

# Package ‘c3net’

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**Title** C3NET

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**Description** This package allows inferring regulatory networks from expression data using C3NET.

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**Depends** igraph

## R topics documented:

c3 . . . . .	1
c3net . . . . .	3
checknet . . . . .	4
copula . . . . .	5
makemim . . . . .	6
netplot . . . . .	7
sigtestfdr . . . . .	8
sigtestp . . . . .	9
<b>Index</b>	<b>11</b>

c3

*C3NET second step: Selecting maximum valued elements***Description**

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

**Usage**

```
c3( mim )
```

**Arguments**

mim                      A symmetric square mutual information matrix, where  $i,j$  th element is the mutual information  $I(i, j)$  or  $I(j, i)$  between variables  $i$  and  $j$ .

**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 is eliminated statistically if not significant. The second step of C3NET keeps all the 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).

**Value**

c3 returns a symmetric mutual information matrix, which is obtained after implementing the second step of C3NET algorithm. Specifically, the non-zero elements in the returned matrix represents undirected links between variables if it is statistically significant (the first step of C3NET).

**References**

G. Altay, F. Emmert-Streib, "Inferring the conservative causal core of gene regulatory networks", BMC Systems Biology, in press.

**See Also**

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

**Examples**

```
data(expdata)

expdata <- copula(expdata)

mim <- makemim(expdata)

Ic <- mean(mim[upper.tri(mim)]) #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)
```

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, alpha=0.01, methodstep1="cutoff", cutoffMI= 0,
      fdmethod="BH", itnum=5, network=FALSE)
```

**Arguments**

dataset	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.
methodstep1	If it is "cutoff" then the input cutoffMI is used as threshold for elimination in step 1. If it is "fdr" then fdmethod input is used as the specific FDR method to employ. If it is "justp" then only significance threshold alpha is used to compute significance threshold MI.
fdmethod	It can be any of the options available in the R function p.adjust (e.g. "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 "fdr" then the FDR method from input fdmethod, 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, in press.

## See Also

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

## 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  $\leftarrow c(\text{precision}, \text{Fscore}, \text{recall}, \text{TP}, \text{FP}, \text{FN})$ .

## References

G. Altay, F. Emmert-Streib, "Inferring the conservative causal core of gene regulatory networks", BMC Systems Biology, in press.

**See Also**

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

**Examples**

```
data(expdata)

data(truenet)

expdata <- copula(expdata)

mim <- makemim(expdata)

Ic <- mean(mim[upper.tri(mim)]) #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)

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

---

copula

*Copula transformation of data set*


---

**Description**

`copula` takes the data set as input and copula transform it - see details.

**Usage**

```
copula( expdata )
```

**Arguments**

`expdata`            Data set where rows are variables (e.g. genes) and columns are 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, in press.

## See Also

[c3](#)

## Examples

```
data(expdata)

expdata <- copula(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 are 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, in press.

**See Also**[c3](#), [copula](#)**Examples**

```
data(expdata)

expdata <- copula(expdata)

mim <- makemim(expdata)
```

---

netplot*Plotting the inferred network*

---

**Description**

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

**Usage**

```
netplot(gnet)
```

**Arguments**

gnet	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.
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**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 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, in press.

**See Also**

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

**Examples**

```
data(expdata)

data(truenet)

expdata <- copula(expdata)

mim <- makemim(expdata)

Ic <- mean(mim[upper.tri(mim)]) #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)
```

---

sigtestfdr

*Significance test for elimination of nonsignificant edges with FDR*


---

**Description**

sigtestfdr takes the data set as input and computes the mutual information matrix in which the nonsignificant elements are eliminated by a FDR method. - see details.

**Usage**

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

**Arguments**

data	Data set where rows are variables (e.g. genes) and columns are samples.
alpha	Significance threshold
itnum	Number of iterations to resample data to get sampling distribution.
methodsig	A FDR method.

**Details**

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



**Value**

sigtestfdr returns environment res that contains the new MI matrix, res\$Inew, that is obtained after elimination of nonsignificant elements with FDR.

**References**

G. Altay, F. Emmert-Streib, "Inferring the conservative causal core of gene regulatory networks", BMC Systems Biology, in press.

**See Also**

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

**Examples**

```
data(expdata)

data(truenet)

alpha <- 0.001

itnum <-2

res <- sigtestfdr( 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 only significance threshold alpha. - 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`.

**References**

G. Altay, F. Emmert-Streib, "Inferring the conservative causal core of gene regulatory networks", BMC Systems Biology, in press.

**See Also**

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

**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)
```

# Index

## \*Topic **misc**

c3, [1](#)

c3net, [2](#)

checknet, [4](#)

copula, [5](#)

makemim, [6](#)

netplot, [7](#)

sigtestfdr, [8](#)

sigtestp, [9](#)

c3, [1](#), [3–8](#), [10](#)

c3net, [2](#)

checknet, [4](#)

copula, [2–4](#), [5](#), [6–8](#), [10](#)

makemim, [2–4](#), [6](#), [7](#), [8](#), [10](#)

netplot, [7](#)

sigtestfdr, [2](#), [4](#), [7](#), [8](#), [10](#)

sigtestp, [2–4](#), [7](#), [8](#), [9](#)