Package ‘DeMAND’

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Title DeMAND
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Description DEMAND predicts Drug MoA by interrogating a cell context specific regulatory net-
work with a small number (N >= 6) of compound-induced gene expression signatures, to eluci-
date specific proteins whose interactions in the network is dysregulated by the compound.
Depends R (>= 2.14.0), KernSmooth, methods
License file LICENSE
biocViews SystemsBiology, NetworkEnrichment, GeneExpression,
StatisticalMethod, Network
NeedsCompilation no

R topics documented:

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bcellAnno  Annotation for the expression data

Description
Annotation information for the probes of the gene expression matrix
<table>
<thead>
<tr>
<th>Column</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>bcellExp</td>
<td>B cell expression data</td>
</tr>
<tr>
<td></td>
<td>subest of a gene expression profiles from DLBCL cells treated by Geldanamycin and by DMSO as control.</td>
</tr>
<tr>
<td>bcellNetwork</td>
<td>B cell network</td>
</tr>
<tr>
<td></td>
<td>A subset of a molecular interaction network of Bcell assembled by the ARACNeMargolin2006 algorithm for protein-DN interactions and Bayesian methodLefebvre2010 for protein-protein interactions.</td>
</tr>
<tr>
<td>caseIndex</td>
<td>Case sample index</td>
</tr>
<tr>
<td></td>
<td>Column indices of the gene expression matrix for the samples treated by Geldanamycin.</td>
</tr>
<tr>
<td>controlIndex</td>
<td>Control sample index</td>
</tr>
<tr>
<td></td>
<td>Column indices of the gene expression matrix for the samples treated by DMSO</td>
</tr>
</tbody>
</table>
**demand-instance**

*The DeMAND instance*

**Description**

This instance stores parameters and results of the DeMAND algorithm.

**Arguments**

- **exp**: A N by M numeric matrix and the rows are N probes and the columns are M samples.
- **anno**: A N by 2 character matrix. The rows are probes but the order should be the same with the *demand* matrix. The first column can be anything (usually probe IDs) but the second column should include Official Gene Symbol information for each probe.
- **network**: A K by 4 character matrix which contains K interactions. The 1st column and the 2nd column contain pairs of interacted genes. The 3rd and 4th columns indicate whether the interactions are protein-protein interaction (ppi) or protein-DNA (pdi) interaction. Column name should be as follows: c("Gene1", "Gene2", "ppi", "pdi")
- **moa**: A data frame contains DeMAND MoA predictions (e.g. Gene, p-value, adjusted p-values)
- **KLD**: A matrix containing the KL-divergence of the interactions that were analysed, the KL-divergence that was evaluated, and the p-value associated with the divergence.

**demandClass**

*The demand class constructor*

**Description**

This function generates demand class instances.

**Usage**

```
demandClass(exp, anno, network, moa=NULL, KLD=NULL)
```

**Arguments**

- **exp**: A N-by-M numeric matrix where the rows represent N probes (or genes) and the columns represent M samples.
- **anno**: A N-by-2 character matrix where the rows represent probes or genes in the same order as the exp matrix. The first column must hold the probe id or gene name as appears in the exp matrix, and the second column should hold their corresponding names (e.g. gene symbol) as appears in the network matrix.
network A K-by-L (L>1) character matrix containing K interactions. The 1st column
and the 2nd column contain the names of the interacting genes. If the following
columns include a column called "ppi" then genes connected by ppi will be used
without estimating the residuals in the Brown correction method. The rest of the
columns are used only to distinguish duplicates.

moa Filled by the runDeMAND function. A data frame containing DeMAND MoA
predictions (i.e. Gene, p-value, adjusted p-values)

KLD Filled by the runDeMAND function. A matrix containing the interactions that
were analysed, their KL-divergence, and the p-value associated with the diver-
genecence

Value
Instance of class demand

Examples

## Load toy example
data(inputExample)
dobj <- demandClass(exp=bcellExp, anno=bcellAnno, network=bcellNetwork)
printDeMAND(dobj)

Description
This document lists a series of basic methods for the class DeMAND

Usage

printDeMAND(x)

Arguments

x An instance of class demand which includes: a gene expression data, annotation
information, and a molecular interaction network.

Value

printDeMAND return summary information about the diggit object

Examples

data(inputExample)
dobj <- demandClass(exp=bcellExp, anno=bcellAnno, network=bcellNetwork)
printDeMAND(dobj)
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**Run DeMAND algorithm**

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**Description**

DeMAND.

This function is based on the realization that drugs affect the protein activity of their targets, but not necessarily their mRNA expression levels. In contrast, the change in protein activity directly affects the mRNA expression levels of downstream genes. Based on this hypothesis, DeMAND identifies drug MoA by comparing gene expression profiles following drug perturbation with control samples, and computing the change in the individual interactions within a pre-determined integrated transcriptional and post-translational regulatory model (interactome).

**Usage**

```r
runDeMAND(x, fgIndex, bgIndex, verbose=TRUE, method="bandwidth", 
keepLeaves=FALSE, alpha=0.05)
```

**Arguments**

- `x`: An instance of class demand which includes: a gene expression data, annotation information, and a molecular interaction network.
- `fgIndex`: A numeric vector contains indices of columns which represent case samples (e.g. drug treated). The sample size should be greater than 3.
- `bgIndex`: A numeric vector contains indices of columns which represent control samples (e.g. drug treated). The sample size should be greater than 3.
- `verbose`: A boolean value (TRUE by default) indicating whether to print progression outputs.
- `method`: A string value indicating whether to evaluate the KL-divergence using grid points based on 'bandwidth' (default) or on the 'integers' space.
- `keepLeaves`: A boolean value indicating whether to return a p-value for genes the have only a single neighbor in the network (default is FALSE, which returns 1 for such genes).
- `alpha`: The cutoff for estimating a p-value using pareto fitting (default=0.05)

**Details**

For each edge in the interactome we determine the two-dimensional probability distribution of the gene expression levels both in the control state, and following drug treatment. Any changes in the probability distribution are estimated using the Kullback-Leibler (KL) divergence, from which we determine the statistical significance of the dysregulation of each edge. In the second step of DeMAND, we interrogate each gene independently to determine whether its interactions are enriched in dysregulated ones, suggesting that it is a candidate mechanism of action.

**Value**

Returns a DeMAND class object holding the same exp, anno, and network slots as the input, and where the moa and KLD slots hold the results of DeMAND algorithm. The moa slot is a matrix containing a list of genes, corresponding p-value, and adjusted p-value. The KLD slot is a matrix with the gene names of the edges that were evaluated, their KL-divergence, and the p-value assigned to that divergence.
Examples

```
## Load toy example
data(inputExample)
dobj <- demandClass(exp=bcellExp, anno=bcellAnno, network=bcellNetwork, moa=NULL)
dobj <- runDeMAND(dobj, fgIndex=caseIndex, bgIndex=controlIndex)
## results (head)
printDeMAND(dobj)
## results (all)
print(dobj@moa)
print(dobj@KLD)
```
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