

Package ‘DCGL’

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Type Package

Title Differential Coexpression Analysis of Gene Expression Microarray Data

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Description Functions for basic differential coexpression analyses:
gene filtering, link filtering, DCG (Differentially-Coexpressed
Gene) identification and DCL (Differentially-Coexpressed Links) identification.

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DCGL-package

*Differential Coexpression Analysis of Microarray Data***Description**

Functions for basic differential coexpression analyses: gene filtering, link filtering, DCG (Differentially-Coexpressed Gene) identification and DCL (Differentially-Coexpressed Links) identification. Five algorithms, named DCp, DCe, ASC, LRC and WGCNA, are provided for DCG-identification and DCL-identification.

Details

Package:	DCGL
Type:	Package
Version:	1.02
Date:	2010-12-08
License:	GPL (>2)
LazyLoad:	yes

Author(s)

Bao-Hong Liu, Hui Yu

Maintainer: Bao-hong Liu <bhliu@scbit.org>

References

Friedrich Leisch, 2008 Creating R Packages: A Tutorial

Examples

```
data(dataC)
exprs.1=dataC[1:100,1:10]
exprs.2=dataC[1:100,11:20]
DCp(exprs.1,exprs.2,method='qth',cutoff=0.25,N=0)
DCe(exprs.1,exprs.2,method='qth',cutoff=0.25,nbins=20,p=0.1)
```

```

ASC(exprs.1,exprs.2,method='qth',cutoff=0.25)
LRC(exprs.1,exprs.2,method='qth',cutoff=0.25)
WGCNA(exprs.1,exprs.2,power=12,variant='WGCNA')

```

ASC	<i>Identify DCGs (Differentially-Coexpressed genes) based on 'Average Specific Connection'</i>
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Description

A method to pick out DCGs from microarray data based on 'Average Specific Connection' (ASC) (Choi et al. 2005).

Usage

```

ASC(exprs.1, exprs.2, method=Linkfilter.methods,cutoff)

Linkfilter.methods
# c("rth", "qth", "percent")

```

Arguments

exprs.1	a data frame or matrix for condition A, with rows as variables (genes) and columns as samples.
exprs.2	a data frame or matrix for condition B, with rows as variables (genes) and columns as samples.
method	link filtering method
cutoff	the cutoff of correlation-value,q-value or percent of links after link filtering. must be within [0,1].

Details

ASC is the average value of the specific degree of the two conditions.

Value

ASC	the Average specific connections of genes. This measure can be used to rank gene in terms of differential coexpression.
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Author(s)

Bao-Hong Liu, Hui Yu

References

Choi, J.K., Yu, U., Yoo, O.J. and Kim, S. (2005) Differential coexpression analysis using microarray data and its application to human cancer, *Bioinformatics*, 21, 4348-4355.

Examples

```
data(dataC)
ASC(dataC[1:100,1:10],dataC[1:100,11:20],method = 'qth', cutoff=0.25)
```

dataA	<i>Simulated dataset based on deliberately-perturbed gene regulation networks (Yu, et al., 2010)</i>
-------	--

Description

Simulated gene expression dataset, each containing 1000 rows and 20 columns (Yu, et al., 2010).

Usage

```
data(dataA)
```

Format

A data frame with 1000 observations 20 variables.

- dataA A data frame with 1000 observations 20 columns. The expression values.

Details

We simulated three dataset pairs (denoted dataA, dataB, dataC) using SynTReN based on a pre-defined E.coli gene regulatory network of a total of 1300 genes (Van den Bulcke, et al., 2006). Specifically, we selected a sub-network of 1000 genes as the original network, and exerted artificial perturbation on 10 percent of its links as if it was from a different condition. The three groups had different perturbation types. For dataA, we used regulation-elimination (removing a link between a pair of genes). In each data matrix, the first ten columns correspond to one condition and the second ten correspond to the other.

Author(s)

Bao-hong Liu, Hui Yu

References

Yu H., Liu B-H., et al., Link-specific Quantitative Methods to Identify Differentially Coexpressed Genes and Gene Pairs. Submitted. 2010

Van den Bulcke, T., et al. (2006) SynTReN: a generator of synthetic gene expression data for design and analysis of structure learning algorithms, BMC Bioinformatics, 7, 43.

Examples

```
data(dataA)
dataA[,1:10] # exprssion data for condition 1
dataA[,11:20] # exprssion data for condition 2
row.names(dataA) # gene identifier
```

dataB	<i>Simulated dataset based on deliberately-perturbed gene regulation networks (Yu, et al., 2010)</i>
-------	--

Description

Simulated gene expression dataset, each containing 1000 rows and 20 columns (Yu, et al., 2010).

Usage

```
data(dataB)
```

Format

A data frame with 1000 observations 20 variables.

- dataB A data frame with 1000 observations 20 columns. The expression values.

Details

We simulated three dataset pairs (denoted dataA, dataB, dataC) using SynTReN based on a pre-defined E.coli gene regulatory network of a total of 1300 genes (Van den Bulcke, et al., 2006). Specifically, we selected a sub-network of 1000 genes as the original network, and exerted artificial perturbation on 10 percents of its links as if it was from a different condition. The three groups had different perturbation types. For dataB, we used regulation-alteration (alter a link between a pair of genes between repress and active). In each data matrix, the first ten columns correspond to one condition and the second ten correspond to the other.

Author(s)

Bao-hong Liu, Hui Yu

References

- Yu H., Liu B-H., et al., Link-specific Quantitative Methods to Identify Differentially Coexpressed Genes and Gene Pairs. Submitted. 2010
- Van den Bulcke, T., et al. (2006) SynTReN: a generator of synthetic gene expression data for design and analysis of structure learning algorithms, BMC Bioinformatics, 7, 43.

Examples

```
data(dataB)
dataB[,1:10] # exprssion data for condition 1
dataB[,11:20] # exprssion data for condition 2
row.names(dataB) # gene identifier
```

dataC	<i>Simulated dataset based on deliberately-perturbed gene regulation networks (Yu, et al., 2010)</i>
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Description

Simulated gene expression dataset, each containing 1000 rows and 20 columns (Yu, et al., 2010).

Usage

```
data(dataC)
```

Format

A data frame with 1000 observations 20 variables.

- dataC A data frame with 1000 observations 20 columns. The expression values.

Details

We simulated three dataset pairs (denoted dataA, dataB, dataC) using SynTReN based on a pre-defined E.coli gene regulatory network of a total of 1300 genes (Van den Bulcke, et al., 2006). Specifically, we selected a sub-network of 1000 genes as the original network, and exerted artificial perturbation on 10 percents of its links as if it was from a different condition. The three groups had different perturbation types. For dataC, we used regulation-elimination-alteration (removing 5 percents links and altering 5 percents links). In each data matrix, the first ten columns correspond to one condition and the second ten correspond to the other.

Author(s)

Bao-hong Liu, Hui Yu

References

- Yu H., Liu B-H., et al., Link-specific Quantitative Methods to Identify Differentially Coexpressed Genes and Gene Pairs. Submitted. 2010
- Van den Bulcke, T., et al. (2006) SynTReN: a generator of synthetic gene expression data for design and analysis of structure learning algorithms, BMC Bioinformatics, 7, 43.

Examples

```
data(dataC)
dataC[,1:10] # exprssion data for condition 1
dataC[,11:20] # exprssion data for condition 2
row.names(dataC) # gene identifier
```

DCe *To identify DCGs (Differentially-Coexpressed Genes) and DCLs (Differentially-Coexpressed Links)*

Description

The algorithm first determines DCLs using a LFC model originally proposed for differential expression analysis, then determines DCGs with their surrounding links enriched for DCLs.

Usage

```
DCe(exprs.1, exprs.2, method=Linkfilter.methods, cutoff, nbins=20, p=0.1, figname=c('LFC.s.jpeg', 'LFC.c'),
    Linkfilter.methods
    # c("rth", "qth", "percent"))
```

Arguments

exprs.1	a data frame or matrix for condition A, with rows as variables (genes) and columns as samples.
exprs.2	a data frame or matrix for condition B, with rows as variables (genes) and columns as samples.
method	link filtering method
cutoff	cutoff used for link filtration, can be rth, qth, or percent depending on Linkfilter.method. must be within [0,1].
nbins	number of x bins for fitting $y=a+(b/x)$.
p	the cutoff of q-value; must be within [0,1].
figname	names of figures of the LFC fitting results

Details

DCe is based on the 'Limit Fold Change' or 'LFC' model, a robust statistical method originally proposed for selecting DEGs from microarray data (Mutch et al. 2002). With the analysis units changed from expression values to coexpression values, the LFC method with moderate adaption can be applied to screen for putative DCLs. DCGs with their surrounding links enriched for DCLs are determined through a binomial probability model.

Value

A list with four components:

DCGs	Differentially Coexpressed Genes
DCL.same	Differentially Coexpressed Links of the same sign
DCL.diff	Differentially Coexpressed Links of different signs
DCL.switched	Differentially Coexpressed Links of switched value

Author(s)

Bao-Hong Liu, Hui Yu

References

Mutch, D.M., Berger, A., Mansourian, R., Rytz, A. and Roberts, M.A. (2002) The limit fold change model: a practical approach for selecting differentially expressed genes from microarray data, *BMC Bioinformatics*, 3, 17.

Yu H., Liu B-H., et al., Link-specific Quantitative Methods to Identify Differentially Coexpressed Genes and Gene Pairs. Submitted. 2010

Examples

```
data(dataC)
DCe(dataC[1:100,1:10],dataC[1:100,11:20],method = 'qth',cutoff=0.25,nbins=20,p=0.1)
```

DCp

To identify DCGs (Differentially-Coexpressed genes) based on the 'Differential Coexpression Profile'

Description

A method to pick out DCGs from microarray data based on a novel concept of 'Differential Coexpression Profiles' (DCp) (Yu et al. 2010).

Usage

```
DCp(exprs.1, exprs.2, method=Linkfilter.methods,cutoff, N=0)
```

```
Linkfilter.methods
# c("rth", "qth", "percent")
```

Arguments

exprs.1	a data frame or matrix for condition A, with rows as variables (genes) and columns as samples.
exprs.2	a data frame or matrix for condition B, with rows as variables (genes) and columns as samples.
method	link filtering method
cutoff	cutoff used for link filtration, can be rth, qth, or percent depending on Linkfilter.method. must be within [0,1].
N	permutation times. If N>0, the permutation step will be implemented. The default value for N is 0.

Details

DCp starts with a set of gene coexpression value pairs, where each pair is made up with two co-expression values of a gene pair calculated under two different conditions. For a particular gene, a 'condition-specific coexpression profile' is defined as the vector of the coexpression values that relate to it in one condition, and the two condition-specific coexpression profiles of one gene become the two components of the gene's 'differential coexpression profile'. A differential coexpression measure (dC) is calculated from the differential coexpression profile as a length-normalized Euclidean Distance.

Then the samples between the two conditions will be disturbed and the samples will be separated to two conditions. Calculate dC of this condition. Repeat the above process for N times. Pool all the dC together to form a null distribution of dC. The corresponding statistical significance (p-value) is estimated against null statistics.

Value

A table with DCGs will be listed including 'dC' value and profile 'length' or 'dC' value, profile 'length', 'p value' and 'FWER' value.

Author(s)

Bao-Hong Liu, Hui Yu

References

Yu H., Liu B-H., et al., Link-specific Quantitative Methods to Identify Differentially Coexpressed Genes and Gene Pairs. Submitted. 2010

Examples

```
data(dataC)
DCp(dataC[1:100,1:10],dataC[1:100,11:20],method='qth',cutoff=0.25,N=0)
```

expressionBasedfilter *To filter genes according to expression level*

Description

Genes which have a higher between-sample mean expression signal are retained, while other genes are discarded..

Usage

```
expressionBasedfilter(exprs)
```

Arguments

exprs a data frame or matrix with rows as variables (genes) and columns as samples.

Details

Genes which have a Between-Experiment Mean Expression Signal (BEMES) lower than the median of BEMES's of all genes will be filtered out.

Value

A data frame or matrix with a reduced number of rows.

Author(s)

Bao-hong Liu, Hui Yu

Examples

```
data(dataC)
expressionBasedfilter(dataC)
```

LFC

Select DCLs based on 'Limit Fold Change' model

Description

The limit fold change (LFC) model is a robust statistical method modeling the relationship between maximum coexpression and log coexpression ratio of genes. (Mutch, et al., 2002). The algorithm starts with a set of gene coexpression value pairs each comprising two coexpression values of a gene pair calculated under two different conditions respectively.

Usage

```
LFC(exprs, nbins, p, sign, figname = "LFC.jpeg")
```

Arguments

<code>exprs</code>	a two-column data matrix, with column one the coexpression values for one condition and column two those for another.
<code>nbins</code>	number of x bins for fitting $y=a+(b/x)$.
<code>p</code>	the fraction at y axis for determining boundary points; must be within [0,1].
<code>sign</code>	Specifies the sign type of exprs. Exprs is either 'same-sign', with coexpression pairs of the same sign, or 'different-sign', with coexpression pairs of opposite signs.
<code>figname</code>	names of figures of the LFC fitting results.

Details

According to how the signs of coexpression values are paired, gene links are divided into two parts: the 'same-signed' set and the 'differently-signed' set. From the 'differently-signed' set, the 'correlation-switched' gene links that have two differently-signed coexpression values both surpassing a cutoff value are subtracted, who make the first part of DCLs. The remaining differently-signed gene links in aggregate inherit the title of 'differently-signed' set. For the 'same-signed' set, gene links are binned with respect to their maximum coexpression values, and those links ranked the top p of highest fold changes in each bin are fitted with a simple equation of the form $y = a + (b/x)$; for the 'differently-signed set', the horizontal and vertical axes are exchanged and similar binning and fitting procedures are applied. Links lie above the fitted curves are considered DCLs.

Value

the identified DCLs will be returned, as a subset of coexpression pairs.

Author(s)

Bao-Hong Liu, Hui Yu

References

Mutch, D.M., Berger, A., Mansourian, R., Rytz, A. and Roberts, M.A. (2002) The limit fold change model: a practical approach for selecting differentially expressed genes from microarray data, *BMC Bioinformatics*, 3, 17.

LRC

Identify DCGs (Differentially-Coexpressed genes) based on 'Log Ratio Connections'

Description

A method to pick out DCGs from microarray data based on 'Log Ratio of Connections' (LRC) (Reverter et al. 2006).

Usage

```
LRC(exprs.1, exprs.2, method=Linkfilter.methods,cutoff)
```

```
Linkfilter.methods  
# c("rth", "qth", "percent")
```

Arguments

exprs.1	a data frame or matrix for condition A, with rows as variables (genes) and columns as samples.
exprs.2	a data frame or matrix for condition B, with rows as variables (genes) and columns as samples.

method	link filtering method.
cutoff	cutoff used for link filtration, can be rth, qth, or percent depending on Linkfilter.method. must be within [0,1].

Details

'Log Ratio of Connections' (LRC) calculates the logarithm of the ratio of the connectivities of a gene between two conditions (Reverter, et al., 2006). A connectivity of zero is changed to one.

Value

LRC	the log Ratio Connections of genes. This measure can be used to rank gene in terms of differential coexpression.
-----	--

Author(s)

Bao-Hong Liu, Hui Yu

References

Reverter, A., Ingham, A., Lehnert, S.A., Tan, S.H., Wang, Y., Ratnakumar, A. and Dalrymple, B.P. (2006) Simultaneous identification of differential gene expression and connectivity in inflammation, adipogenesis and cancer, *Bioinformatics*, 22, 2396-2404.

Examples

```
data(dataC)
LRC(dataC[1:100,1:10],dataC[1:100,11:20],method = 'qth', cutoff=0.25)
```

percentLinkfilter *To filter gene coexpression links according to the max expression correlation value*

Description

Keep a fraction (specified with 'percent') of the links (gene pairs) with the highest max correlation values.

Usage

```
percentLinkfilter(exprs.1, exprs.2, percent)
```

Arguments

exprs.1	a data frame or matrix for condition A, with rows as variables (genes) and columns as samples.
exprs.2	a data frame or matrix for condition B, with rows as variables (genes) and columns as samples.
percent	fraction of links to be retained.

Details

Each gene link is associated with two correlation values (one out of condition A and the other out of condition B) and thus a list of 'maximum absolute values' of the two values is decided. Then these 'maximum absolute values' are sorted in decreasing order. At last, a fraction of gene pairs with the highest max correlation values will be retained.

Value

A list with two components of data frames, one for filtered data of condition A, the other for the counterpart of condition B.

Author(s)

Bao-Hong Liu, Hui Yu

Examples

```
data(dataC)
percentLinkfilter(dataC[,1:10],dataC[,11:20],percent=0.1)
```

qLinkfilter	<i>To filter gene coexpression links according to the q-values of expression correlation values</i>
-------------	---

Description

Gene links with q-values of coexpression value pairs in either of two conditions higher than the cutoff (qth) are retained, while the coexpression values of other links are set to zero.

Usage

```
qLinkfilter(exprs.1, exprs.2, qth)
```

Arguments

exprs.1	a data frame or matrix for condition A, with rows as variables (genes) and columns as samples.
exprs.2	a data frame or matrix for condition B, with rows as variables (genes) and columns as samples.
qth	the cutoff of q-value; must be within [0,1].

Details

For each of the two conditions, the coexpression values are associated with the corresponding p-values (student T-test of the zero nature of a PCC), and these p-values are sorted and transformed to q-values (or formally, false discovery rates). Gene links with q-values of coexpression values in either of two conditions higher than the cutoff (qth) are reserved.

Value

A list with two components of data frames, one for filtered data of condition A, the other for the counterpart of condition B.

Author(s)

Bao-hong Liu, Hui Yu

Examples

```
data(dataC)
qLinkfilter(dataC[,1:10],dataC[,11:20],qth=0.25)
```

Simulated.ABC	<i>Simulated datasets based on deliberately-perturbed gene regulation networks (Yu, et al., 2010)</i>
---------------	---

Description

Simulated datasets of 1000-gene scaled(Yu, et al., 2010).

Usage

```
data(dataC)
```

Format

A data frame with 1000 observations 20 variables.

- dataAA data frame with 1000 observations 20 columns. The expression values.
- dataBA data frame with 1000 observations 20 columns. The expression values.
- dataCA data frame with 1000 observations 20 columns. The expression values.

Details

There are three sets of 1000-gene-scaled simulated datasets used in the paper of Yu et al.(2010) for which the expression data were simulated by software SynTReN using networks originated from E.coli regulatory network. For the three datasets, the underlying networks for condition one were identical but were different for condition two.

Author(s)

Bao-hong Liu, Hui Yu

References

Yu, H., Liu, B.-H., Ye, Z.-Q., Li, Y.-Y. and Li, Y.-X. (2010) Improved Quantitative Differential Coexpression Analysis to Explore Gene Coexpression Properties in Type II Diabetes,prepare to submit.

Examples

```
data(dataC)
dataC[,1:10] # exprssion data for condition 1
dataC[,11:20] # exprssion data for condition 2
row.names(dataC) # gene identifier
```

systematicLinkfilter *A systematic procedure for estimating a cutoff threshold of coexpression networks*

Description

A procedure that generates a plot of the correlation threshold versus the clustering coefficient for helping define a correlation threshold in coexpression network construction.

Usage

```
systematicLinkfilter(exprs)
```

Arguments

exprs a data frame or matrix with rows as variables (genes) and columns as samples.

Details

A systematic procedure for inferring a cutoff threshold of coexpression networks directly from their topological properties. The objective is to automatically select a threshold that preserves as many valid coexpression links as possible, while simultaneously controlling the number of false detections. The procedure is based on comparing the observed clustering coefficient and its randomized counterpart as the number of connections is gradually decreased. This method is computation-intensive and is optimal for a total gene number less than 500.

Value

A table of 'correlation threshold' vs. 'clustering coefficient' that may assist the user to determine correlation threshold.

Author(s)

Bao-hong Liu, Hui Yu

References

Elo, L.L., Jarvenpaa, H., Oresic, M., Lahesmaa, R. and Aittokallio, T. (2007) Systematic construction of gene coexpression networks with applications to human T helper cell differentiation process, *Bioinformatics*, 23, 2096-2103.

Examples

```
data(dataC)
exprs <- dataC[1:50,]
C_r <- systematicLinkfilter(exprs)
```

varianceBasedfilter *To filter genes according to expression variability*

Description

Those genes not significantly more variable than the median gene are filtered out.

Usage

```
varianceBasedfilter(exprs,p)
```

Arguments

exprs	a data frame or matrix with rows for variables (genes) and columns for samples.
p	the probability cut-off of the chi-squared probability model of the gene-sepcific variance-like statistics.

Details

This is an approximate test of the hypothesis that gene has the same variance as the median variance. A statistical significance criterion based on the variance can be used. If the significance criterion is chosen, then the variance of the log-values for each gene is compared to the median of all the variances. The quantity for each gene compared to a percentile of the chi-square distribution with $n-1$ degrees of freedom. Those genes not significantly more variable than the median gene are filtered out [BRB-ArrayTools Version 3.7].

Value

A data frame or matrix with a reduced number of rows.

Author(s)

Bao-hong Liu, Hui Yu

References

Dr. Richard Simon & Amy Peng Lam, BRB-ArrayTools (v3.7) User's Manual: 'Log expression variation filter'.

Examples

```
data(dataC)
varianceBasedfilter(dataC,0.01)
```

WGCNA	<i>To identify DCGs (Differentially-Coexpressed genes) based on the 'Weighted Gene Coexpression Network Analysis'</i>
-------	---

Description

A method to pick out DCGs from microarray data based on 'Weighted Gene Coexpression Network Analysis' (WGCNA) (Mason, MJ. Et al. 2009; van Nas et al. 2009).

Usage

```
WGCNA(exprs.1, exprs.2, power,variant)
```

Arguments

exprs.1	a data frame or matrix for condition A, with rows as variables (genes) and columns as samples.
exprs.2	a data frame or matrix for condition B, with rows as variables (genes) and columns as samples.
power	the thresholding parameter, an integer >1.
variant	if the variant is 'WGCNA' the original version is evoked; if it is 'DCp', the length-normalized Euclidean distance is adopted to replace the connectivity difference measure.

Details

The 'weighted gene coexpression network analysis' (WGCNA) weights links with correlation coefficients and compares the sums of the correlation coefficients of a gene (Mason, et al., 2009; van Nas, et al., 2009). Correlation coefficients are firstly softly thresholded by a 'power'.

Value

WGCNA	score of 'WGCNA' to identify DCGs
-------	-----------------------------------

Author(s)

Bao-Hong Liu, Hui Yu

References

Mason, M.J., et al. (2009) Signed weighted gene co-expression network analysis of transcriptional regulation in murine embryonic stem cells, *BMC Genomics*, 10, 327.

van Nas, A., Guhathakurta, D., Wang, S.S., Yehya, N., Horvath, S., Zhang, B., Ingram-Drake, L., Chaudhuri, G., Schadt, E.E., Drake, T.A., Arnold, A.P. and Lusa, A.J. (2009) Elucidating the role of gonadal hormones in sexually dimorphic gene coexpression networks, *Endocrinology*, 150, 1235-1249.

Examples

```
data(dataC)
WGCNA(dataC[1:100,1:10],dataC[1:100,11:20],power=12,variant='WGCNA')
```

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