1 Overview

BiRewire is an R package implementing high-performing routines for the randomisation of bipartite graphs preserving their node degrees (i.e. Network Rewiring), through the Switching Algorithm (SA) [5].

This package is particularly useful for the randomisation of ‘0-1’ tables (or presence-absence matrices) in which the distributions of non-null entries (i.e. presence distributions) must be preserved both across rows and columns. By considering these tables as incidence matrices of bipartite graphs then this problem reduces to bipartite network rewiring.

For example, by modeling a genomic dataset as a binary event matrix (BEM),
in which rows correspond to samples, columns correspond to genes and the 
\((i,j)\) entry is non-null if the \(i\)-th sample harbours a mutation in the \(j\)-th gene, 
then with BiRewire is possible to randomise the dataset preserving its mutation 
rates both across samples and genes. This is crucial to preserve tumour 
specific alterations, dependencies between gene-mutations and heterogeneity in 
mutation/copy-number-alteration rates across patients.

Large collections of such randomised tables can be then used to approximate 
samples from the uniform distribution of all the possible genomic datasets with 
the same mutation-rates of the initial one. Finally this data can be used as null 
model to test the statistical significance of several combinatorial properties of 
the original dataset: for example the tendency of a group of genes to be co- or 
mutually-mutated [7].

Moreover, with se same routines, it is possible to generate a rewired version 
of a given directed signed network (DSG), encoding for example a patway or a 
signaling network (for details see section 5 and [2]). Similar procedures have 
been implemented in order to manage undirected networks. Since version 3.6.0, 
the SA can be performed also on matrices containing NAs. In this case the 
SA works as usual but the position of NA will be preserved. This feature is 
available if the graph is encoded with its incidence/adjacency matrix and not 
in the case of DSG.

Specifically, with BiRewire users can:

1. create bipartite graphs from genomic BEMs (or, generally, from any kind 
of presence-absence matrix);

2. perform an analysis, which consists of studying the trend of Jaccard Sim-
ilarity between the original network and its rewired versions across the 
switching steps (by using a user-defined sampling time), and analytically 
estimating the number of steps at which this similarity reaches a plateau 
(i.e. the maximal level of randomness is achieved) according to the lower 
bound derived in [1];

3. generate rewired versions of a bipartite graph with the analytically derived 
bound as number of switching steps or a user-defined one;

4. derive projections of the starting network and its rewired version and 
perform different graph-theory analysis on them;

5. generate a set of networks correctly drawn from the suitable null-model 
starting from the initial BEM;

6. monitoring the behaviour of the Markov chain underlying the SA

7. perform the same analysis described in point 1,2,3,5 and 6 for undirected 
graphs and directed signed graphs (DGS).

All the functions of the package are written in C-code and R-wrapped. A 
reduced version of the packages has been also implemented in Python https: 
//github.com/andreagobbi/pyBiRewire.
2 Installation

It is possible to download the package from http://www.ebi.ac.uk/~iorio/BiRewire and install it with the shell-command:

```r
R CMD INSTALL BiRewire_xx.yy.zz.tar.gz
```

or with biocLite() directly in R:

```r
source("http://bioconductor.org/biocLite.R")
biocLite("BiRewire")
```

Moreover, the sources of the development version are available here http://www.bioconductor.org/packages/devel/bioc/html/BiRewire.html. Alternatively, the source files can be cloned from the github repositories: https://github.com/andreagobbi/BiRewire and https://github.com/andreagobbi/BiRewire--release using the command

```bash
git clone git@github.com:andreagobbi/BiRewire--release.git
git clone git@github.com:andreagobbi/BiRewire.git
```

We suggest to use the biocLite function from R in order to have the last working release package (build and check procedure).

To load BiRewire use the following commands:

```r
> library(BiRewire)
```

3 Package Dependencies


4 Notation

Let $G$ be a bipartite graph, i.e. a graph containing two classes of nodes $V_r$ and $V_c$ such that every edge $e \in E$ connects one node in the first class to a node in the second class.

Let $B$ be the incidence matrix of $G$, i.e. the $|V_r| \times |V_c|$ binary matrix whose generic entry $m_{i,j}$ is not null if and only if $(i,j) \in E$.

The number of edges is indicated with $e = |E|$ and the edge density with $d = \frac{e}{|V_r||V_c|}$.

The SA performs $N$ Switching Steps (SSs), in which:

1. two edges $(a, b)$ and $(c, d)$ both $\in E$ are randomly selected,

2. if $a \neq c$, $b \neq d$, $(a, d) \not\in E$ and $(b, d) \not\in E$ then:
   
   (a) the edges $(a, d)$ and $(b, d)$ are added to $E$ and
   
   (b) the edges $(a, b)$ and $(c, d)$ are removed from $E$.
Notice that we count a SS only if it is successfully performed.

The Jaccard Index (JI, [10]) is used to quantify the similarity between the original graph and its rewired version at the $k$-th SS. Since the SA preserves the degree distribution and does not alter the number of nodes, the JI, indicated with $s^{(k)}$, can be computed as

$$s^{(k)} = \frac{x^{(k)}}{2e - x^{(k)}},$$

where $x^{(k)}$ is the number of edges in common between the two graphs. Fixed a small error $\delta$, the number $N$ of SSs providing the rewired version of a network with the maximally achievable level of randomness (in terms of average dissimilarity from the original network) is asymptotically equal to

$$\frac{e(1 - d)}{2} \ln \frac{1 - d}{\delta}.$$

More detailed, we analytically derived the fixed point of the underlying Markov chain $\bar{x}$; fixed a $\delta$ we can estimate the distance of the current state of the chain respect to this fixed point in terms of fraction of edges $\delta$. For large network we can assume that a distance less than one edge is satisfiable (see [?]!), so the bound reads:

$$\frac{e(1 - d)}{2} \ln e(1 - d),$$

but in order to manage smaller network the bound with the parameter $\delta$ results to be more general. This bound is much lower than the empirical one proposed in [5] (see Reference for details).

## 5 Directed Signed Network

A directed signed network (DSG) $G$ is a directed network in which the edges are encoded with a triplet $(a, b, *)$ where $a$ denotes the source node, $b$ the target node and $*$ the sign of the relation (the sign of the edge). In our case (pathways and signaling) $*$ can be positive + and negative −. In [2] we show how to create a correspondence between a DSG and a couple $(B^+, B^-)$ of bipartite networks. This correspondence $f$, and its inverse $f^{-1}$ are useful for the creation of a rewired version of $G$: we rewire independently $B^+$ and $B^-$ and we rebuild the final DSG $G^*$ using $f^{-1}$. A DGS is usually encoded in a SIF format (Simple Interaction File see http://wiki.cytoscape.org/Cytoscape_User_Manual/Network_Formats for more informations). In the case of DSG a suitable SIF file has 3 columns: the first encodes the source nodes, the second the sign and the last the source nodes.

## 6 Function Description

In this section all the functions implemented in BiRewire are described with a simple practical example in which a real breast cancer dataset is modeled as a bipartite network, and randomised preserving the mutation-rate both across
samples and genes (i.e. the corresponding bipartite network is rewired). In each of the following functions it is possible to perform $N$ successful switching steps (see [1] for more details about this more general bound) using the flag exact=TRUE. To prevent a possible infinite loop, the program performs at maximum \text{MAXITER} \times \text{mul} \times \text{max.iter} iterations.

6.1 birewire.analysis.bipartite and undirected
First of all, we create a bipartite network modeling a genomic breast cancer dataset downloaded from the Cancer Genome Atlas (TCGA) projects data portal \text{http://tcga.cancer.gov/dataportal/}, used in [1]. From this dataset germline mutations were filtered out with state-of-the-art softwares; synonymous mutations and mutations identified as benign and tolerated were also removed. The resulting bipartite graph has $n_r = 757$ nodes (corresponding to samples), $n_c = 9,757$ nodes (corresponding to genes), and $e = 19,758$ edges connecting a node in $n_r$ to a node in $n_c$ if the gene corresponding to the node in $n_r$ is mutated to the samples corresponding to the node in $n_C$. The edge density of this network is 0.27%.

The genomic dataset (in the form of a binary matrix in which rows correspond to samples, columns correspond to genes and the $(i,j)$ entry is non null if the $i$-th sample harbours a mutation in the $j$-th gene) can be loaded and modeled as a bipartite graph, with the following commands:

```
> data(BRCA_binary_matrix)##loads an binary genomic event matrix for the
> ##breast cancer dataset
> g=birewire.bipartite.from.incidence(BRCA_binary_matrix)##models the dataset
> ##as igraph bipartite graph
```

Once the bipartite graph is created it is possible to conduct the analysis by calling the \text{birewire.analysis.bipartite} function, using the following commands:

```
> step=5000
> max=100*sum(BRCA_binary_matrix)
> scores<-birewire.analysis.bipartite(BRCA_binary_matrix,step,
+   verbose=FALSE,max.iter=max,n.networks=5,display=F)
```

The function \text{birewire.analysis.bipartite} returns the Jaccard similarity sampled every step SSs (in the example above step is equal to 5000). The SA is independently applied on the initial data for $n.networks$ times in order to estimate the mean value of the JI and the relative CI (as $1.96 \pm \sigma/\sqrt{n.networks}$). A plot such information is displayed if the parameter $n.display$ is set to true. The routine returns a list of two elements: $\text{${N}$}$ is the analytically derived bound and $\text{${data}$}$ the similarity score table.

The same analysis can be performed on general undirected networks.

```
> g.und<-erdos.renyi.game(directed=F,loops=F,n=1000,p.or.m=0.01)
> m.und<-get.adjacency(g.und,sparse=FALSE)
> step=100
```
> max=100*length(E(g.und))
> scores.und<-birewire.analysis.undirected(m.und,step=step,
> + verbose=FALSE,max.iter=max,n.networks=5)
>
6.2 birewire.rewire.bipartite

To rewire a bipartite graph two modalities are available. Both of them can be used with the analytical bound N as number of switching steps or with a user defined value. The function takes in input an incidence matrix $B$ or the an igraph bipartite graph.

> m2<-birewire.rewire.bipartite(BRCA_binary_matrix,verbose=FALSE)
> g2<-birewire.rewire.bipartite(g,verbose=FALSE)

The first function recieves in output the incidence matrix of the rewired graph while the second one a bipartite igraph graph. See documentation for further details.

6.3 birewire.rewire.undirected

To rewire a general undirected graph the following functions can be used:

> m2.und<-birewire.rewire.undirected(m.und,verbose=FALSE)
> g2.und<-birewire.rewire.undirected(g.und,verbose=FALSE)

6.4 birewire.similarity

This function computes the Jaccard index between two incidence matrices with same dimensions and node degrees. It is possible also to use directly two suitable graphs.

> sc=birewire.similarity(BRCA_binary_matrix,m2)
> sc=birewire.similarity(BRCA_binary_matrix,t(m2))#also works

6.5 birewire.rewire.bipartite.and.projections

The following functions execute the Switching Algorithm and computes similarity trends across its switching steps for the two natural projections of the starting bipartite graph

> #use a smaller graph!
> gg <- graph.bipartite( rep(0:1,length=10), c(1:10))
> result=birewire.rewire.bipartite.and.projections(gg,step=10,
> + max.iter="n",accuracy=0.00005,verbose=FALSE)
> plot(result$similarity_scores.proj2,type='l',col='red',ylim=c(0,1))
> lines(result$similarity_scores.proj1,type='l',col='blue')
> legend("top",1, c("Proj2","Proj1"), cex=0.9, col=c("blue","red"), lty=1:1,lwd=3)
6.6 birewire.sampler.bipartite

This function uses the SA to generate a set of $K$ bipartite networks drawn from the null model given by an initial bipartite graph. The function creates a main folder (path input parameter) and a set of subfolders in order to have maximum 1000 files per folder. Notice that the initial graph is used only for the first rewiring process, and the output of the first process is used as input for the second and so on.

```r
> # use a smaller graph!
> gg <- graph.bipartite(rep(0:1,length=10), c(1:10))
> ## NOT RUN
> ## birewire.sampler.bipartite(get.incidence(g), K=10, path='TESTBIREWIRE', verbose=F)
> ## unlink('TESTBIREWIRE', recursive = T)
```

6.7 birewire.visual.monitoring.bipartite and .undirected

These functions allow to visualize the Markov Chain underlying the SA. More in detail, given a sequence of steps to test, we sample from the SA each indicated step generating a bunch of networks. We compute the pairwise Jaccard distance among them, i.e. the Jaccard index is defined as 1 minus the Jaccard similarity. Then we perform a dimensional scaling using tsne [12] and plot the result.

```r
> ggg <- graph.bipartite(rep(0:1,length=10), c(1:10))
> ## NOT RUN
> ## birewire.visual.monitoring.bipartite(ggg, display=F, n.networks=10)
> g <- erdos.renyi.game(1000, 0.1)
> ## birewire.visual.monitoring.undirected(g, display=F, n.networks=10)
```

6.8 birewire.load.dsg and birewire.save.dsg

The first function reads a SIF DSG from a given path and the second writes a DSG in a specific path.

6.9 birewire.induced.bipartite and birewire.build.dsg

These two functions encoded the correspondence between a DSG and a ordered couple of bipartite graphs ($B^+, B^-$). The first takes a SIF object, loaded with birewire.load.dsg and produces a list with the positive and negative bipartite graph, the second one builds a SIF object starting from a list of two bipartite networks.

```r
> data(test_dsg)
> dsg=birewire.induced.bipartite(test_dsg, delimiters=list(negative='-', positive='+'))
> tmp=birewire.build.dsg(dsg, delimiters=list(negative='-', positive='+'))
```

6.10 birewire.rewire.dsg

Function for generating a rewired version of a given DSG $G$. The parameters are quite the same of birewire.rewire.bipartite: in this case it is possible to control the number of SS independently for the positive max.iter.pos and negative max.iter.neg part of $G$. 

7
> dsg2=birewire.rewire.dsg(dsg=dsg)
DONE in 0 seconds
DONE in 0 seconds
> tmp=birewire.build.dsg(dsg2,delimitators=list(negative='-',positive='+'))

6.11 birewire.similarity.dsg
Computes the Jaccard index between two DSGs.
> birewire.similarity.dsg(dsg,dsg2)
[1] 0.4666667

6.12 birewire.sampler.dsg
This function uses the SA to generate a set of $K$ DSG in SIF format drawn from the null model given by an initial DSG. The function creates a main folder (path input parameter) and a set of subfolders in order to have maximum 1000 files per folder. See birewire.sampler.bipartite for more details.
> ##NOT RUN
> ##birewire.sampler.dsg(dsg,K=10,path='TESTBIREWIREDSG',verbose=F,
> ##   delimitators=list(negative='-',positive='+'))
> ##unlink('TESTBIREWIREDSG',recursive = T)

7 Directed graphs
Notice that a directed graph can be encoded as a DSG with only positive (negative) part. All the routines involving DSG could be used also for directed graphs building a DSN as a R list with just one element named positive.

8 Example
Here we collect the functionalities of the package in a single example. The output plot of the analysis is showed in Fig.1 on the left side and the output of the monitoring procedure is displayed in Fig.1 on the right side.
> ##NOT RUN
> #ggg <- bipartite.random.game(n1=100,n2=40,p=0.2)
> #For recovering quickly the bound $N$ we can perform a short analysis
> #N=birewire.analysis.bipartite(get.incidence(ggg,sparse=F),max.iter=2,step=1)$N
> #Now we can perform the real analysis
> #res=birewire.analysis.bipartite(get.incidence(ggg,sparse=F),
> #   max.iter=10*N,n.networks=10)
> #and monitoring the markov chain
> #birewire.visual.monitoring.bipartite(ggg,display=T,n.networks=75,
> #   sequence=c(1,10,200,500,"n",10000),ncol=3)
> #Now we can generate a null model
> #birewire.sampler.bipartite(ggg,K=10000,path="TESTBIREWIREDSPARTITE")
Figure 1: The output plots of \texttt{birewire.analyis.bipartite} (left side) and of \texttt{birewire.visual.monitoring.bipartite} (right side) relative to the example in section 8. The gradient of the colour from blue to red indicates the position of the sampling network respect the others. The starting network (blue) is marked with the text \textit{start}.
References


