

Package ‘netgsa’

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Author Ali Shojaie and Jing Ma

Maintainer Jing Ma <mjing@umich.edu>

Description Functions for carrying out Network-based Gene Set Analysis by incorporating external information about interactions among genes, as well as novel interactions learned from data

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netgsa-package

Network-based Gene Set Analysis

Description

The netgsa-package provides functions for carrying out Network-based Gene Set Analysis by incorporating external information about interactions among genes, as well as novel interactions learned from data.

Details

Package: netgsa
Type: Package
Version: 1.0
Date: 2014-12-01
License: GPL (>=2)

Author(s)

Ali Shojaie <ashojaie@uw.edu> and Jing Ma <mjing@umich.edu>

References

Ma, J., Shojaie, A. & Michailidis, G. (2014). Network-based pathway enrichment analysis with incomplete network information, submitted. <http://arxiv.org/abs/1411.7919>.

Shojaie, A., & Michailidis, G. (2010). Network enrichment analysis in complex experiments. *Statistical applications in genetics and molecular biology*, 9(1), Article 22.

Shojaie, A., & Michailidis, G. (2009). Analysis of gene sets based on the underlying regulatory network. *Journal of Computational Biology*, 16(3), 407-426.

See Also

[glasso](#), [glmnet](#)

covsel*Covariance selection*

Description

Estimates a sparse inverse covariance matrix using a lasso (L1) penalty.

Usage

```
covsel(X, zero = NULL, one = NULL, lambda, rho=0.01, verbose = FALSE, eps = 1e-08)
```

Arguments

<code>X</code>	The $n \times p$ data matrix.
<code>zero</code>	(Optional) indices of entries of the matrix to be constrained to be zero. The input should be a matrix of $p \times p$, with 1 at entries to be constrained to be zero and 0 elsewhere. The matrix must be symmetric.
<code>one</code>	(Optional) indices of entries of the matrix to be kept regardless of the regularization parameter for lasso. The input is similar to that of <code>zero</code> and needs to be symmetric.
<code>lambda</code>	(Non-negative) numeric scalar representing the regularization parameter for lasso.
<code>rho</code>	(Non-negative) numeric scalar representing the regularization parameter for estimating the weights in the inverse covariance matrix.
<code>verbose</code>	Whether to print out information as estimation proceeds. Default = FALSE.
<code>eps</code>	Numeric scalar ≥ 0 , indicating the tolerance level for differentiating zero and non-zero edges: entries $< \text{eps}$ will be set to 0.

Details

The function `covsel` performs constrained estimation of sparse inverse covariance (concentration) matrices using a lasso (L1) penalty, as described in Ma, Shojaie and Michailidis (2014). Two sets of constraints determine subsets of entries of the inverse covariance matrix that should be exactly zero (the option `zero` argument), or should take non-zero values (option `one` argument). The remaining entries will be estimated from data.

The arguments `one` and/or `zero` can come from external knowledge on the 0-1 structure of underlying concentration matrix, such as a list of edges and/or non-edges learned from available databases. Then the function `edgelist2adj` can be used to first construct `one` and/or `zero`.

`covsel` estimates both the support (0-1 structure) of the concentration matrix, or equivalently, the adjacency matrix of the corresponding Gaussian graphical model, for a given tuning parameter, `lambda`; and the concentration matrix with diagonal entries set to 0, or equivalently, the weighted adjacency matrix. The weighted adjacency matrix is estimated using maximum likelihood based on the estimated support. The parameter `rho` controls the amount of regularization used in the maximum likelihood step. A small `rho` is recommended, as a large value of `rho` may result in too much regularization in the maximum likelihood estimation, thus further penalizing the support of the weighted adjacency matrix. Note this function is suitable only for estimating the adjacency matrix of a undirected graph.

This function is closely related to `NetGSA`, which requires the weighted adjacency matrix as input. When the user does not have complete information on the weighted adjacency matrix, but has data (`X`, not necessarily the same as the `x` in `NetGSA`) and external information (`one` and/or `zero`) on the adjacency matrix, then `covsel` can be used to estimate the remaining interactions in the adjacency matrix using the data. Further, when it is anticipated that the adjacency matrices under conditions 1 and 2 are different, and data from both conditions are available, the user needs to run `covsel` twice to obtain estimates of the adjacency matrices under each condition.

The algorithm used in covsel is based on glmnet and glasso. Please refer to glmnet and glasso for computational details.

Value

A list with components

Adj	The estimated adjacency matrix of dimension $p \times p$.
wAdj	The estimated weighted adjacency matrix of dimension $p \times p$, with diagonal entries set to 0.

Author(s)

Jing Ma

References

Ma, J., Shojaie, A. & Michailidis, G. (2014). Network-based pathway enrichment analysis with incomplete network information, submitted. <http://arxiv.org/abs/1411.7919>.

See Also

[edgelist2adj](#), [cv.covsel](#), [glmnet](#), [glasso](#)

Examples

```
library(MASS)
library(glmnet)
library(glasso)
set.seed(1)

## Generate the covariance matrix for the AR(1) process
phi <- 0.5
p <- 50
n <- 50
Sigma <- diag(rep(1,p))
Sigma <- phi^(abs(row(Sigma)-col(Sigma)))/(1-phi^2)

## The inverse covariance matrix is sparse
Omega <- solve(Sigma)

## Generate multivariate normal data
x <- mvrnorm(n, mu=rep(0, p), Sigma=Omega)

## Covariance selection without external information
fit <- covsel(x, lambda = 0.2)

## Covariance selection with external information
##-Not run-
#oneMat = edgelist2adj(file="edgelist.txt", vertex.names=1:p, mode="undirected")
#zeroMat = edgelist2adj(file="nonedgelist.txt", vertex.names=1:p, mode="undirected")
#fit2 <- covsel(x, zero=zeroMat, one=oneMat, lambda = 0.2)
```

`cv.covsel`*Cross-validation for covsel*

Description

Performs k-fold cross validation for covsel.

Usage

```
cv.covsel(X, zero = NULL, one = NULL, lambda, nfolds = NULL, verbose = FALSE)
```

Arguments

<code>X</code>	The $n \times p$ data matrix as in covsel.
<code>zero</code>	(Optional) indices of entries of the matrix to be constrained to be zero. The input should be a matrix of $p \times p$, with 1 at entries to be constrained to be zero and 0 elsewhere. The matrix must be symmetric.
<code>one</code>	(Optional) indices of entries of the matrix to be kept regardless of the regularization parameter for lasso. The input is similar to that of zero and needs to be symmetric.
<code>lambda</code>	(Non-negative) user-supplied lambda sequence.
<code>nfolds</code>	Number of folds. Default is 5-fold cross validation.
<code>verbose</code>	Whether to print out information as estimation proceeds. Default=FALSE.

Details

The function splits the data `X` into `nfolds` and runs `covsel` `nfolds` times to compute the fit with each of the folds omitted. The error is accumulated and the average error over the folds is computed.

Value

A list with components

<code>lambda</code>	The values of lambda used.
<code>cve</code>	The mean cross-validated error(s), a vector of length(<code>lambda</code>).

Author(s)

Jing Ma

References

Ma, J., Shojaie, A. & Michailidis, G. (2014). Network-based pathway enrichment analysis with incomplete network information, submitted. <http://arxiv.org/abs/1411.7919>.

See Also[covsel](#)**Examples**

```
library(MASS)
library(glmnet)
library(cvTools)
set.seed(1)

## Generate the covariance matrix for the AR(1) process
phi <- 0.5
p <- 50
n <- 50
Sigma <- diag(rep(1,p))
Sigma <- phi^(abs(row(Sigma)-col(Sigma)))/(1-phi^2)

## The inverse covariance matrix is sparse
Omega <- solve(Sigma)

## Generate multivariate normal data
x <- mvrnorm(n, mu=rep(0, p), Sigma=Omega)

## Covariance selection with external information
cv.fit <- cv.covsel(x, lambda=seq(0.1,0.3,0.1), nfolds=5)
```

edgelist

An example edge list

Description

An example edge list corresponding to known connections in a network.

Usage

```
data(edgelist)
```

Format

A matrix with two columns, each row defining one edge.

Examples

```
data(edgelist)
```

`edgelist2adj`*Construct an adjacency matrix from an edge list*

Description

Read the edge list of a graph from a file and construct the adjacency matrix.

Usage

```
edgelist2adj(file, vertex.names, mode = c("directed", "undirected"))
```

Arguments

<code>file</code>	The connection to read from. This should be a .txt file, with one edge in a line, the two vertices separated by a delimiter.
<code>vertex.names</code>	The names of all vertices in the graph.
<code>mode</code>	Whether the graph to read is directed.

Details

The function `edgelist2adj` accepts a list of edges and constructs the 0-1 adjacency matrix corresponding to the graph. If `file` contains an incomplete list of edges, the function determines the actual size of the graph through the vector `vertex.names`.

Although named as `edgelist2adj`, the user can also construct a 0-1 matrix corresponding to non-edges, i.e. connections that do not exist between any two vertices.

When `file` contains incomplete information, the returned 0-1 adjacency matrix (for edges or non-edges) can be used as input in `covsel` to estimate the complete (and weighted) adjacency matrix.

Value

A 0-1 adjacency matrix of dimension $p \times p$ corresponding to the edges defined in `file`, where p is the length of the vector `vertex.names`.

Author(s)

Ali Shojaie and Jing Ma

References

Ma, J., Shojaie, A. & Michailidis, G. (2014). Network-based pathway enrichment analysis with incomplete network information, submitted. <http://arxiv.org/abs/1411.7919>.

See Also

[covsel](#)

Examples

```
#Read the data
data(edgelist)
data(nonedgelist)

#Generate the .txt files
write.table(edgelist, file="edgelist.txt", row.names=FALSE)
write.table(nonedgelist, file="nonedgelist.txt", row.names=FALSE)

#Read the edge/nonedge list from files
oneMat = edgelist2adj(file="edgelist.txt", vertex.names=1:50, mode="undirected")
zeroMat = edgelist2adj(file="nonedgelist.txt", vertex.names=1:50, mode="undirected")
```

NetGSA

Network-based Gene Set Analysis

Description

Tests the significance of pre-defined sets of genes (pathways) with respect to an outcome variable, such as the condition indicator (e.g. cancer vs. normal, etc.), based on the underlying biological network.

Usage

```
NetGSA(A1, A2, x, y, B, lklMethod = c("REML", "ML"), directed = FALSE, eta = 0.1,
       lim4kappa = 500)
```

Arguments

A1	The weighted adjacency matrix for condition 1.
A2	The weighted adjacency matrix for condition 2.
x	The $p \times n$ data matrix.
y	Vector of class indicators of length n .
B	The n path by p indicator matrix for pathways.
lklMethod	Method used for likelihood calculation: options are ML (maximum likelihood) or REML (restricted maximum likelihood).
directed	Whether the networks are directed.
eta	Approximation limit for the Influence matrix. See 'Details'.
lim4kappa	Limit for condition number (used to adjust eta). See 'Details'.

Details

The function NetGSA carries out a Network-based Gene Set Analysis, using the method described in Shojaie and Michailidis (2009) and Shojaie and Michailidis (2010). It differs from Gene Set Analysis (Efron and Tibshirani, 2007) in that it incorporates the underlying biological networks.

The NetGSA method is formulated in terms of a mixed linear model. Let X represent the rearrangement of data x into an $np \times 1$ column vector.

$$X = \Psi\beta + \Pi\gamma + \epsilon$$

where β is the vector of fixed effects, γ and ϵ are random effects and random errors, respectively. The underlying biological networks are encoded in the weighted adjacency matrices $A1$ and $A2$, which determine the influence matrix under each condition. The influence matrices further determine the design matrices Ψ and Π in the mixed linear model. Formally, the influence matrix under each condition represents the effect of each gene on all the other genes in the network and is calculated from the adjacency matrix ($A1$ or $A2$). A small value of η is used to make sure that the influence matrices are well-conditioned (i.e. their condition numbers are bounded by $\lim_{\eta \rightarrow 0} \kappa(\Psi) < 4$.)

The problem is then to test the null hypothesis $\ell\beta = 0$ vs. the alternative $\ell\beta \neq 0$, where ℓ is a contrast vector, optimally defined through the underlying networks. The test statistic T for each gene set is then a function of β , variances of γ and ϵ , the contrast vector ℓ and the underlying biological network(s) in both conditions. Under the null hypothesis, T has approximately a t -distribution, whose degrees of freedom are estimated using the Satterthwaite approximation method. The fixed effects β are estimated by generalized least squares, and the estimate depends on estimates of the variance components of γ and ϵ . The variance components (σ_ϵ^2 and σ_γ^2) are estimated using Newton's method based on the profiling out σ_ϵ .

This function can deal with both directed and undirected networks, which are specified via the option `directed`. Note NetGSA uses slightly different procedures to calculate the influence matrices for directed and undirected networks. In the case of undirected networks, the user can still apply NetGSA if only partial information on the adjacency matrices is available. The function `covsel` provides one way to estimate the weighted adjacency matrices from data based on available network information.

Value

A list with components

beta	Vector of fixed effects of length $2p$, of which the first half is for condition 1 and the second half for condition 2.
df	Degrees of freedom for the test statistics.
p.value	P-values for gene sets (pathways).
s2.epsilon	Variance of the random errors ϵ .
s2.gamma	Variance of the random effects γ .

Author(s)

Ali Shojaie and Jing Ma

References

- Ma, J., Shojaie, A. & Michailidis, G. (2014). Network-based pathway enrichment analysis with incomplete network information, submitted. <http://arxiv.org/abs/1411.7919>
- Shojaie, A., & Michailidis, G. (2010). Network enrichment analysis in complex experiments. *Statistical applications in genetics and molecular biology*, 9(1), Article 22.
- Shojaie, A., & Michailidis, G. (2009). Analysis of gene sets based on the underlying regulatory network. *Journal of Computational Biology*, 16(3), 407-426.

See Also

[edgelist2adj, covsel](#)

Examples

```
set.seed(1)
library(igraph)
data(netgsaex)

A1 = netgsaex$A1
A2 = netgsaex$A2
B = netgsaex$B
x = netgsaex$x
y = netgsaex$y

##Visualize the networks
par(mar = c(0.5, 0.5, 3, 0.5))
plot(netgsaex$g.alt, vertex.size = 5, vertex.label = NA, main="Network - alt")

par(mar = c(0.5, 0.5, 3, 0.5))
plot(netgsaex$g.null, vertex.size = 5, vertex.label = NA, main="Network - null")

out = NetGSA(A1, A2, x, y, B, lk1Method = "REML")
out2 = NetGSA(A1, A2, x, y, B, lk1Method = "ML")
```

netgsaex

Toy example for using NetGSA on a two-class test

Description

This dataset contains an example for using Network-based Gene Set Analysis on a two-sample test.

Usage

```
data(netgsaex)
```

Format

A list with components

A1 The weighted adjacency matrix for condition 1.

A2 The weighted adjacency matrix for condition 2.

x The $p \times n$ data matrix.

y The vector of class indicators of length n .

B The n path by p indicator matrix for pathways.

g.null, g.alt The networks under the null and alternative hypothesis, respectively. Node colors in the two graphs represent different mean values. Note the network structures between g.null and g.alt differ slightly.

References

Ma, J., Shojaie, A. & Michailidis, G. (2014). Network-based pathway enrichment analysis with incomplete network information, submitted.

Examples

```
data(netgsaex)
```

nonedgelist

An example for not-an-edge list

Description

An example for not-an-edge list corresponding to the connections that do not exist in a network.

Usage

```
data(nonedgelist)
```

Format

A matrix with two columns, each row defining one pair of vertices that is not an edge in the network.

Examples

```
data(nonedgelist)
```

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