

NetPredictor

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Table of Contents

1. Introduction
 2. Installation
 3. Examples
 4. Analyzing Results
 5. Citations
-

1. Introduction

Social and biological systems can be represented by graphs where nodes represent individuals ,biological

Consider an undirected, unweighted network $G = (V, E)$, where V is the set of nodes and E is the set of links. For each pair of nodes $\{a, b\} \in V$ we can assign a proximity score by executing the random walk procedure as follows :

- we start a random walker from a .
- At each time step, with the probability $1 - c$, the walker walks to one of the neighbors, b , according to the transition probability matrix $W_{ab} = \frac{S_{ab}}{K_a}$ where S_{ab} is the adjacency matrix of the network and (S_{ab} equals 1 if node a and b are connected, 0 otherwise) K_a denotes the degree of a .
- With the probability c , the walker goes back to a .
- After many time steps the probability of finding the random walker at node x converges to the steady-state probability, which is our proximity score $S_{a \rightarrow x}$.

One of the most widely used ways to solve random walk with restart is the matrix iteration method, iterating the equation (1) until convergence, i.e, until the L2 norm of successive estimates of below our threshold 10^{-7} .

$$P_{t+1} = (1 - c)W^T P_t + cP_0 \quad (1)$$

2. Installation

A stable tested version of SAGA is available from the CRAN repository or the most recent version may be installed from github using the devtools package:

Installing from github

```
install.packages("devtools")
install_github("abhik1368/netpredictor")
```

3. Examples

Here at first we look at the properties which can be calculated on unipartite graphs.

```
require(igraph)
require(netpredictor)
g1 <- upgrade_graph(erdos.renyi.game(100, 1/100))
V(g1)$name <- seq(1,100,1)
score_mat <- unetSim(g1,"aa")
head(which(score_mat!=0, arr.ind = T))

## Common neighbors vertex similarity
score_mat <- unetSim(g1,"cn")
head(which(score_mat!=0, arr.ind = T))

## Jaccard Index similarity
score_mat <- unetSim(g1,"jc")

## Dice similarity
score_mat <- unetSim(g1,"dice")

## Katz Index similarity
score_mat <- unetSim(g1,"katz")

## Geodesic distance vertex similarity
score_mat <- unetSim(g1,"dist")

## Cosine vertex similarity/ Salton index
score_mat <- unetSim(g1,"cosine")

## Preferential attachment vertex similarity
score_mat <- unetSim(g1,"pa")

## Local Paths Index
## This function counts the number of two-paths and three-paths between nodes,
# with three-paths weighted by a parameter  $\epsilon$ .
score_lpsim <- unetSim(g1,"lp")

## Hub promoted Index
## This measures assigns higher scores to links adjacent to hubs (high degree nodes). It
## counts common neighbors of two vertices and weights the result.
score_hpsim <- unetSim(g1,"hpi")

## Similarity measure based on resource allocation process (number of common neighbours
## weighted by the inverse of their degrees)
```

```
score_hpsim <- unetSim(g1,"ra")
```

Next we look at the properties which can be calculated on Bipartite graphs.

```
suppressPackageStartupMessages(library(igraph))
suppressPackageStartupMessages(library(netpredictor))
## dataset enzyme is provide in netpredictor package
data(Enzyme)

## Get the Enzyme and compound adjacency matrix
A <- t(enzyme_ADJ)

## degree Centrality of the Bipartite Graph
get.biDegreeCentrality(A)

## Compute Graph density of Bipartite Graph
get.biDensity(A)

## Compute betweenness centrality of Bipartite Graph
get.biBetweennessCentrality(A)

## Projects Bipartite Networks into monopartite networks default method is shared
## neighbours.
get.biWeightedProjection(A)
```

Next we will use the different methods to predict links. Here we have shown examples based on drug target prediction. With the growing understanding of complex diseases, the focus of drug discovery has shifted away from “one target, one drug” model, to a new “multi-target, multi-drug” model. Predicting potential drug-target interactions from heterogeneous biological data is critical not only for better understanding of the various interactions and biological processes, but also for the development of novel drugs and the improvement of human medicines. To predict polypharmacology people use bayesian methods, SVM and Random Forest models, but in all of those algorithms the methods depends on labelled data to predict unknown links. Network based approaches does not rely on labelled data . Two of the algorihtms implemented in this package Random walk based Restart(RWR) and Network based Inference(NBI) to do it. For performing RWR we used Drug target network which is a bipartite graph in which every links connects drugs to proteins.

```
suppressPackageStartupMessages(require(igraph))
suppressPackageStartupMessages(require(netpredictor))

## We use the enzyme data provided in the netpredictor package. The example
# below shows how to perform random walk with restart

data(Enzyme)
## load the adjacency matrix
A <- enzyme_ADJ

## load the chemical similarity matrix calculated from other packages or softwares
S2 = enzyme_Csim

## load the protein similarity matrix

S1 = enzyme_Gsim
```

```
## Convert the adjacency matrix to igraph object because biNetwalk function used igraph object
g1 = graph.incidence(A)

## Run the RWR in bipartite network.
pScore <- biNetwalk(g1,s1=S1,s2=S2,normalise="laplace", dataSeed=NULL,
                    restart=0.8, parallel=TRUE, multicores=NULL, verbose=T)
```

```
## First, get the adjacency matrix of the input graph (2015-09-27 12:43:20) ...
## Notes: using unweighted graph!
## got the transition matrix for RWR
## do parallel computation using 2 cores ...
## Executing parallel:
## Rescaling steady probability vector (2015-09-27 12:43:36) ...
## Runtime in total is: 16 secs
```

```
dim(pScore)
```

```
[1] 478 212
```

In this example we attempt to use the dataset file which contains the pairs relations between targets and drugs. This can be useful when one is trying to investigate relations for a specific set of relations . The Drug names and proteins names should be included in the adjacency matrix when one uses the file option to provide dataset. In the dataset file the first column contains the proteins names and the second column the drug names. Output is a matrix of unique drugs against the number of targets in the adjacency matrix.

```
suppressPackageStartupMessages(require(igraph))
suppressPackageStartupMessages(require(netpredictor))
library(printr)
data(Enzyme)

A <- t(enzyme_ADJ)
g1 <- upgrade_graph(graph.incidence(A,mode = 'all'))
S1 = enzyme_Csim
S2 = enzyme_Gsim
## Read the dataset file from the user
dataF<- read.csv("seedFile.csv",header=FALSE)
```

```
## Warning in read.table(file = file, header = header, sep = sep, quote =
## quote, : incomplete final line found by readTableHeader on 'seedFile.csv'
```

```
knitr::kable(dataF)
```

V1	V2
hsa2936	D00014
hsa2950	D00014
hsa5033	D00018
hsa5351	D00018

```
Mat <- biNetwalk(g1,s1=S1,s2=S2,normalise="laplace", dataSeed =dataF,
                restart=0.8,parallel=TRUE, multicores=NULL, verbose=T)
```

```
## First, get the adjacency matrix of the input graph (2015-09-27 12:43:36) ...
## Notes: using unweighted graph!
## got the transition matrix for RWR
## do parallel computation using 2 cores ...
## Executing parallel:
## Rescaling steady probability vector (2015-09-27 12:43:37) ...
## Runtime in total is: 1 secs
```

```
dim(Mat)
```

```
[1] 212 2
```

In this next example we will see how we can plot the significant communities of drugs from the final RWR computed matrix. For community detection we used the walktrap algorithm [13], which places nodes into communities based on neighborhood similarity from short random walks. We also input a list of drugs as vector and retrieve top 10 interactions for each of those drugs. In this package after getting the results one can easily write the results in GML format for visualization in Gephi or cytoscape. It also support export to GEXF format (Gephi specific file format) . Below shows the example of exporting to GML format.

```
suppressPackageStartupMessages(require(igraph))
suppressPackageStartupMessages(require(netpredictor))
```

```
A <- enzyme_ADJ
S1 = enzyme_Gsim
S2 = enzyme_Csim
g1 = graph.incidence(A)
Q = biNetwalk(g1,s1=S1,s2=S2,normalise="laplace",dataSeed=NULL,restart=0.8,
              parallel=TRUE,multicores=NULL, verbose=T)
```

```
## First, get the adjacency matrix of the input graph (2015-09-27 12:43:37) ...
## Notes: using unweighted graph!
## got the transition matrix for RWR
## do parallel computation using 2 cores ...
## Executing parallel:
## Rescaling steady probability vector (2015-09-27 12:43:51) ...
## Runtime in total is: 14 secs
```

```
## Get the top results of RWR prediction. This function returns the associations
## of drugs and target names with scores and type interaction whether
## True / predicted interactions.
```

```
knitr::kable(head(getTopresults(A,Q,top=10,druglist=NULL)))
```

drug	pnames	score	type
D00014	hsa2936	0.396969136434142	True Interactions
D00014	hsa2950	0.393772891664937	True Interactions
D00014	hsa1719	0.0011479214893255	Predicted Interactions
D00014	hsa55312	0.00104834689722637	Predicted Interactions
D00014	hsa7172	0.0010385344733581	Predicted Interactions
D00014	hsa4128	0.000974699916298979	Predicted Interactions

```
## Get top results of RWR prediction using a list of drug names. One should be careful using
## a drug list it should contain drug names which are in the adjacency matrix.
```

```
drugs = c("D00014","D00018", "D00029", "D00036","D00045","D00049")
result <- getTopresults(A,Q,top=10,druglist=drugs)
```

```
## Get the results
head(result)
```

drug	pnames	score	type
D00014	hsa2936	0.396969136434142	True Interactions
D00014	hsa2950	0.393772891664937	True Interactions
D00014	hsa1719	0.0011479214893255	Predicted Interactions
D00014	hsa55312	0.00104834689722637	Predicted Interactions
D00014	hsa7172	0.0010385344733581	Predicted Interactions
D00014	hsa4128	0.000974699916298979	Predicted Interactions

```
## Save the top results in GML format for visualization in Gephi.
g<-graph.data.frame(result[,1:2],directed=FALSE)
```

```
## Set the edge values
g <- set.edge.attribute(g, "weight", value=result[,3])
saveGML(g,"netresult.gml","netresult")
```

```
## Get the significance graph
Z = sig.net(data=A,g=g1,Amatrix=Q,num.permutation=100,adjp.cutoff=0.01,
p.adjust.method="BH",parallel=FALSE)
```

```
## Third, generate the distribution of contact strength based on 100 permutations on nodes respecting r:
## Also, construct the contact graph under the cutoff 1.0e-02 of adjusted-pvalue (2015-09-27 12:44:01).
## Runtime in total is: 3 secs
```

```
## Get the graph for plotting communities
g <- Z$cgraph

gp <- get.Communities(g)

## Get members from the first community
print(gp[[1]]$community)
```

```
IGRAPH clustering walktrap, groups: 11, mod: 0.38 + groups: $1 [1] "D00109" "D00151" "D00452" "D01122"
"D01513" "D01811"
```

```
$2 [1] "D00463" "D01547" "D01565" "D01765"
```

```
$3 [1] "D00904" "D01475"
```

```
$4 + ... omitted several groups/vertices
```

```
## Total number of communities
length(gp)
```

[1] 8

```
## Plot the communities with 5 columns
plot_Community(gp,cols=5)
```

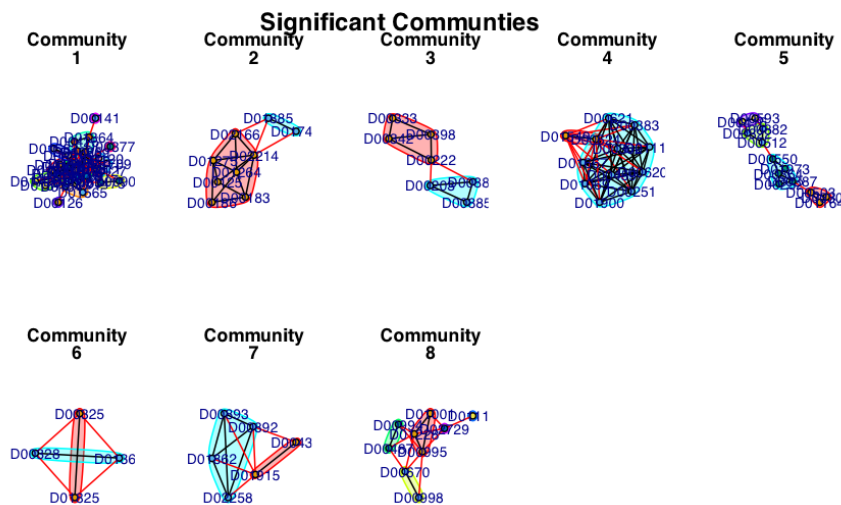


Figure 1:

One can use net.perf function it samples and removes links from the adjacency matrix and predicts them and calculates area under accumulation curve, AUC, BEDROC (bdr), and Enrichment factor (EF). The area under the receiver operating characteristic (ROC) curve (AUC) is widely used metric for evaluation of predictive models. The advantage of using AUC is that it is bounded, between 0 to 1 with 0.5 corresponding to random prediction. But AUC method has been criticized in cheminformatics based virtual screening methods because it is not sensitive to early recognition compounds. The EF tries to solve early recognition problem but it is dependent on the ratio of actives to inactives and the choice of subset X (fraction of active and inactive set). To try and overcome these limitations numerous other evaluation methods, such as robust initial enhancement (RIE) [10] and Boltzmann-enhanced discrimination of ROC (BEDROC) have been proposed[11]. Sheridan et al. developed an exponential weighted scoring scheme RIE which gives heavier weight in “early recognized” hits. The BEDROC is constructed on top of RIE by, in essence, forcing the RIE to be bounded by 0 and 1, avoiding the dependence on the active/inactive ratio. In the example below we remove 50 links and repredict those links. While repredicting them we calculate performance metrics like AUC,bedroc and enrichment factor. As the number of links (relinks) increases the performance of prediction drops. ‘Calgo’ option uses different algorithms like “nbi”, “rwr” and “netcombo”.

```
data(Enzyme)
A = enzyme_ADJ
```

```

S1 = enzyme_Gsim
S2= enzyme_Csim

m = net.perf(A,S1,S2,relinks = 50,numT=2,Calgo="nbi")

## Detected (212) drugs & (478) proteins with (1515) interactions...
## Running prediction for (50) links removed using (nbi) ..
## Running NBI Algorithm
## Running computation of the input graph (2015-09-27 12:44:01) ...
## Done computation of the input graph (2015-09-27 12:44:02) ...
## Runtime in total is: 1 secs

```

```
m
```

```

$sauc [1] 0.8358817
$sauc [1] 0.8930818
$sauctop [1] 0.4683116
$bdr [1] 0.356991
$efc [1] 5.411765

```

In 2010 Zhou et al., proposed a recommendation method based on the bipartite network projection technique implementing the concept of resources transfer within the network. The method developed here is from the article DT-Hybrid where they integrated the similarity matrices of drugs and proteins in order to make the prediction with the heatS equation [12]. The example given below one can use both the methods of either using similarity matrices and also simply using heatS equation with the adjacency matrix.

```

data(Enzyme)
A <- t(enzyme_ADJ)
S1 = as.matrix(enzyme_Csim)
S2 = as.matrix(enzyme_Gsim)
g1 = graph.incidence(A)
## Using the similarity matrices
P1 <- nbiNet(A,alpha=0.5, lamda=0.5, s1=S1, s2=S2,format = "matrix")

## Running computation of the input graph (2015-09-27 12:44:03) ...
## Done computation of the input graph (2015-09-27 12:44:04) ...
## Runtime in total is: 1 secs

## Get the significance graph
Z = sig.net(data=A,g=g1,Amatrix=P1,num.permutation=100,adjp.cutoff=0.01,
            p.adjust.method="BH",parallel=FALSE)

## Third, generate the distribution of contact strength based on 100 permutations on nodes respecting r:
## Also, construct the contact graph under the cutoff 1.0e-02 of adjusted-pvalue (2015-09-27 12:44:10).
## Runtime in total is: 6 secs

## Get the graph for plotting communities
g <- Z$cgraph

gp <- get.Communities(g)

```



```
## Get members from the first community
print(gp[[1]]$community)
```

```
IGRAPH clustering walktrap, groups: 21, mod: 0.23 + groups: $1 [1] "hsa10188" "hsa1445" "hsa2241"
"hsa5608" "hsa657" "hsa7294" [7] "hsa90" "hsa9088" "hsa91"
```

```
$2 [1] "hsa3055" "hsa55359"
```

```
$3 [1] "hsa130399" "hsa2242" "hsa25" "hsa2534" "hsa29941" [6] "hsa3702" "hsa3716" "hsa3717" "hsa3718"
"hsa5604"
```

```
+ ... omitted several groups/vertices
```

```
## Total number of communities
length(gp)
```

```
[1] 11
```

```
## Plot the communities with 5 columns
plot_Community(gp,cols=3)
```

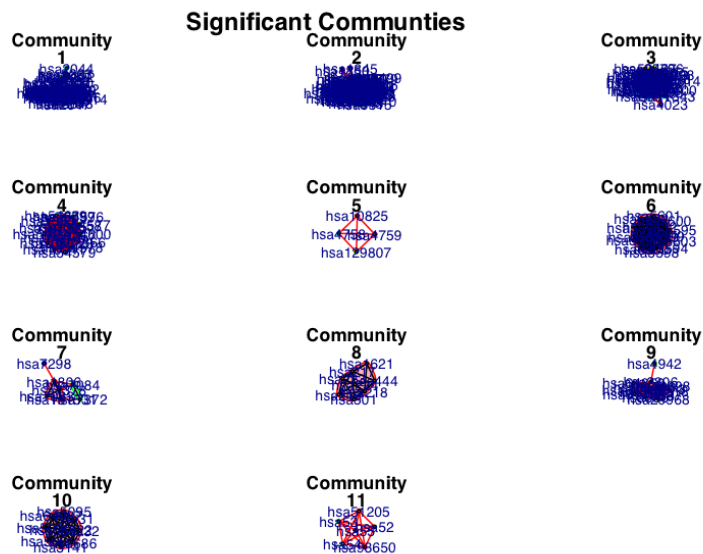


Figure 2:

```
## Using the heatS equation with the adjacency matrix.
P2 <- nbiNet(A,alpha=0.5,lamda=0.5,format="matrix")

## Running computation of the input graph (2015-09-27 12:44:10) ...
## Done computation of the input graph (2015-09-27 12:44:11) ...
## Runtime in total is: 1 secs
```

4. Analyzing Results

6. Citations

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