Package 'BiRewire'

October 7, 2014

graph (or a binary event matrix) preserving degree distribution (or marginal totals).

Title High-performing routines for the randomization of a bipartite

Version 1.6.5

Date 2014-09-16

Maintainer Andrea Gobbi <gobbi.andrea@mail.com></gobbi.andrea@mail.com>
Description Fast functions for bipartite network rewiring through N consecutive switching steps (See References) and for the computation of the minimal number of switching steps to be performed in order to maximise the dissimilarity with respect to the original network. Includes function for the analysis of the introduced randomness across the switching and several other routines to analyse the resulting networks and their natural projections. Extension to undirected networks (not bipartite) is also provided.
License GPL-3
Depends igraph
Suggests RUnit, BiocGenerics
Author Andrea Gobbi [aut], Davide Albanese [cbt], Francesco Iorio [cbt], Giuseppe Jurman [cbt], Julio Saez-Rodriguez [cbt].
<pre>URL http://www.ebi.ac.uk/~iorio/BiRewire</pre>
biocViews Network
R topics documented:
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Description

R package for computationally-efficient rewiring of bipartite graphs (or randomisation of 0-1 tables with prescribed marginal totals). The package provides useful functions for the analysis and the randomisation of large biological datasets that can be encoded as 0-1 tables, hence modeled as bipartite graphs by considering a 0-1 table as an incidence matrix. Large collections of such randomised tables can be used to approximate null models, preserving event-rates both across rows and columns, for statistical significance tests of combinatorial properties of the original dataset. Routines for undirected graphs are also provided.

Details

Summary:

Package: BiRewire Version: 1.3.2

Date: 2013-07-15

Require: igraph, R>=2.10

URL: http://www.ebi.ac.uk/~iorio/BiRewire

License: GPL-3

Author(s)

Andrea Gobbi [aut], Davide Albanese [cbt], Francesco Iorio [cbt], Giuseppe Jurman [cbt].

Maintainer: Andrea Gobbi <gobbi.andrea@mail.com>

References

Gobbi, A. and Iorio, F. and Dawson, K. J. and Wedge, D. C. and Tamborero, D. and Alexandrov, L. B. and Lopez-Bigas, N. and Garnett, M. J. and Jurman, G. and Saez-Rodriguez, J. (2014) *Fast randomization of large genomic datasets while preserving alteration counts* Bioinformatics 2014 30 (17): i617-i623 doi: 10.1093/bioinformatics/btu474.

Jaccard, P. (1901), Étude comparative de la distribution florale dans une portion des Alpes et des Jura, Bulletin de la Société Vaudoise des Sciences Naturelles 37: 547–579.

David J. Rogers and Taffee T. Tanimoto, A Computer Program for Classifying Plants, Science Vol 132 pp 1115-1118, October 1960

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Hamming, Richard W. (1950), *Error detecting and error correcting codes*, Bell System Technical Journal 29 (2): 147–160, MR 0035935.

R. Milo, N. Kashtan, S. Itzkovitz, M. E. J. Newman, U. Alon (2003), *On the uniform generation of random graphs with prescribed degree sequences*, eprint arXiv:cond-mat/0312028

Csardi, G. and Nepusz, T (2006) *The igraph software package for complex network research*, Inter-Journal, Complex Systems http://igraph.sf.net

birewire.analysis

Analysis of Jaccard similarity trends across switching steps.

Description

This function performs a sequence of max.iter switching steps on the input bipartite graph g and compute the Jaccard similarity between g (the initial network) and its rewired version each step switching steps.

Usage

```
birewire.analysis(incidence, step=10, max.iter="n",accuracy=1,
verbose=TRUE,MAXITER_MUL=10,exact=F)
```

Arguments

incidence	Incidence matrix of the initial bipartite graph g (can be extracted from an igraph bipartite graph using the get.incidence)function;
step	10 (default): the interval (in terms of switching steps) at which the Jaccard index between g and the its current rewired version is computed;
max.iter	"n" (default) the number of switching steps to be performed (or if $exact==TRUE$ the number of successful switching steps). If equal to "n" then this number is considered equal to the analytically derived lower bound presented in $Gobbi\ et\ al.$ (see References): $N=e/2(1-d)\ln{(e-de)}$ if exact is FALSE, $N=e(1-d)/2\ln{(e-de)}$ otherwise , where e is the number of edges of g and d its edge density . This bound is much lower than the empirical one proposed in $Milo\ et\ al.\ 2003$ (see References);
accuracy	1 (default) is the desired level of accuracy reflecting the average distance between the Jaccard index at the N-th step and its analytically derived fixed point;
verbose	TRUE (default). When TRUE a progression bar is printed during computation;
MAXITER_MUL	10 (default). If <i>exact==TRUE</i> in order to prevent a possible infinite loop the program stops anyway after MAXITER_MUL*max.iter iterations;
exact	FALSE (default). If TRUE the program performs <i>max.iter</i> successful swithcing steps, otherwise the program will count also the not-performed swithcing steps;

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Details

This function performs max.iter switching steps (see references). In particular, at each step two edges are randomly selected from the current version of g. Let these two edges be (a,b) and (c,d) (where a and c belong to the first class of nodes whereas b and d belong to the second one), with $a \neq c$ and $b \neq d$.

If the (a, d) and (c, b) edges are not already present in the current current version of g then (a, d) and (c, b) replace (a, b) and (c, d).

At each *step* number of switching steps the function computes the **Jaccard index** between the original graph g and its current version.

Value

A list containing a vector of Jaccard index values computed each (*scores*) switching steps, whose length is equal to max.iter/step, and the analytically derived lower bound (N) of switching steps to be performed by the switching algorithm in order to provide the revired version of g with the maximal level of achievable randomness (in terms of dissimilarity from the initial g).

Author(s)

Andrea Gobbi

Maintainer: Andrea Gobbi <gobbi.andrea@mail.com>

Special thanks to: Davide Albanese

References

Gobbi, A. and Iorio, F. and Dawson, K. J. and Wedge, D. C. and Tamborero, D. and Alexandrov, L. B. and Lopez-Bigas, N. and Garnett, M. J. and Jurman, G. and Saez-Rodriguez, J. (2014) *Fast randomization of large genomic datasets while preserving alteration counts* Bioinformatics 2014 30 (17): i617-i623 doi: 10.1093/bioinformatics/btu474.

Jaccard, P. (1901), Étude comparative de la distribution florale dans une portion des Alpes et des *Jura*, Bulletin de la Société Vaudoise des Sciences Naturelles 37: 547–579.

David J. Rogers and Taffee T. Tanimoto, *A Computer Program for Classifying Plants*, Science Vol 132 pp 1115-1118, October 1960

Hamming, Richard W. (1950), *Error detecting and error correcting codes*, Bell System Technical Journal 29 (2): 147–160, MR 0035935.

R. Milo, N. Kashtan, S. Itzkovitz, M. E. J. Newman, U. Alon (2003), *On the uniform generation of random graphs with prescribed degree sequences*, eprint arXiv:cond-mat/0312028

Examples

```
library(igraph)
library(BiRewire)
g <- simplify(graph.bipartite( rep(0:1,length=100),</pre>
c(c(1:100), seq(1,100,3), seq(1,100,7), 100, seq(1,100,13),
seq(1,100,17),seq(1,100,19),seq(1,100,23),100
)))
##get the incidence matrix of g
m<-as.matrix(get.incidence(graph=g))</pre>
## set parameters
step=1
max=100*length(E(g))
## perform two different analysis using two different maximal number of switching steps
scores<-birewire.analysis(m, step, max)</pre>
scores2<-birewire.analysis(m,step,"n")</pre>
## plot the Jaccard index scores across intervals of switching steps
plot(x=step*seq(1:length(scores$similarity_scores)),y= scores$similarity_scores,
type=1,xlab="Number of rewiring",ylab="Index value",ylim=c(0,1))
lines(x=step*seq(1:length(scores2$similarity_scores)),y= scores2$similarity_scores,
col="red")
legend(max*0.5,1, c("Jaccard index", "Jaccard index with lower-bound N"), cex=0.9,
col=c("black","red"), lty=1:1,lwd=3)
```

birewire.analysis.undirected

Analysis of the randomness trend across switching steps in a general undirected graph.

Description

This function performs a sequence of *max.iter* switching steps on the input undirected graph *g* and compute the Jaccard similarity between *g* and its rewired version each *step* switching steps.

Usage

```
birewire.analysis.undirected(adjacency, step=10, max.iter="n",accuracy=1,
verbose=TRUE,MAXITER_MUL=10,exact=F)
```

Arguments

adjacency matrix of the undirected graph g (can be extracted from a igraph adjacency graph using the get.adjacency) function; step 10 (default): the interval (in terms of switching steps) at which the Jaccard index between g and the its current rewired version is computed; "n" (default) the number of switching steps to be performed (or if exact = TRUEmax.iter the number of successful switching steps). If equal to "n" then this number is considered equal to the analytically derived lower bound presented in Gobbi et al. (see References): $N = e/(2d^3 - 6d^2 + 2d + 2) \ln(e - de)$ if exact is FALSE, $N = e(1-d)/2 \ln{(e-de)}$ otherwise, where e is the number of edges of g and d its edge density. This bound is much lower than the empirical one proposed in Milo et al. 2003 (see References); 1 (default) is the desired level of accuracy reflecting the average distance beaccuracy tween the Jaccard index at the N-th step and its analytically derived fixed point. TRUE (default). When TRUE a progression bar is printed during computation. verbose MAXITER_MUL 10 (default). If exact==TRUE in order to prevent a possible infinite loop the program stops anyway after MAXITER MUL*max.iter iterations; FALSE (default). If TRUE the program performs max.iter successful swithcing exact steps, otherwise the program will count also the not-performed swithcing steps;

Details

This function performs max.iter switching steps (see references). In particular, at each step two edges are randomly selected from the current version of g. Let these two edges be (a,b) and (c,d), with $a \neq c$, $b \neq d$, $a \neq d$, $b \neq c$.

If the (a,d) and (c,b) (or (a,d) and (b,d)) edges are not already present in the current version of g then (a,d) and (c,b) replace (a,b) and (c,d) (or (a,b) and (c,d) replace (a,c) and (b,d)). If both of the configurations are allowed, then one of them is randomly selected.

At each *step* switching steps the function computes the **Jaccard index** between the original graph *g* and its current rewired version.

Value

A list containing a vector of Jaccard index values computed each (scores) switching steps whose length is max.iter/step and the analytically derived lower bound (N) of switching steps to be performed by the switching algorithm in order to provide the rewired version of g with maximal achievable level of randomness (in terms of dissimilarity from the initial g).

Author(s)

Andrea Gobbi

Maintainer: Andrea Gobbi <gobbi.andrea@mail.com>

Special thanks to: Davide Albanese

References

Gobbi, A. and Iorio, F. and Dawson, K. J. and Wedge, D. C. and Tamborero, D. and Alexandrov, L. B. and Lopez-Bigas, N. and Garnett, M. J. and Jurman, G. and Saez-Rodriguez, J. (2014) *Fast randomization of large genomic datasets while preserving alteration counts* Bioinformatics 2014 30 (17): i617-i623 doi: 10.1093/bioinformatics/btu474.

Gobbi, A. and Jurman, G. (in preparation), Number of required Switching Steps in the Switching Algorithm for undirected graphs.

Jaccard, P. (1901), Étude comparative de la distribution florale dans une portion des Alpes et des *Jura*, Bulletin de la Société Vaudoise des Sciences Naturelles 37: 547–579.

David J. Rogers and Taffee T. Tanimoto, *A Computer Program for Classifying Plants*, Science Vol 132 pp 1115-1118, October 1960

Hamming, Richard W. (1950), Error detecting and error correcting codes, Bell System Technical Journal 29 (2): 147–160, MR 0035935.

R. Milo, N. Kashtan, S. Itzkovitz, M. E. J. Newman, U. Alon (2003), On the uniform generation of random graphs with prescribed degree sequences, eprint arXiv:cond-mat/0312028

Examples

```
library(igraph)
library(BiRewire)
g <- erdos.renyi.game(1000,0.1)
##get the incidence matrix of g
m<-as.matrix(get.adjacency(graph=g,sparse=FALSE))</pre>
## set parameters
step=1000
max=100*length(E(g))
## perform two different analysis using two different numbers of switching steps
scores<-birewire.analysis.undirected(m, step, max)</pre>
scores2<-birewire.analysis.undirected(m, step, "n")</pre>
## plot the Jaccard index scores across intervals of switching steps
plot(x=step*seq(1:length(scores$similarity_scores)),y= scores$similarity_scores,
type=1,xlab="Number of rewiring",ylab="Index value",ylim=c(0,1))
lines(x=step*seq(1:length(scores2$similarity_scores)),y= scores2$similarity_scores,
legend(max*0.5,1, c("Jaccard index","Jaccard index with lower-bound N"), cex=0.9,
col=c("black","red"), lty=1:1,lwd=3)
```

birewire.bipartite.from.incidence

Converts an incidence matrix into a bipartite graph.

Description

This function creates an igraph bipartite graph from an incidence matrix.

Usage

birewire.bipartite.from.incidence(matrix,directed=FALSE,reverse=FALSE)

Arguments

matrix incidence matrix: an (n-by-m) binary matrix where rows correspond to vertices

in the frist class while columns correspond to vertices in the second one;

directed Logical, if TRUE a directed graph is created.

reverse Logical, if TRUE the edges will be directed from the nodes in the second class

to those in the first one.

Details

The function calls graph.bipartite of package igraph. See igraph documentation for more details.

Value

Bipartite igraph graph.

Author(s)

Andrea Gobbi

Maintainer: Andrea Gobbi <gobbi.andrea@mail.com>

References

Csardi, G. and Nepusz, T (2006) *The igraph software package for complex network research*, Inter-Journal, Complex Systems url http://igraph.sf.net

Examples

```
library(igraph)
library(BiRewire)
g <- simplify(graph.bipartite( rep(0:1,length=100),
c(c(1:100),seq(1,100,3),seq(1,100,7),100,seq(1,100,13),
seq(1,100,17),seq(1,100,19),seq(1,100,23),100
)))</pre>
```

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```
##gets the incidence matrix of g
m<-as.matrix(get.incidence(graph=g))

##rewire the current graph
m2=birewire.rewire.bipartite(m,100)

#create the rewired bipartite graph
g2<-birewire.bipartite.from.incidence(m2,TRUE,FALSE)</pre>
```

birewire.rewire

Efficient rewiring of undirected graphs

Description

Optimal implementation of the switching algorithm. It returns the rewired version of the initial undirected graph or its adjacency matrix.

Usage

```
birewire.rewire(adjacency, max.iter="n",accuracy=1,
verbose=TRUE,MAXITER_MUL=10,exact=F)
```

Arguments

adjacency	An igraph undirected graph g or its adjacency matrix (can be extracted from g using get.adjacency(g));
max.iter	"n" (default) the number of switching steps to be performed (or if $exact==TRUE$ the number of successful switching steps). If equal to "n" then this number is considered equal to the analytically derived lower bound presented in <i>Gobbi</i> et al . (see References): $N = e/(2d^3 - 6d^2 + 2d + 2) \ln{(e - de)}$ if exact is FALSE, $N = e(1-d)/2 \ln{(e-de)}$ otherwise, where e is the number of edges of g and d its edge density. This bound is much lower than the empirical one proposed in $Milo$ et al . 2003 (see References);
accuracy	1 (default) is the desired level of accuracy reflecting the average distance between the Jaccard index at the N-th step and its analytically derived fixed point;
verbose	TRUE (default) boolean value. If TRUE print a processing bar during the rewiring algorithm.
MAXITER_MUL	10 (default). If <i>exact</i> == <i>TRUE</i> in order to prevent a possible infinite loop the program stops anyway after MAXITER_MUL*max.iter iterations;
exact	FALSE (default). If TRUE the program performs max.iter successful swithcing steps, otherwise the program will count also the not-performed swithcing steps;

Details

Performs at most max.iter number of rewiring steps producing a rewired version of an initial undirected graph.

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Value

Adjacency matrix of the rewired graph.

Author(s)

Andrea Gobbi Special thanks to: Maintainer: Andrea Gobbi <gobbi.andrea@mail.com> Davide Albanese

References

Gobbi, A. and Iorio, F. and Dawson, K. J. and Wedge, D. C. and Tamborero, D. and Alexandrov, L. B. and Lopez-Bigas, N. and Garnett, M. J. and Jurman, G. and Saez-Rodriguez, J. (2014) *Fast randomization of large genomic datasets while preserving alteration counts* Bioinformatics 2014 30 (17): i617-i623 doi: 10.1093/bioinformatics/btu474.

Gobbi, A. and Jurman, G. (in preparation), Number of required Switching Steps in the Switching Algorithm for undirected graphs.

R. Milo, N. Kashtan, S. Itzkovitz, M. E. J. Newman, U. Alon (2003), *On the uniform generation of random graphs with prescribed degree sequences*, eprint arXiv:cond-mat/0312028

Examples

```
library(igraph)
library(BiRewire)
g <- erdos.renyi.game(1000,0.1)
##gets the incidence matrix of g
m<-as.matrix(get.adjacency(graph=g,sparse=FALSE))

## sets parameters
step=1000
max=100*length(E(g))

##rewiring
m2=birewire.rewire(m,100*length(E(g)))
##creates the corresponding bipartite graph
g2<-graph.adjacency(m2,mode="undirected")</pre>
```

birewire.rewire.bipartite

Efficient rewiring of bipartite graphs

Description

Optimal implementation of the switching algorithm. It returns the rewired version of the initial bipartite graph or its incidence matrix.

Usage

```
birewire.rewire.bipartite (incidence, max.iter="n", accuracy=1, verbose=TRUE, \\ MAXITER\_MUL=10, exact=F)
```

Arguments

incidence	Incidence matrix of the initial bipartite graph g (can be extracted from an igraph bipartite graph using the get.incidence) function; or the entire bipartite igraph graph
max.iter	"n" (default) the number of switching steps to be performed (or if $exact==TRUE$ the number of successful switching steps). If equal to "n" then this number is considered equal to the analytically derived lower bound presented in $Gobbi\ et$ $al.$ (see References): $N=e/2(1-d)\ln{(e-de)}$ if exact is FALSE, $N=e(1-d)/2\ln{(e-de)}$ otherwise , where e is the number of edges of g and d its edge density . This bound is much lower than the empirical one proposed in $Milo\ et\ al.\ 2003$ (see References);
accuracy	1 (default) is the desired level of accuracy reflecting the average distance between the Jaccard index at the N-th step and its analytically derived fixed point;
verbose	TRUE (default). When TRUE a progression bar is printed during computation.
MAXITER_MUL	10 (default). If <i>exact==TRUE</i> in order to prevent a possible infinite loop the program stops anyway after MAXITER_MUL*max.iter iterations;
exact	FALSE (default). If TRUE the program performs <i>max.iter</i> successful swithcing steps, otherwise the program will count also the not-performed swithcing steps. ;

Details

Main function of the package. It performs at most max.iter switching steps producing a rewired version of an initial bipartite graph.

Value

Incidence matrix of the rewired graph.

Author(s)

Andrea Gobbi Special thanks to:

Maintainer: Andrea Gobbi <gobbi.andrea@mail.com>

Davide Albanese

References

Gobbi, A. and Iorio, F. and Dawson, K. J. and Wedge, D. C. and Tamborero, D. and Alexandrov, L. B. and Lopez-Bigas, N. and Garnett, M. J. and Jurman, G. and Saez-Rodriguez, J. (2014) *Fast randomization of large genomic datasets while preserving alteration counts* Bioinformatics 2014 30 (17): i617-i623 doi: 10.1093/bioinformatics/btu474.

R. Milo, N. Kashtan, S. Itzkovitz, M. E. J. Newman, U. Alon (2003), *On the uniform generation of random graphs with prescribed degree sequences*, eprint arXiv:cond-mat/0312028

Examples

```
library(igraph)
library(BiRewire)
g <- simplify(graph.bipartite( rep(0:1,length=100),
    c(c(1:100),seq(1,100,3),seq(1,100,7),100,seq(1,100,13),
    seq(1,100,17),seq(1,100,19),seq(1,100,23),100
)))

##gets the incidence matrix of g
    m<-as.matrix(get.incidence(graph=g))

##rewiring
m2=birewire.rewire.bipartite(m,100*length(E(g)))
##creates the corresponding bipartite graph
g2<-birewire.bipartite.from.incidence(m2,directed=TRUE,reverse=FALSE)</pre>
```

birewire.rewire.bipartite.and.projections

Analysis and rewiring function processing a bipartite graphs and its two projections

Description

This function performs the same analysis of birewire.analysis but additionally it provides in output a rewired version of the two networks resulting from the natural projections of the initial graph, together with the corresponding Jaccard index trends.

Usage

birewire.rewire.bipartite.and.projections(graph, step=10, max.iter="n",
accuracy=1, verbose=TRUE, MAXITER_MUL=10)

Arguments

graph	A bipartite graph <i>g</i> ;
max.iter	"n" (default) the number of successful switching steps to be performed. If equal to "n" then this number is considered equal to the analytically derived lower bound $N=e(1-d)/2\ln{(e-de)}$ presented in <i>Gobbi et al.</i> (see References);
step	10 (default): the interval (in terms of switching steps) at which the Jaccard index between g and the its current rewired version is computed;
accuracy	1 (default) is the desired level of accuracy reflecting the average distance between the Jaccard index at the N-th step and its analytically derived fixed point;
verbose	TRUE (default) boolean value. If TRUE print a processing bar during the rewiring algorithm.
MAXITER_MUL	10 (default).Since N indicates the number of successful switching steps, in order to prevent a possible infinite loop the program stops anyway after MAX-ITER_MUL*max.iter iterations ;

Details

See birewire.analysis for details.

Value

A list containing the three sequences of Jaccard index values (similarity_scores, similarity_scores.proj1, similarity_scores.proj2) for the three resulting graphs respectively (rewired, rewired.proj1, rewired.proj2). The first one is the rewired version of the initial graph g, while the second and the third one are rewired versions of its natural projections.

Author(s)

Andrea Gobbi

Maintainer: Andrea Gobbi <gobbi.andrea@mail.com>

References

Gobbi, A. and Iorio, F. and Dawson, K. J. and Wedge, D. C. and Tamborero, D. and Alexandrov, L. B. and Lopez-Bigas, N. and Garnett, M. J. and Jurman, G. and Saez-Rodriguez, J. (2014) *Fast randomization of large genomic datasets while preserving alteration counts* Bioinformatics 2014 30 (17): i617-i623 doi: 10.1093/bioinformatics/btu474.

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Examples

birewire.similarity

Compute the Jaccard similarity index between two binary matrices with the same number of non-null entries and the sam row- and column-wise sums.

Description

Compute the Jaccard similarity index between two binary matrices with the same number of non-null entries and the sam row- and column-wise sums.

Usage

```
birewire.similarity( m1,m2)
```

Arguments

m1 First matrix; m2 Second matrix.

Details

The **Jaccard** index between two sets *M* and *N* is defined as:

$$|M \cup N|/|M \cap N|$$

With M and N binary matrices, the Jaccard index is computed as:

$$\frac{\sum N_{i,j} \wedge M_{i,j}}{\sum N_{i,j} \vee M_{i,j}}.$$

The Jaccard index ranges between 0 and 1.

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Value

Returns the Jaccard similarity index between the two matrices

Author(s)

Andrea Gobbi

Maintainer: Andrea Gobbi <gobbi.andrea@mail.com>

Examples

```
library(igraph)
library(BiRewire)
g <- simplify(graph.bipartite( rep(0:1,length=100),
c(c(1:100),seq(1,100,3),seq(1,100,7),100,seq(1,100,13),
seq(1,100,17),seq(1,100,19),seq(1,100,23),100
)))
g2=birewire.rewire.bipartite(g)
birewire.similarity(get.incidence(g,sparse=FALSE),get.incidence(g2,sparse=FALSE))</pre>
```

BRCA_binary_matrix

TCGA Brest Cancer data

Description

Breast cancer samples and their respective mutations downloaded from the Cancer Cancer Genome Atlas (TCGA), used in *Gobbi et al.*. Germline mutations were filtered out of the list of reported mutations; synonymous mutations and mutations identified as benign and tolerated were also removed from the dataset. The bipartite graph resulting when considering this matrix as an incidence matrix has $n_r = 757, n_c = 9757, e = 19758$ for an edge density equal to 0.27%.

Usage

```
data(BRCA_binary_matrix)
```

Source

http://tcga.cancer.gov/dataportal/

References

Gobbi, A. and Iorio, F. and Dawson, K. J. and Wedge, D. C. and Tamborero, D. and Alexandrov, L. B. and Lopez-Bigas, N. and Garnett, M. J. and Jurman, G. and Saez-Rodriguez, J. (2014) *Fast randomization of large genomic datasets while preserving alteration counts* Bioinformatics 2014 30 (17): i617-i623 doi: 10.1093/bioinformatics/btu474.

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