

# Package ‘c3net’

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**Title** Inferring large-scale gene networks with C3NET

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**Description** This package allows inferring gene regulatory networks with direct physical interactions from microarray expression data using C3NET.

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c3

*C3NET second step: Selecting maximum valued elements*

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### Description

c3 takes the mutual information matrix as input and implements the second step of C3NET - see details.

### Usage

```
c3( mim, sym = TRUE )
```

### Arguments

mim	A symmetric square mutual information matrix, where the elements (i,j) correspond to the mutual information $I(i, j)$ or $I(j, i)$ between variables i and j.
sym	Decides the output matrix to be symmetric or not.

### Details

The C3NET algorithm consists of two main steps. The first step is the same as for relevance networks (RELNET), where all the non-significant mutual information values in the matrix are eliminated if statistically not significant. The second step of C3NET keeps all maximum valued mutual information values for each row in the matrix and sets the rest of the elements in the matrix zero (the diagonal of the matrix is ignored). The output is normally symmetric matrix but if the argument sym is set to FALSE then the output becomes non-symmetric.

### Value

c3 implements the second step of the C3NET algorithm returning a symmetric mutual information matrix. Specifically, the non-zero elements in the returned matrix represent undirected links between variables which are statistically significant (tested in the first step of C3NET).

### References

G. Altay, F. Emmert-Streib, "Inferring the conservative causal core of gene regulatory networks", BMC Systems Biology (2010) 4:132.

### See Also

[makemim](#), [copula](#), [sigtestp](#), [sigtestMTC](#), [netplot](#), [c3net](#)

## Examples

```

data(expdata)

expdata <- copula(expdata)

mim <- makemim(expdata)

Ic <- mean(mim[upper.tri(mim)]) #Example cut-off for the first step of C3NET

# Ic <- 2 can be set for the example.

mim[mim < Ic] <-0 #nonsignificant values eliminated wrt C3NET step 1.

net <- c3(mim) # regulatory network inferred (non zero elements stand for links of
#the predicted network)

```

---

c3net

*All in one function to infer network with C3NET*


---

## Description

c3net takes a data set as input and computes the inferred network using C3NET - see details.

## Usage

```

c3net(dataset, cop=TRUE, alpha=0.01, methodstep1="cutoff", cutoffMI= 0,
      MTCmethod="BH", itnum=5, network=FALSE)

```

## Arguments

dataset	Data set where rows are variables (e.g. genes) and columns are samples.
cop	The data set is copula transformed by default. If not wanted, then "cop" is set to FALSE.
alpha	Statistical significance threshold
itnum	Number of iterations to resample data to get sampling distribution.
methodstep1	If it is "cutoff" then the input cutoffMI is used as threshold for elimination in step 1. If it is "MTC" then MTCmethod input is used as the specific multiple testing correction method to employ. If it is "justp" then only significance threshold alpha is used to compute significance threshold MI.
MTCmethod	Available option are "holm", "hochberg", "hommel", "bonferroni", "BH", "BY".
cutoffMI	If methodstep1 is set to "cutoff" then this value is used for MI threshold. If this is set to 0 (or by default) it uses mean MI for threshold.
network	If TRUE, the network is plotted in the end.

## Details

For Step 1 of C3NET, there are three options that can be used. If `methodstep1="cutoff"` then `cutoffMI` input is taken as the significance threshold for step 1. In case `cutoffMI` is set to 0 then by default mean MI is taken as `cutoffMI`. If `methodstep1` is set to "MTC" then the method from input `MTCmethod`, `itnum` for iteration number to get null distribution and `alpha` for statistical significance is taken for computations. If `methodstep1` is set to "justp" or anything else then just `alpha` and `itnum` is used for computations.

## Value

`c3net` returns a symmetric mutual information matrix, which is obtained after implementing C3NET. Specifically, non-zero elements in the returned matrix represents undirected link between variables. The inferred network may also be plotted if the argument `network` is set TRUE.

## References

G. Altay, F. Emmert-Streib, "Inferring the conservative causal core of gene regulatory networks", *BMC Systems Biology* (2010) 4:132.

## See Also

[makemim](#), [copula](#), [c3](#), [sigtestp](#), [sigtestMTC](#)

## Examples

```
data(expdata)
data(truenet)

net <- c3net(expdata, network=TRUE)
scores <- checknet(net, truenet)
```

---

checknet

*Validating the inferred network*

---

## Description

`checknet` takes the inferred mutual information matrix and the true network for validation. - see details.

## Usage

```
checknet( finalrelationmatrix, realrelationmatrix)
```

## Arguments

`finalrelationmatrix`

The inferred symmetric mutual information matrix, where  $i,j$  th element is the mutual information  $I(i, j)$  or  $I(j, i)$  between two variables  $i$  and  $j$ . The diagonal is set to zero.

`realrelationmatrix`

A symmetric reference connection matrix, where a 1 at  $i,j$  th element defines the connection between variables  $i$  and  $j$  and non-connection is represented by 0. The diagonal is all zero.

## Value

`checknet` returns a vector with 6 elements, that contains the parameters as output `<- c(precision, Fscore, recall, TP, FP, FN)`.

## References

G. Altay, F. Emmert-Streib, "Inferring the conservative causal core of gene regulatory networks", *BMC Systems Biology*, (2010) 4:132.

## See Also

[makemim](#), [copula](#), [c3](#), [c3net](#), [c3](#), [makemim](#), [copula](#), [sigtestp](#), [sigtestMTC](#)

## Examples

```
data(expdata)

data(truenet)

expdata <- copula(expdata)

mim <- makemim(expdata)

Ic <- 2 #Example cut-off value for mutual information for the first step of C3NET

mim[mim < Ic] <-0 #nonsignificant values eliminated wrt C3NET step 1.

net <- c3(mim) # regulatory network inferred (non zero elements stand for links of
# the predicted network)

scores <- checknet(net, truenet)
```

---

`copula`*Copula transformation of data set*

---

### Description

`copula` takes a data set as input and applies a copula transformation - see details.

### Usage

```
copula( expdata )
```

### Arguments

`expdata`            Data set; rows correspond to variables (e.g. genes) and columns to samples.

### Details

The data set can be copula transformed for more stable estimations of the mutual information matrix. Each row of the data set (gene samples of each gene) is copula transformed and obtained `rdata`. Here, the formula for conversion is `copuladata =(rdata- 0.5)/numberofsamples`.

### Value

`copula` returns a copula transformed data set.

### References

G. Altay, F. Emmert-Streib, "Inferring the conservative causal core of gene regulatory networks", *BMC Systems Biology* (2010) 4:132.

### See Also

[c3](#), [c3net](#), [makemim](#)

### Examples

```
data(expdata)
```

```
expdata <- copula(expdata)
```

---

expdata

*Example data set*

---

### Description

expdata This data set has been generated by SynTREN. The source network corresponds to a subnetwork of E.coli (file name "EColi\_full\_HongWu\_Ma\_NAR2004.sif" from Ma HW, et. al. Nuc. Ac. Res. 2004).

### Usage

```
data( expdata )
```

### Arguments

expdata            Example data; rows correspond to variables (e.g. genes) and columns to samples.

### Details

The example is also given to provide a sample data set so that one can take it as reference while formatting the new data set as entry to c3net. Data sets must be complete and no empty or non-numerical character allowed.

### Value

expdata returns an example data set where rows are variables (e.g. genes) and columns are samples. It consists of 400 genes, 898 edges, and 800 steady-state samples.

### References

Ma HW, Kumar B, Ditges U, Gunzer F, Buer J, Zeng AP: An extended transcriptional regulatory network of Escherichia coli and analysis of its hierarchical structure and network motifs. Nucleic Acids Res 2004 , 32:6643-6649

Bulcke, T.V., Leemput, K.V., Naudts, B., et. al. (2006) Syntren: a generator of synthetic gene expression data for design and analysis of structure learning algorithms. BMC Bioinformatics, 7(1), 43.

G. Altay, F. Emmert-Streib, "Inferring the conservative causal core of gene regulatory networks", BMC Systems Biology (2010) 4:132.

### See Also

[c3](#), [c3net](#), [makemim](#)

### Examples

```
data(expdata)
```

---

`makemim`*Constructing mutual information matrix*

---

**Description**

`makemim` takes the data set as input and computes mutual information values for each pair of variables (e.g. gene). - see details.

**Usage**

```
makemim( expdata )
```

**Arguments**

`expdata` Data matrix where rows correspond to variables (e.g. genes) and columns to samples.

**Details**

A mutual information matrix is generated from a data set using an empirical Gaussian estimator.

**Value**

`makemim` returns a symmetric mutual information matrix using empirical Gaussian estimator.

**References**

G. A. Darbellay, I. Vajda, "Estimation of the information by an adaptive partitioning of the observation space", IEEE Trans. Inf. Theory vol.45 (1999)

G. Altay, F. Emmert-Streib, "Inferring the conservative causal core of gene regulatory networks", BMC Systems Biology, (2010) 4:132.

**See Also**

[c3](#), [c3net](#), [copula](#), [checknet](#)

**Examples**

```
data(expdata)
```

```
expdata <- copula(expdata)
```

```
mim <- makemim(expdata)
```



---

`netplot`*Plotting the inferred network*

---

### Description

`netplot` takes the inferred mutual information matrix and plots a network wrt nonzero elements of the matrix - see details.

### Usage

```
netplot(gnet)
```

### Arguments

<code>gnet</code>	A symmetric squared mutual information matrix that is inferred as final connection matrix, where $i,j$ th element is the mutual information $I(i, j)$ or $I(j, i)$ between variables $i$ and $j$ . The nonzero elements may also be 1. Diagonal is all zero.
-------------------	--

### Details

A labelled undirected network is plotted wrt the row (column) names of the input matrix. When plotted, select "Layout" and then "Fruchterman-Reingold" and "OK" to get a better view. To remove labels, select "View" and deselect "Labels". To change the colors or size of nodes and edges, from "Select", click on "all edges" or "vertices" and on the network right click on nodes and change color or size.

### Value

`netplot` returns an undirected network.

### References

G. Altay, F. Emmert-Streib, "Inferring the conservative causal core of gene regulatory networks", BMC Systems Biology (2010) 4:132.

CSARDI G, NEPUSZ T.: igraph-package for R, 2008

### See Also

[makemim](#), [copula](#), [c3](#), [sigtestp](#), [sigtestMTC](#)

### Examples

```
data(expdata)
```

```
data(truenet)
```

```
expdata <- copula(expdata)
```

```

mim <- makemim(expdata)

Ic <- 2 #Example cut-off for the first step of C3NET

mim[mim < Ic] <-0 #nonsignificant values eliminated wrt C3NET step 1.

net <- c3(mim) # regulatory network inferred (non zero elements stand for links of
# the predicted network)

netplot(net)

```

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sigtestMTC	<i>Elimination of nonsignificant edges by application of a procedure for multiple testing correction</i>
------------	--

---

### Description

sigtestMTC takes a data set as input and computes the mutual information matrix in which the nonsignificant elements are eliminated by a multiple testing correction - see details.

### Usage

```
sigtestMTC( data, alpha, itnum, methodsig="BH")
```

### Arguments

data	Data set where rows correspond to variables (e.g. genes) and columns to samples.
alpha	Significance level
itnum	Number of iterations to resample data to estimate sampling distribution.
methodsig	A procedure to perform a multiple testing correction, either controlling the false discovery rate (FDR) or the family-wise error. Available options are "holm", "hochberg", "hommel", "bonferroni", "BH", "BY".

### Details

The data set is resampled for each iteration and at the end the sampling distribution is obtained.

### Value

sigtestMTC returns an environment `res` that contains the new MI matrix, `res$Inew`, that is obtained after the elimination of nonsignificant elements with a MTC procedure. For advanced users, who are able to write code in R, we provided the variables obtained in the function so that one might want to make further analysis without running the function again. Please see the source code for the additional return values of the environment `res`.

## References

G. Altay, F. Emmert-Streib, "Inferring the conservative causal core of gene regulatory networks", *BMC Systems Biology* (2010) 4:132.

## See Also

[makemim](#), [copula](#), [c3](#), [sigtestp](#)

## Examples

```
data(expdata)

data(truenet)

alpha <- 0.001

itnum <-2

res <- sigtestMTC( expdata, alpha, itnum, methodsig="BH")

net <- c3(res$Inew) # regulatory network inferred (non zero elements stand for links of
# the predicted network)

scores <- checknet(net,truenet)
```

---

sigtestp

*Significance test for elimination of nonsignificant edges*

---

## Description

sigtestp takes the data set as input and computes the mutual information matrix in which the nonsignificant elements are eliminated by using a significance threshold only (no MTC) - see details.

## Usage

```
sigtestp( data, alpha, itnum)
```

## Arguments

data	Data set where rows are variables (e.g. genes) and columns are samples.
alpha	Statistical significance threshold
itnum	Number of iterations to resample data to get sampling distribution.

## Details

The data set is resampled completely at each iteration and at the end the sampling distribution is obtained for using in significance test.

**Value**

sigtestp returns environment res that contains the obtained threshold value res\$I0. For advanced users, who are able to write code in R, we provided the variables obtained in the function so that one might want to make further analysis without running the function again. Please see the source code for the additional return values of the environment res.

**References**

G. Altay, F. Emmert-Streib, "Inferring the conservative causal core of gene regulatory networks", BMC Systems Biology (2010) 4:132.

**See Also**

[makemim](#), [copula](#), [c3,c3](#), [sigtestMTC](#)

**Examples**

```
data(expdata)

data(truenet)

alpha <- 0.001

itnum <- 2

res <- sigtestp( expdata, alpha, itnum)

net <- c3(res$Inew) # regulatory network inferred (non zero elements stand for links of
# the predicted network)

scores <- checknet(net,truenet)
```

---

truenet

*Reference, e.g. true, network of the example data set*

---

**Description**

truenet A symmetric matrix, where non-zero elements correspond to true connections.

**Usage**

```
data( truenet )
```

**Arguments**

truenet            Reference (true) network of the example data set.

**Details**

A symmetric matrix, where non-zero elements correspond to true connections.

**Value**

`truenet` Reference (true) network of the example data set.

**References**

G. Altay, F. Emmert-Streib, "Inferring the conservative causal core of gene regulatory networks", *BMC Systems Biology* (2010) 4:132.

**See Also**

[c3](#), [c3net](#), [makemim](#)

**Examples**

```
data(truenet)
```

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