Package 'DiNAMIC.Duo'

July 21, 2025

Title Finding Recurrent DNA Copy Number Alterations and Differences

Version 1.0.3

Description In tumor tissue, underlying genomic instability can lead to DNA copy number alterations, e.g., copy number gains or losses. Sporadic copy number alterations occur randomly throughout the
genome, whereas recurrent alterations are observed in the same genomic region across multiple independent samples, perhaps because they provide a selective growth advantage. Here we use cyclic shift permutations to identify recurrent copy number alterations in a single cohort or recurrent copy number differences in two cohorts based on a common set of genomic markers. Additional functionality is provided to perform downstream analyses, including the creation of summary files and graphics. DiNAMIC.Duo builds upon the original DiNAMIC package of Walter et al.
(2011) <doi:10.1093/bioinformatics/btq717> and leverages the theory developed in Walter et al. (2015) <doi:10.1093/biomet/asv046>. An article describing DiNAMIC.Duo by Walter et al. (2022)
can be found at <doi:10.1093/bioinformatics/btac542>.

Depends R (>= 3.5.0)

VignetteBuilder R.rsp

Suggests R.rsp

biocViews biomaRt

Imports biomaRt, dinamic, plyr, curl

License GPL-3

Encoding UTF-8

LazyData true

RoxygenNote 7.3.2

SystemRequirements Python, NumPy Python library

NeedsCompilation no

Author Vonn Walter [aut, cre] (ORCID: <https://orcid.org/0000-0001-6114-6714>),
Hyo Young Choi [aut] (ORCID: <https://orcid.org/0000-0002-7627-8493>),
Xiaobei Zhao [aut] (ORCID: <https://orcid.org/0000-0002-5277-0846>),
Yan Gao [aut] (ORCID: <https://orcid.org/0000-0002-6852-2038>),
David Neil Hayes [aut] (ORCID: <https://orcid.org/0000-0001-6203-7771>)

Maintainer Vonn Walter <vwalter1@pennstatehealth.psu.edu>

Repository CRAN

Date/Publication 2025-04-03 19:50:02 UTC

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`cyclicNullR` *Create a cyclic shift-based null distribution for one or two copy number matrices*

Description

Create a cyclic shift-based null distribution for one or two copy number matrices

Usage

```
cyclicNullR(X, Y = NULL, numPerms = 100, randomSeed = NULL)
```

Arguments

`X`	a matrix or a data frame of copy number data. The rows and columns of X correspond to genes and subjects, respectively.
`Y`	a matrix or a data frame of copy number data. The rows and columns of X correspond to genes and subjects, respectively. It is assumed that the rows of X and Y are indexed by the same set of genes that appear in genomic order.
`numPerms`	the number of cyclic shifts used to create the null distribution. Default = 1e2.
`randomSeed`	a random seed. Default = NULL.

Details

This function iteratively calls cyclicShiftColR to create an empirical permutation-based null distribution to assess the statistical significance of either (i) the maximum and minimum difference row means of X - row means of Y, or (ii) the maximum and minimum row means of X, depending on whether two or one copy number matrices are being analyzed. The application of cyclic shift permutations to DNA copy number matrices was originally described by Walter et al. (Bioinformatics, 2011;27(5):678–685).

Value

a matrix with two columns. The first column, maxNull, is an empirical permutation-based null distribution for the maximum difference of row means of X - row means of Y based on cyclic shift permutations of the columns of each matrix; the second column, minNull, is an empirical distribution of the minimum difference of the row means of X - the row means of Y based on the same permutations. If Y = NULL, the null distributions apply to the maximum and minimum row means of X.

Examples

```
data(DiNAMIC.Duo)
output = cyclicNullR(X = pD[["X"]], Y = pD[["Y"]], numPerms = 25, randomSeed = NULL)
```

---

cyclicShiftColR *Perform the cyclic shift procedure on the columns of a matrix*

Description

Perform the cyclic shift procedure on the columns of a matrix

Usage

```
cyclicShiftColR(X, randomSeed = NULL)
```

Arguments

X	a matrix or a data frame of copy number data. The rows and columns of X correspond to genes and subjects, respectively.
randomSeed	a random seed. Default = NULL.

Details

Many algorithms for identifying recurrent DNA copy number alterations, e.g., amplifications and deletions, assess statistical significance using permutation-based null distributions. Like many genomic data types, DNA copy number data has an underlying spatial correlation structure. Randomly permuting the values within a given subject ignores this structure, and this can impact type I error rates. In contrast, cyclic permutation largely preserves the local correlation structure.

Value

a matrix Z whose dimensions are the same as X. Each column of Z is obtained by perform a cyclic shift of the corresponding column of X.

Examples

```
test = matrix(c(1:50), 10, 5)
cyclicShiftColR(test, randomSeed = NULL)
```

`dataPrep` *Prepare copy number data for downstream analysis*

Description

Prepare copy number data for downstream analysis

Usage

```
dataPrep(
  X,
  Y = NULL,
  species = c("human", "mouse"),
  ensemblHost = "http://aug2020.archive.ensembl.org"
)
```

Arguments

`X`	a matrix or a data frame of copy number data. The rows and columns of X correspond to genes and subjects, respectively. X must have gene symbols as its row names.
`Y`	an optional matrix or data frame of copy number data to compare with X. As is the case for X, the rows and columns of Y correspond to genes and subjects, respectively. Y must have gene symbols as its row names.
`species`	a value specifying species for Ensembl database to be used; Default is "human".
`ensemblHost`	an Ensembl Archive that is used to access the Ensembl database; Default is "http://aug2020.archive.ensembl.org".

Details

This helper function is designed to prepare input matrices or data frames X and Y containing DNA copy number data for analysis. The downstream functions that X and Y are indexed by a common set of genes that appear in genomic order. In addition, the peelingOne and peelingTwo functions require information about the cytoband for each gene, and the resultsProcess function uses information about gene position. The dataPrep function queries biomaRt so users are not required to provide this information.

Value

a list of processed X and Y with a data frame containing gene annotation information.

Examples

```
#This runtime for this code slightly exceeds the limits imposed by CRAN.
data(DiNAMIC.Duo)
output = dataPrep(X=luadSubset,Y=NULL)
```

`findNull` *Find DiNAMIC's null distribution*

Description

Find DiNAMIC's null distribution

Usage

```
findNull(x, num.perms, random.seed = NULL)
```

Arguments

`x`	An n by m numeric matrix containing DNA copy number data from n subjects at m markers.
`num.perms`	A positive integer that represents the number of cyclic shifts used to create the empirical distribution.
`random.seed`	An optional random seed (default = NULL).

Details

The cyclic shift procedure is detailed in Bioinformatics (2011) 27(5) 678 - 685. Briefly, cyclic shift is a permutation procedure for DNA copy number data that largely preserves the underlying correlation of the markers. This function uses `num.perms` cyclic shifts of the copy number matrix `x` to create an approximate null distribution for `max(colSums(x))` or `min(colSums(x))`. The statistical significance of the observed value of `max(colSums(x))` or `min(colSums(x))` as assessed by the quickLook and detailedLook procedures described in the Bioinformatics paper.

Value

A numerical vector of length num.perms

Examples

```
random.seed = 12345
set.seed(random.seed)
x = matrix(rnorm(50), 5, 10)
num.perms = 10
findNull(x, num.perms, random.seed)
```

---

genomeChrPlot *A Function for Plotting Mean Copy Number Values and Differences Across Multiple Chromosomes*

Description

This function plots mean copy number values from one or two cohorts at a common set of markers across multiple chromosomes.

Usage

```
genomeChrPlot(
  inputList,
  plottingChrs = NULL,
  lwdVec = rep(1, 3),
  ltyVec = c(1:3),
  lineColorVec = c("red", "blue", "black"),
  ylimLow = -1,
  ylimHigh = 1,
  chrLabel = TRUE,
  xaxisLabel = "Chromosome",
  yaxisLabel = NULL,
  mainLabel = NULL,
  axisCex = 1,
  labelCex = 1,
  xaxisLine = 2.5,
  yaxisLine = 2.5,
  mainLine = 0,
  marginVec = c(4, 4, 3, 3),
  legendText = NULL,
  highThreshold = NULL,
  lowThreshold = NULL,
  showLegend = FALSE,
  legendXQuantile = 0.55,
  legendYCoord = 1
)
```

Arguments

inputList	A list produced by dataPrep.
plottingChrs	A numeric list of chromosomes to be plotted. A separate plot is produced for each chromosome.
lwdVec	A vector of line widths. Default = rep(1, 3). See par.
ltyVec	A vector of line types. Default = c(1:3). See par.
lineColorVec	A vector of line colors. Default = c("red", "blue", "black").
ylimLow	The lower limit of the y-values in the plot. Default = -1. See plot.
ylimHigh	The upper limit of the y-values in the plot. Default = 1. See plot.
chrLabel	Binary value determining whether or not chromosomes are labeled. Default = TRUE.
xaxisLabel	Label for the x-axis in the plot. Default = "Chromosome". See plot.
yaxisLabel	Label for the y-axis in the plot. Default = NULL. See plot.
mainLabel	Main label in the plot. Default = NULL. See plot.
axisCex	Point size for the scale on the axis. Default = 1. See par.
labelCex	Point size for the axis label. Default = 1. See par.
xaxisLine	Numerical value used to specify the location (line) of the x-axis label. Default = 2.5. See mtext.
yaxisLine	Numerical value used to specify the location (line) of the y-axis label. Default = 2.5. See mtext.
mainLine	Numerical value used to specify the location (line) of the main.label. Default = 0. See mtext.
marginVec	Numerical vector specifying margin sizes. Default = c(4, 4, 3, 3). See par.
legendText	Character vector used in the legend. Only shown if showLegend = TRUE. Default = NULL. See legend.
highThreshold	Numerical value representing the position of the upper horizontal line, e.g., a threshold for assessing statistical significance. Default = NULL.
lowThreshold	Numerical value representing the position of the lower horizontal line, e.g., a threshold for assessing statistical significance. Default = NULL.
showLegend	Binary value determining whether or not the legend is shown. Default = FALSE. See legend.
legendXQuantile	Quantile to specify the "x" location of the legend. Only relevant if showLegend = TRUE Default = 0.55. See legend.
legendYCoord	Numerical value to specify the "y" location of the legend. Only relevant if showLegend = TRUE. Default = 1. See legend.

Details

Although genomePlot can be used to visualize copy number values and copy number alterations across the genome, the scale makes it difficult to see events that affect small genomic regions. These events are easier to see if the viewing window is restricted to individual chromosomes, as is done here. If Y = NULL in the input list, then the plot shows a single line corresponding to the mean DNA copy number values based on the entries in X. If both X and Y are specified, the plot shows three lines corresponding to the mean DNA copy number values in X, the mean DNA copy number values in Y, and the difference of the mean DNA copy number values.

Value

Creates a multi-page plot of mean copy number values and differences by chromosome.

Examples

```
genomeChrPlot(inputList = pD, ylimLow = -1.4, ylimHigh = 1.4)
```

---

genomePlot *A Function for Plotting Mean Copy Number Values and Differences Across the Genome*

Description

This function plots mean copy number values from one or two cohorts at a common set of markers across the genome.

Usage

```
genomePlot(
  inputList,
  lwdVec = rep(1, 3),
  ltyVec = c(1:3),
  lineColorVec = c("red", "blue", "black"),
  ylimLow = -1,
  ylimHigh = 1,
  chrLabel = TRUE,
  xaxisLabel = "Chromosome",
  yaxisLabel = NULL,
  mainLabel = NULL,
  rectColors = c("light gray", "gray"),
  axisCex = 1,
  labelCex = 1,
  xaxisLine = 2.5,
  yaxisLine = 2.5,
  mainLine = 0,
  marginVec = c(4, 4, 3, 3),
```

```
  legendText = NULL,
  highThreshold = NULL,
  lowThreshold = NULL,
  showLegend = FALSE,
  legendXQuantile = 0.55,
  legendYCoord = 1
)
```

Arguments

inputList	A list produced by dataPrep.
lwdVec	A vector of line widths. Default = rep(1, 3). See par.
ltyVec	A vector of line types. Default = c(1:3). See par.
lineColorVec	A vector of line colors. Default = c("red", "blue", "black"). See par.
ylimLow	The lower limit of the y-values in the plot. Default = -1. See plot.
ylimHigh	The upper limit of the y-values in the plot. Default = 1. See plot.
chrLabel	Binary value determining whether or not chromosomes are labeled. Default = TRUE.
xaxisLabel	Label for the x-axis in the plot. Default = "Chromosome". See plot.
yaxisLabel	Label for the y-axis in the plot. Default = NULL. See plot.
mainLabel	Main label in the plot. Default = NULL. See plot.
rectColors	Background colors for different chromosomes. Default = c("light gray", "gray").
axisCex	Point size for the scale on the axis. Default = 1. See par.
labelCex	Point size for the axis label. Default = 1. See par.
xaxisLine	Numerical value used to specify the location (line) of the x-axis label. Default = 2.5. See mtext.
yaxisLine	Numerical value used to specify the location (line) of the y-axis label. Default = 2.5. See mtext.
mainLine	Numerical value used to specify the location (line) of the main.label. Default = 0. See mtext.
marginVec	Numerical vector specifying margin sizes. Default = c(4, 4, 3, 3). See par.
legendText	Character vector used to legend. Only shown if showLegend = TRUE. Default = NULL. See legend.
highThreshold	Numerical value representing the position of the upper horizontal line, e.g., a threshold for assessing statistical significance. Default = NULL.
lowThreshold	Numerical value representing the position of the lower horizontal line, e.g., a threshold for assessing statistical significance. Default = NULL.
showLegend	Binary value determining whether or not the legend is shown. Default = FALSE. See legend.
legendXQuantile	Quantile to specify the "x" location of the legend. Only relevant if showLegend = TRUE Default = 0.55. See legend.
legendYCoord	Numerical value to specify the "y"location of the legend. Only relevant if showLegend = TRUE. Default = 1. See legend.

Details

This function is used to visualize copy number values and copy number alterations across the genome. If Y = NULL in the input list, then the plot shows a single line corresponding to the mean DNA copy number values based on the entries in X. If both X and Y are specified, the plot shows three lines corresponding to the mean DNA copy number values in X, the mean DNA copy number values in Y, and the difference of the mean DNA copy number values.

Value

Creates a genomewide plot of mean copy number values and differences.

Examples

```
genomeChrPlot(inputList = pD, ylimLow = -1.4, ylimHigh = 1.4)
```

---

luadSubset *DNA copy number data for lung adenocarcinoma.*

Description

A subset of the DNA copy number data from the TCGA lung lung adenocarcinoma cohort.

Usage

```
luadSubset
```

Format

A numeric matrix of quantitative DNA copy number values with 3475 rows and 65 columns. Rows are indexed by genes, and columns are indexed by samples. The entries are on the log ratio scale and were produced by the GISTIC pipeline.

Details

The original data set downloaded from https://gdac.broadinstitute.org/ contained gene-level segmented DNA copy number values for 24776 genes and 516 samples that were produced by the GISTIC pipeline. Because of the size limitations on data in R packages, a random subset of genes and samples was selected. By construction, the number of genes and samples in the lung adenocarcinoma data is different than the number of genes and samples in the lung squamous cell carcinoma data.

Source

https://gdac.broadinstitute.org/

luscSubset *DNA copy number data for lung squamous cell carcinoma.*

Description

A subset of the DNA copy number data from the TCGA lung lung squamous cell carcinoma cohort.

Usage

```
luscSubset
```

Format

A numeric matrix of quantitative DNA copy number values with 3480 rows and 60 columns. Rows are indexed by genes, and columns are indexed by samples. The entries are on the log ratio scale and were produced by the GISTIC pipeline.

Details

The original data set downloaded from https://gdac.broadinstitute.org/ contained gene-level segmented DNA copy number values for 24776 genes and 501 samples that were produced by the GISTIC pipeline. Because of the size limitations on data in R packages, a random subset of genes and samples was selected. By construction, the number of genes and samples in the lung squamous cell carcinoma data is different than the number of genes and samples in the lung adenocarcinoma data.

Source

https://gdac.broadinstitute.org/

pD *Prepped data for DiNAMIC.Duo.*

Description

A list produced by the dataPrep() function.

Usage

```
pD
```

Format

A list containing three components for a common set of genes.

Details

The components of the list are named X, Y, and posDT. They contain the DNA copy number data for lung adenocarcinoma, the DNA copy number data for lung squamous cell carcinoma, and gene position data, respectively. This data object was produced by applying `dataPrep` using the `luadSubset` and `luscSubset` data sets. This reduces run time when the package is compiled by CRAN, thus eliminating run time errors.

`peelingOne` *A Function to Apply the Peeling Algorithm in a Single Copy Number Matrix*

Description

This function applies the peeling algorithm described in Walter et al. (Bioinformatics, 2011;27(5):678–685)

Usage

```
peelingOne(X, posDT, k, threshold = NULL)
```

Arguments

`X`	A matrix of normalized gene-level copy number data (rows = genes, columns = subjects).
`posDT`	A data frame containing genomic position information for the genes in X.
`k`	The location (row of X) containing the peak that will be peeled.
`threshold`	A tuning parameter that controls the size of the peeled region. Rows of X with mean copy number less than threshold will not be peeled.

Details

to remove a peak from a copy number data set and define a genomic interval of interest around

the peak.

Tumor genomes often contain multiple DNA copy number alterations, e.g., amplifications or deletions. The locus that harbors the most extreme alteration, k, as evidenced by the maximum or minimum column mean, provides a point estimate for the location of an underlying driver gene. Also, loci near k may be affected by the same underlying genomic event. The peeling procedure is applied to "nullify" entries in X that contribute to the alteration at k, thus making it possible to identify altered regions elsewhere in the genome. This function is called by `peelingOneIterate`.

Value

A list containing two elements: X and interval. X is an updated version of the input copy number matrix in which the peak at k has been removed, and interval is genomic region containing k. By construction, interval cannot extend beyond the chromosome arm containing k.

Examples

```
lusc=pD[["X"]]

 posDT=pD[["posDT"]]

 kLusc=which.max(rowMeans(lusc))

 peeledLusc=peelingOne(X=lusc,posDT=posDT,k=kLusc,threshold=NULL)
```

`peelingOneIterate` *A Function to Apply the Peeling Algorithm in a Single Copy Number Matrix*

Description

This function iteratively applies the peelingOne function, thereby identifying multiple

Usage

```
peelingOneIterate(
  X,
  posDT,
  gain = TRUE,
  nullDist = NULL,
  threshold = NULL,
  numIters = 5
)
```

Arguments

`X`	A matrix of normalized gene-level copy number data (rows = genes, columns = subjects).
`posDT`	A data frame containing genomic position information for the genes in X.
`gain`	A logical value indicating whether gains (TRUE) or losses (FALSE) will be peeled. Default = TRUE.
`nullDist`	An empirical null distribution produced by the cyclic shift algorithm. Default = NULL.
`threshold`	A tuning parameter that controls the size of the peeled region. Rows of X with mean copy number less than threshold will not be peeled. Default = NULL.
`numIters`	The number of times peelingOne will be iterated. Default = 5.

Details

peaks across the genome in a single cohort. Gains and losses should be analyzed separately.

The peelingOne function applies the peeling algorithm described by Walter et al. (Bioinformatics, 2011;27(5):678–685) at a given marker k. Because tumor genomes may contain multiple regions of copy number gain or loss, it important to apply the peeling process iteratively, thereby identifying multiple markers and surrounding genomic regions.

Value

A list containing two elements: X and interval. X is an updated version of the input copy number matrix in which the peak at k has been removed, and interval is genomic region containing k. By construction, interval cannot extend beyond the chromosome arm containing k.

Examples

```
lusc=pD[["X"]]

 posDT=pD[["posDT"]]

 gain = TRUE

 nullDist = NULL

 threshold = NULL

 numIters = 3

 peeledLusc=peelingOneIterate(X=lusc,posDT=posDT,gain=TRUE,nullDist=NULL,threshold=NULL,numIters=3)
```

---

peelingTwo *A Function to Apply the Peeling Algorithm in a Two Copy Number Matrices*

Description

This function applies a modified version of the peeling algorithm originally described in Walter et al.,

Usage

```
peelingTwo(X, Y, posDT, k, threshold = NULL)
```

Arguments

X	A matrix of normalized gene-level copy number data (rows = genes, columns = subjects).
Y	A matrix of normalized gene-level copy number data (rows = genes, columns = subjects).
posDT	A data frame containing genomic position information for the genes in X.
k	The location (row of X and Y) containing the peak that will be peeled.
threshold	A tuning parameter that controls the size of the peeled region. Rows in which rowMeans(X) - rowMeans(Y) are less than threshold will not be peeled.

Details

(PMID 21183584) to remove a peak from the copy number differences and define a genomic interval of interest

around the peak.

When tumor genomes from two cohorts are compared, there may be multiple regions that harbor copy number differences. For example, gains or losses may be present in only one of the two cohorts, and this could give rise to copy number differences. Alternatively, the same region of the genome may exhibit gain or loss in both cohorts. If the magnitudes of the common gain or loss are distinct, then this also gives rise to copy number differences. The locus that harbors the most extreme difference, k, provides a point estimate for the underlying driver gene that gives rise to the difference. Loci near k may also be affected by the underlying difference in copy number. The peeling procedure for two cohorts is applied to "nullify" entries of both X and Y that contribute to the alteration at k, thus making it possible to identify other regions of the genome that harbor copy number differences. This function is called by peelingTwoIterate.

Value

A list containing three elements: X, Y, and interval. X and Y are updated versions of the input copy number matrices X and Y in which the peak at k has been removed, and interval is genomic region containing k. By construction, interval cannot extend beyond the chromosome arm containing k.

Examples

```
luad=pD[["X"]]

 lusc=pD[["Y"]]

 posDT=pD[["posDT"]]

 kDiff=which.max(rowMeans(luad)-rowMeans(lusc))

 peeledDiff=peelingTwo(X=luad,Y=lusc,posDT=posDT,k=kDiff,threshold=NULL)
```

peelingTwoIterate *A Function to Apply the Peeling Algorithm for Two Copy Number Matrices*

Description

This function iteratively applies the peelingTwo function, thereby identifying multiple

Usage

```
peelingTwoIterate(
  X,
  Y,
  posDT,
  gain = TRUE,
  nullDist = NULL,
  threshold = NULL,
  numIters = 5
)
```

Arguments

X	A matrix of normalized gene-level copy number data (rows = genes, columns = subjects).
Y	A matrix of normalized gene-level copy number data (rows = genes, columns = subjects).
posDT	A data frame containing genomic position information for the genes in X.
gain	A logical value indicating whether gains (TRUE) or losses (FALSE) will be peeled. Default = TRUE.
nullDist	An empirical null distribution produced by the cyclic shift algorithm. Default = NULL.
threshold	A tuning parameter that controls the size of the peeled region. Rows of X and Y with mean copy number differences less than threshold will not be peeled. Default = NULL.
numIters	The number of times peelingTwo will be iterated. Default = 5.

Details

differences across the genome between a two cohorts. Gains and losses should be analyzed separately.

The peelingTwo function applies the peeling procedure for two cohorts to "nullify" entries in two copy number matrices X and Y that give rise to the most significant copy number difference. Because tumor genomes may contain multiple regions that harbor copy number differences, it is important to apply the peeling procedure for two cohorts iteratively, thereby identifying multiple markers and surrounding genomic regions.

Value

A list containing two elements: X, Y, and interval. X and Y are updated versions of the input copy number matrices in which the peak difference at k has been removed, and interval is genomic region containing k. By construction, interval cannot extend beyond the chromosome arm containing k.

Examples

```
luad=pD[["X"]]

 lusc=pD[["Y"]]

 posDT=pD[["posDT"]]

 gain = TRUE

 nullDist = NULL

 threshold = NULL

 numIters = 3

out=peelingTwoIterate(X=luad,Y=lusc,posDT=posDT,gain=TRUE,nullDist=NULL,threshold=NULL,numIters=3)
```

`resultsProcess` *Processing peeling results*

Description

Processing peeling results

Usage

```
resultsProcess(peel.results, posDT)
```

Arguments

`peel.results`	peeling results
`posDT`	a data frame containing gene annotation information; a list component created by `dataPrep`.

Details

The `peelingOneIterate` function identifies (i) multiple loci across the genome where copy number gains are losses, and (ii) regions around those loci that also exhibit copy number changes. Similarly, `peelingTwoIterate` identifies loci and surrounding regions that harbor copy number differences. The output of either `peelingOneIterate` or `peelingTwoIterate` is processed to produce a tab-delimited text file that provides a summary of the peeling results. Each column corresponds to a

peeled locus, and the column contains the genomic location of the locus, the start and end positions of the surrounding peeled region, the mean copy number value (one matrix X) or difference of mean copy number values (two matrices X and Y), the cyclic shift-based p-value, and the names of the genes in the peeled region (in alphabetical order).

Value

processed peeling results with a list of genes corresponding to each peeled region

See Also

dataPrep

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