numeric'
cv_edgenet(
  X,
  Y,
  G.X = NULL,
  G.Y = NULL,
  lambda = NA_real_,
  psigx = NA_real_,
  psigy = NA_real_,
  thresh = 1e-05,
  maxit = 1e+05,
  learning.rate = 0.01,
  family = gaussian,
  optim.thresh = 0.01,
  optim.maxit = 100,
  lambda_range = seq(0, 2, length.out = 10),
  psigx_range = seq(0, 500, length.out = 10),
  psigy_range = seq(0, 500, length.out = 10),
  nfolds = 2,
  cv_method = c("grid_search", "optim")
)

## S4 method for signature 'matrix,matrix'
cv_edgenet(
  X,
  Y,
  G.X = NULL,
  G.Y = NULL,
  lambda = NA_real_,
  psigx = NA_real_,
  psigy = NA_real_,
  thresh = 1e-05,
  maxit = 1e+05,
  learning.rate = 0.01,
  family = gaussian,
  optim.thresh = 0.01,
  optim.maxit = 100,
  lambda_range = seq(0, 2, length.out = 10),
  psigx_range = seq(0, 500, length.out = 10),
  psigy_range = seq(0, 500, length.out = 10),
  nfolds = 2,
  cv_method = c("grid_search", "optim")
```

)

Arguments

X	input matrix, of dimension (n x p) where n is the number of observations and p is the number of covariables. Each row is an observation vector.
Y	output matrix, of dimension (n x q) where n is the number of observations and q is the number of response variables Each row is an observation vector.
G.X	non-negativ affinity matrix for X, of dimensions (p x p) where p is the number of covariables. Providing a graph G.X will optimize the regularization parameter psi.gx. If this is not desired just set G.X to NULL.
G.Y	non-negativ affinity matrix for Y, of dimensions (q x q) where q is the number of responses Y. Providing a graph G.Y will optimize the regularization parameter psi.gy. If this is not desired just set G.Y to NULL.
lambda	numerical shrinkage parameter for LASSO. Per default this parameter is set to NA_real_ which means that lambda is going to be estimated using cross-validation. If any numerical value for lambda is set, estimation of the optimal parameter will *not* be conducted.
psigx	numerical shrinkage parameter for graph-regularization of G.X. Per default this parameter is set to NA_real_ which means that psigx is going to be estimated in the cross-validation. If any numerical value for psigx is set, estimation of the optimal parameter will *not* be conducted.
psigy	numerical shrinkage parameter for graph-regularization of G.Y. Per default this parameter is set to NA_real_ which means that psigy is going to be estimated in the cross-validation. If any numerical value for psigy is set, estimation of the optimal parameter will *not* be conducted.
thresh	numerical threshold for the optimizer
maxit	maximum number of iterations for the optimizer (integer)
learning.rate	step size for Adam optimizer (numerical)
family	family of response, e.g. *gaussian* or *binomial*
optim.thresh	numerical threshold criterion for the optimization to stop. Usually 1e-3 is a good choice.
optim.maxit	the maximum number of iterations for the optimization (integer). Usually 1e4 is a good choice.
lambda_range	range of lambda to use in CV grid.
psigx_range	range of psigx to use in CV grid.
psigy_range	range of psigy to use in CV grid.
nfolds	the number of folds to be used - default is 10.
cv_method	which cross-validation method to use.

Value

An object of class `cv_edgenet`

`parameters`	the estimated, optimal regularization parameters
`lambda`	optimal estimated value for regularization parameter lambda (or, if provided as argument, the value of the parameter)
`psigx`	optimal estimated value for regularization parameter psigx (or, if provided as argument, the value of the parameter)
`psigy`	optimal estimated value for regularization parameter psigy (or, if provided as argument, the value of the parameter)
`estimated.parameters`	names of parameters that were estimated
`family`	family used for estimated
`fit`	an `edgenet` object fitted with the optimal, estimated paramters
`call`	the call that produced the object

Examples

```
X <- matrix(rnorm(100 * 10), 100, 10)
b <- matrix(rnorm(100), 10)
G.X <- abs(rWishart(1, 10, diag(10))[, , 1])
G.Y <- abs(rWishart(1, 10, diag(10))[, , 1])
diag(G.X) <- diag(G.Y) <- 0

# estimate the parameters of a Gaussian model
Y <- X %*% b + matrix(rnorm(100 * 10), 100)

## dont use affinity matrices and estimate lambda
fit <- cv_edgenet(
  X = X,
  Y = Y,
  family = gaussian,
  maxit = 1,
  lambda_range = c(0, 1)
)
## only provide one matrix and estimate lambda
fit <- cv_edgenet(
  X = X,
  Y = Y,
  G.X = G.X,
  psigx = 1,
  family = gaussian,
  maxit = 1,
  lambda_range = c(0, 1)
)
## estimate only lambda with two matrices
fit <- cv_edgenet(
  X = X,
  Y = Y,
```

```
  G.X = G.X,
  G.Y,
  psigx = 1,
  psigy = 1,
  family = gaussian,
  maxit = 1,
  lambda_range = c(0, 1)
)
## estimate only psigx
fit <- cv_edgenet(
  X = X,
  Y = Y,
  G.X = G.X,
  G.Y,
  lambda = 1,
  psigy = 1,
  family = gaussian,
  maxit = 1,
  psigx_range = c(0, 1)
)
## estimate all parameters
fit <- cv_edgenet(
  X = X,
  Y = Y,
  G.X = G.X,
  G.Y,
  family = gaussian,
  maxit = 1,
  lambda_range = c(0, 1),
  psigx_range = c(0, 1),
  psigy_range = c(0, 1)
)
## if Y is vectorial, we cannot use an affinity matrix for Y
fit <- cv_edgenet(
  X = X,
  Y = Y[, 1],
  G.X = G.X,
  family = gaussian,
  maxit = 1,
  lambda_range = c(0, 1),
  psigx_range = c(0, 1),
)
```

---

edgenet *Fit a graph-regularized linear regression model using edge-based regularization. Adapted from https://github.com/dirmeier/netReg.*

Description

Fit a graph-regularized linear regression model using edge-penalization. The coefficients are computed using graph-prior knowledge in the form of one/two affinity matrices. Graph-regularization

is an extension to previously introduced regularization techniques, such as the LASSO. See the vignette for details on the objective function of the model: `vignette("edgenet", package="netReg")`

Usage

```
edgenet(
  X,
  Y,
  G.X = NULL,
  G.Y = NULL,
  lambda = 0,
  psigx = 0,
  psigy = 0,
  thresh = 1e-05,
  maxit = 1e+05,
  learning.rate = 0.01,
  family = gaussian
)

## S4 method for signature 'matrix,numeric'
edgenet(
  X,
  Y,
  G.X = NULL,
  G.Y = NULL,
  lambda = 0,
  psigx = 0,
  psigy = 0,
  thresh = 1e-05,
  maxit = 1e+05,
  learning.rate = 0.01,
  family = gaussian
)

## S4 method for signature 'matrix,matrix'
edgenet(
  X,
  Y,
  G.X = NULL,
  G.Y = NULL,
  lambda = 0,
  psigx = 0,
  psigy = 0,
  thresh = 1e-05,
  maxit = 1e+05,
  learning.rate = 0.01,
  family = gaussian
)
```

Arguments

X	input matrix, of dimension (n x p) where n is the number of observations and p is the number of covariables. Each row is an observation vector.
Y	output matrix, of dimension (n x q) where n is the number of observations and q is the number of response variables. Each row is an observation vector.
G.X	non-negativ affinity matrix for X, of dimensions (p x p) where p is the number of covariables
G.Y	non-negativ affinity matrix for Y, of dimensions (q x q) where q is the number of responses
lambda	numerical shrinkage parameter for LASSO.
psigx	numerical shrinkage parameter for graph-regularization of G.X
psigy	numerical shrinkage parameter for graph-regularization of G.Y
thresh	numerical threshold for optimizer
maxit	maximum number of iterations for optimizer (integer)
learning.rate	step size for Adam optimizer (numerical)
family	family of response, e.g. *gaussian* or *binomial*

Value

An object of class edgenet

beta	the estimated (p x q)-dimensional coefficient matrix B.hat
alpha	the estimated (q x 1)-dimensional vector of intercepts
parameters	regularization parameters
lambda	regularization parameter lambda)
psigx	regularization parameter psigx
psigy	regularization parameter psigy
family	a description of the error distribution and link function to be used. Can be a pareg::family function or a character string naming a family function, e.g. gaussian or "gaussian".
call	the call that produced the object

References

Cheng, Wei and Zhang, Xiang and Guo, Zhishan and Shi, Yu and Wang, Wei (2014), Graph-regularized dual Lasso for robust eQTL mapping.
Bioinformatics

Examples

```
X <- matrix(rnorm(100 * 10), 100, 10)
b <- matrix(rnorm(100), 10)
G.X <- abs(rWishart(1, 10, diag(10))[, , 1])
G.Y <- abs(rWishart(1, 10, diag(10))[, , 1])
diag(G.X) <- diag(G.Y) <- 0

# estimate the parameters of a Gaussian model
Y <- X %*% b + matrix(rnorm(100 * 10), 100)
## dont use affinity matrices
fit <- edgenet(X = X, Y = Y, family = gaussian, maxit = 10)
## only provide one matrix
fit <- edgenet(
  X = X,
  Y = Y,
  G.X = G.X,
  psigx = 1,
  family = gaussian,
  maxit = 10
)
## use two matrices
fit <- edgenet(X = X, Y = Y, G.X = G.X, G.Y, family = gaussian, maxit = 10)
## if Y is vectorial, we cannot use an affinity matrix for Y
fit <- edgenet(X = X, Y = Y[, 1], G.X = G.X, family = gaussian, maxit = 10)
```

`family` *Family objects for models*

Description

Family objects provide a convenient way to specify the details of the models used by `pareg`. See also `stats::family` for more details.

Usage

```
family(object, ...)

gaussian(link = c("identity"))

bernoulli(link = c("logit", "probit", "log"))

beta(link = c("logit", "probit", "log"))

beta_phi_lm(link = c("logit", "probit", "log"))

beta_phi_var(link = c("logit", "probit", "log"))
```

Arguments

object	a object for which the family shoulr be retured (e.g. edgenet)
...	further arguments passed to methods
link	name of a link function

Value

An object of class pareg.family

family	name of the family
link	name of the link function
linkinv	inverse link function
loss	loss function

Examples

```
gaussian()
bernoulli("probit")$link
beta()$loss
```

---

generate_similarity_matrix

Similarity matrix generation.

Description

Generate block-structured similarity matrices corresponding to cluster structures.

Usage

```
generate_similarity_matrix(cluster_sizes)
```

Arguments

cluster_sizes	List of cluster sizes.

Value

Similarity matrix with samples as row-/colnames.

Examples

```
generate_similarity_matrix(c(1, 2, 3))
```

jaccard *Jaccard similarity.*

Description

Compute Jaccard similarity between two sets.

Usage

```
jaccard(x, y)
```

Arguments

x	First set.
y	Second set.

Value

Jaccard similarity between set x and y.

See Also

Other pathway similarity methods: `overlap_coefficient()`

Examples

```
jaccard(c(1, 2, 3), c(2, 3, 4))
```

overlap_coefficient *Overlap coefficient.*

Description

Compute overlap coefficient between two sets.

Usage

```
overlap_coefficient(x, y)
```

Arguments

x	First set.
y	Second set.

Value

Overlap coefficient between set x and y.

See Also

Other pathway similarity methods: `jaccard()`

Examples

```
overlap_coefficient(c(1, 2, 3), c(2, 3, 4))
```

`pareg` *Pathway enrichment using a regularized regression approach.*

Description

Run model to compute pathway enrichments. Can model inter-pathway relations, cross-validation and much more.

Usage

```
pareg(
  df_genes,
  df_terms,
  lasso_param = NA_real_,
  network_param = NA_real_,
  term_network = NULL,
  cv = FALSE,
  family = beta,
  response_column_name = "pvalue",
  max_iterations = 1e+05,
  lasso_param_range = seq(0, 2, length.out = 10),
  network_param_range = seq(0, 500, length.out = 10),
  ...
)
```

Arguments

`df_genes`	Dataframe storing gene names and DE p-values.
`df_terms`	Dataframe storing pathway database.
`lasso_param`	Lasso regularization parameter.
`network_param`	Network regularization parameter.
`term_network`	Term similarity network as adjacency matrix.
`cv`	Estimate best regularization parameters using cross-validation.
`family`	Distribution family of response.

response_column_name
: Which column of model dataframe to use as response.

max_iterations
: How many iterations to maximally run optimizer for.

lasso_param_range
: LASSO regularization parameter search space in grid search of CV.

network_param_range
: Network regularization parameter search space in grid search of CV.

...
: Further arguments to pass to '(cv.)edgenet'.

Value

An object of class pareg.

Examples

```
df_genes <- data.frame(
  gene = paste("g", 1:20, sep = ""),
  pvalue = c(
    rbeta(10, .1, 1),
    rbeta(10, 1, 1)
  )
)
df_terms <- rbind(
  data.frame(
    term = "foo",
    gene = paste("g", 1:10, sep = "")
  ),
  data.frame(
    term = "bar",
    gene = paste("g", 11:20, sep = "")
  )
)
pareg(df_genes, df_terms, max_iterations = 10)
```

---

pathway_similarities *Collection of pathway similarity matrices.*

Description

Contains matrices for various pathway databases and similarity measures. Note that the matrices are sparse, upper triangular and subsampled to a maximum size of $1000x1000$ if necessary. They can be transformed to a dense representation using pareg::as_dense_sim.

Usage

```
pathway_similarities
```

Format

A list of lists of matrices. * Pathway database 1 * Similarity measure 1 * Similarity measure 2 * ... * Pathway database 2 * ...

`plot.pareg` *Plot pareg object.*

Description

Check pareg::plot_pareg_with_args for details. Needed because of WARNING in "checking S3 generic/method consistency"

Usage

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

Arguments

`x`	An object of class `pareg`.
`...`	Parameters passed to pareg::plot_pareg_with_args

Value

ggplot object.

`plot_pareg_with_args` *Plot result of enrichment computation.*

Description

Visualize pathway enrichments as network.

Usage

```
plot_pareg_with_args(x, show_term_names = TRUE, min_similarity = 0)
```

Arguments

`x`	An object of class `pareg`.
`show_term_names`	Whether to plot node labels.
`min_similarity`	Don't plot edges for similarities below this value.

Value

ggplot object.

Examples

```
df_genes <- data.frame(
  gene = paste("g", 1:20, sep = ""),
  pvalue = c(
    rbeta(10, .1, 1),
    rbeta(10, 1, 1)
  )
)
df_terms <- rbind(
  data.frame(
    term = "foo",
    gene = paste("g", 1:10, sep = "")
  ),
  data.frame(
    term = "bar",
    gene = paste("g", 11:20, sep = "")
  )
)
fit <- pareg(df_genes, df_terms, max_iterations = 10)
plot(fit)
```

---

similarity_sample *Sample elements based on similarity structure.*

Description

Choose similar object more often, depending on 'similarity_factor'.

Usage

```
similarity_sample(sim_mat, size, similarity_factor = 1)
```

Arguments

sim_mat	Similarity matrix with samples as row/col names.
size	How many samples to draw.
similarity_factor	Uniform sampling for 0. Weights mixture of uniform and similarity vector for each draw.

Value

Vector of samples.

Examples

```
similarity_sample(matrix(runif(100), nrow = 10, ncol = 10), 3)
```

`transform_y` *Transform vector from [0, 1] to (0, 1).*

Description

Make (response) vector conform to Beta assumptions as described in section 2 of the betareg vignette https://cran.r-project.org/web/packages/betareg/vignettes/betareg.pdf.

Usage

```
transform_y(y)
```

Arguments

y	Numeric vector in [0, 1]^N

Value

Numeric vector in (0, 1)^N

Examples

```
transform_y(c(0, 0.5, 1))
```

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