Article

A Matlab algorithm for detection of protein complexes from multiple heterogeneous networks

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Abstract
In present article, we presented the Matlab algorithm of Ou-Yang's model (Ou-Yang et al., 2017). It can be used to explore the shared clustering structure in PPI (protein-protein interaction) and DDI (domain-domain interaction) networks. A final matrix H can be achieved using the algorithm. Protein i belongs to complex k if H_{ik}=1, otherwise H_{ik}=0, i=1, 2, …, N1; k=1, 2, …, K, where N1 is the number of proteins in PPI network, and K is the number of complexes (clusters).

Keywords Matlab algorithm; Ou-Yang's model; protein-protein interactions; protein complexes; heterogeneous networks.

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1 Introduction

Biological systems at different levels are self-organizing systems (Zhang, 2013a, b, 2015, 2016, 2018). The organisms are survived by numerous protein-protein interactions (PPIs) in the cells. Proteins usually generate protein complexes to function (Huang et al., 2013; Zhao et al., 2014; Ou-Yang et al., 2017). Therefore, identification of protein complexes is a necessity. So far, numerous methods have been proposed in this aspect (Enright et al., 2002; Bader and Hogue, 2003; King et al., 2004; Adamcsek et al., 2006; Li et al., 2010; Wang et al., 2010; Nepusz et al., 2012; Ji et al, 2014).

PPIs generally covers the physical interaction between specific protein domains (Wuchty, 2006. Ou-Yang et al., 2017). Since most proteins are multi-domain proteins, it is possible to develop algorithms that allow exploration of mutiple between-node relationships in different networks (Greene et al., 2008; Zhang et al., 2012; Ou-Yang et al., 2013).

Based on previous studies, Ou-Yang et al. (2017) proposed a multi-network clustering (MNC) model to explore the shared clustering structure in PPI and DDI networks, in order to improve the accuracy of protein complex detection. Correspondingly, we here present the Matlab algorithm of Ou-Yang's model (Ou-Yang et al., 2017).

2 Methods

2.1 Ou-Yang’s model

In Ou-Yang’s model, the networks are assumed to be collected from different but related fields, i.e., PPI network and DDI network. And it has a many-to-many (i.e., a protein may contain multiple domains) cross-field instance relationship. Given a PPI network and a DDI network, a model is used to describe the generation processes of two networks. Based on the domain-protein associations, the generation of PPI and DDI networks is assumed to be dominated by a shared clustering structure that describes the degree of proteins belonging to complexes. The protein complex detection finally becomes a parameter estimation problem (Ou-Yang et al., 2017).

According to Ou-Yang et al. (2017), given a PPI network $G1$ with $N1$ proteins, and a DDI network $G2$ with $N2$ domains, two nonnegative score matrices, $A^{(1)}_{N1\times N1}$ and $A^{(2)}_{N2\times N2}$, are the affinity/adjacency matrix of $G1$ and $G2$ respectively. The relationships between nodes in $G1$ and nodes in $G2$ may be many-to-many. The domain-protein associations are described by the domain-protein association matrix $F_{N2\times N1}$, where $F_{xi} = 1$ if protein i in $G1$ contains domain x in $G2$, otherwise $F_{xi} = 0$. The goal is to jointly find clustering structures in PPI network $G1$ and DDI network $G2$, and derive $H^{(m)}_{ik}$ (the weight of node i in the predicted k-th cluster of m-th network) from each network $A^{(m)}$. A higher value of $H^{(m)}_{ik}$ means that node i more likely belongs to cluster k and vice versa. Here, $H^{(1)}=H$, $H^{(2)}=FH^{(1)}=FH$, $H\in R^{N1\times K}$, where H is the protein-complex membership matrix.

Solve the following optimization problem:

$$\begin{aligned}
min_{H,\lambda} & -\Sigma^{N1}_{i,j=1}A^{(1)}_{ij}\log(1-\exp(-\Sigma^{K}_{k=1}H_{ik}H_{jk}))\\
& +\Sigma^{N1}_{i,j=1}(1-A^{(1)}_{ij})\Sigma^{K}_{k=1}H_{ik}H_{jk}\\
& -\Sigma^{N2}_{x,y=1}A^{(2)}_{xy}\log(1-\exp(-FHH'F')_{xy})\\
& +\Sigma^{N2}_{x,y=1}(1-A^{(2)}_{xy})(FHH'F')_{xy}\\
& +\Sigma^{N1}_{i=1}\Sigma^{K}_{k=1}H^{2}_{ik}/(2\lambda_k)\\
& +N1/2*\Sigma^{K}_{k=1}\log\lambda_k\\
& +\Sigma^{K}_{k=1}b/\lambda_k\\
& +(a+1)\Sigma^{K}_{k=1}\log\lambda_k
\end{aligned} \qquad (1)$$

$$H\geq 0$$

in which

$$\lambda_k\leftarrow(2b+\Sigma^{N1}_{i=1}H^{2}_{ik})/(N1+2a+2) \qquad (2)$$
$$k=1, 2, \ldots, K$$

and

$$\begin{aligned}
H_{ik}\leftarrow & H_{ik}/2+H_{ik}/2*(\Sigma^{N1}_{j=1}A^{(1)}_{ij}H_{jk}/(1-\exp(-HH')_{ij})+\Sigma^{N2}_{x,y=1}(A^{(2)}_{xy}F_{xi}\Sigma^{N1}_{j=1}H_{jk}F_{yj})/(1-\exp(-FHH'F')_{xy}))\\
& /(\Sigma^{N1}_{j=1}H_{jk}+\Sigma^{N2}_{x,y=1}F_{xi}\Sigma^{N1}_{j=1}H_{jk}F_{yj}+H_{ik}/(2\lambda_k)) \qquad (3)\\
& i=1, 2, \ldots, N1;\ k=1, 2, \ldots, K
\end{aligned}$$

are alternatively changed and are used to minimize eq. (1) until the permitted iterative error of objective function is achieved. Initial H (binary matrix) should be given before computation. In the initial H, $H_{ik}=1$, if protein i is assigned to complex (cluster) k, and H_{ik}=0 otherwise, where i=1, 2, …, N1; k=1, 2, …, K. Initial H is then positively perturbed with small positive and random values

$$H \leftarrow H + \mathrm{rand}(N1, K)/10$$

For the final H, given a threshold τ. Protein i is assigned to complex k if $H_{ik} \geq \tau$, i.e., let H_{ik}=1, otherwise H_{ik}=0 if $H_{ik} < \tau$.

2.2 Matlab algorithm

The following is the full Matlab algorithm, PPI_DDI, for Ou-Yang's model, using in the Matlab environment.

```
a=input('Input parameter a (e.g., 2) = ');
b=input('Input parameter b (e.g., 0.25N1; e.g., for N1=100, b=250) = ');
sim=input('Input maximum number of iterations (e.g., 1000) = ');
err=input('Input permitted absolute error (e.g., 0.001) = ');
tao=input('Input threshold tao (Suggested: 0.3) = ');
pert=input('Input strength of random perturbation to H (Suggested: 0.1) = ');
strA1=input('Input the file name of A1 matrix (A1=(a1ij)N1×N1): ','s');
strA2=input('Input the file name of A2 matrix (A2=(a2ij)N2×N2): ','s');
strF=input('Input the file name of F matrix (F=(fij)N2×N1): ','s');
strH=input('Input the file name of initial H matrix (H=(hij)N1×K, where hij=1 if protein i is assigned to complex j, or else
hij=0):','s');
H=xlsread(strH);
K=size(H,2);
A1=xlsread(strA1); A2=xlsread(strA2); F=xlsread(strF);
N1=size(A1,1);
N2=size(A2,1);
H0=H;
Hopt=H;
H=H+rand(N1,K)*pert;    %Positive random perturbation to H
objLast=1e+10;
sm=0;
while (sm<=sim)
while (K>0)
lamda=lamda_Update(H,a,b);
%H>=0
if (sum(sum(H<0))>0)
H=H_Update(H,lamda,A1,A2,F);
else break;
end
end
obj=objFun(H,lamda,A1,A2,F,a,b);
if (obj<objLast)
Hopt=H;
end
if (abs(objLast-obj)<err) break; end
```

```
H=H_Update(H,lamda,A1,A2,F);
objLast=obj;
sm=sm+1;
end
Hopt(Hopt>=tao)=1;
Hopt(Hopt<tao)=0;
fprintf(['\nThe original matrix H\n'])
H0
fprintf(['\nThe optimal matrix H\n'])
Hopt
for k=1:K
fprintf(['\n\nThe proteins belonging to complex ' num2str(k) ' :\n'])
for i=1:N1
if (Hopt(i,k)==1)
fprintf([num2str(i) ','])
end
end
end

function objFun=objFun(H,lamda,A1,A2,F,a,b)
N1=size(A1,1);
N2=size(A2,1);
K=size(H,2);
term1=0;
term2=0;
for i=1:N1;
for j=1:N1;
s=0;
for k=1:K;
s=s+H(i,k)*H(j,k);
end;
term1=term1+A1(i,j)*log(1-exp(-s));
term2=term2+(1-A1(i,j))*s;
end
end
EX=F*H*H'*F';
term3=0;
term4=0;
for x=1:N2;
for y=1:N2;
term3=term3+A2(x,y)*log(1-exp(-EX(x,y)));
term4=term4+(1-A2(x,y))*EX(x,y);
end;
end
term5=0;
```

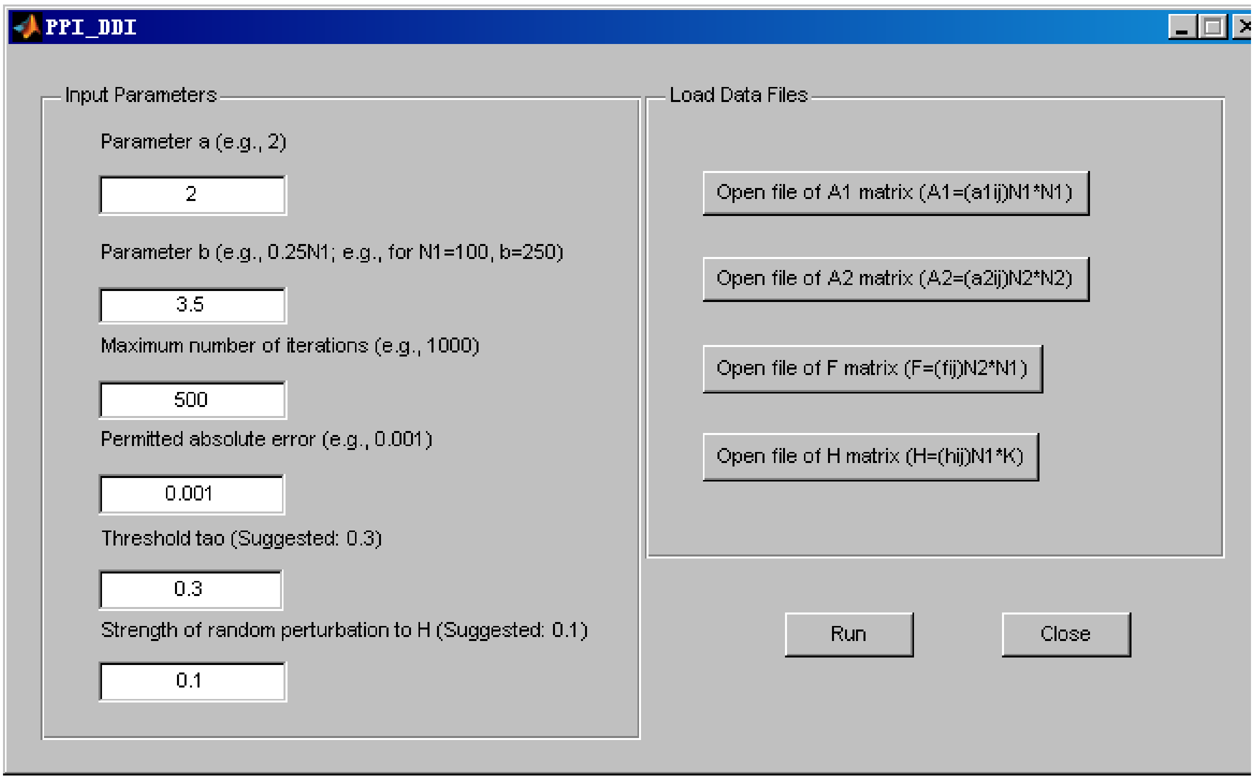
```
for i=1:N1;
for k=1:K;
term5=term5+H(i,k)^2/(2*lamda(k));
end
end
term6=0;
term7=0;
for k=1:K;
term6=term6+log(lamda(k));
term7=term7+b/lamda(k);
end
term8=term6*(a+1);
term6=term6*N1/2;
objFun=-term1+term2-term3+term4+term5+term6+term7+term8;

function lamda=lamda_Update(H,a,b)
N1=size(H,1);
K=size(H,2);
for k=1:K;
lamda(k)=(2*b+sum(H(:,k).^2))/(N1+2*a+2);
end

function H=H_Update(H,lamda,A1,A2,F)
N1=size(A1,1);
N2=size(A2,1);
K=size(H,2);
EX1=-H*H';
EX2=-F*H*H'*F';
for i=1:N1;
for k=1:K;
sn1=0;
for j=1:N1;
sn1=sn1+A1(i,j)*H(j,k)/(1-exp(EX1(i,j)));
end
ss=0;
sn2=0;
for x=1:N2;
for y=1:N2;
s2=0;
for j=1:N1;
s2=s2+H(j,k)*F(y,j);
end
ss=ss+F(x,i)*s2;
s1=A2(x,y)*F(x,i)*s2;
sn2=sn2+s1/(1-exp(EX2(x,y)));
```

```
end
end
deno=sum(H(:,k))+ss+H(i,k)/(2*lamda(k));
no=sn1+sn2;
H(i,k)=H(i,k)/2+H(i,k)/2*no/deno;
end
end
```

The executable GUI software (see supplementary material) of the algorithm above is partly indicated in Fig. 1.



PPI_DDI

Input Parameters

Parameter a (e.g., 2)

2

Parameter b (e.g., 0.25N1; e.g., for N1=100, b=250)

3.5

Maximum number of iterations (e.g., 1000)

500

Permitted absolute error (e.g., 0.001)

0.001

Threshold tao (Suggested: 0.3)

0.3

Strength of random perturbation to H (Suggested: 0.1)

0.1

Load Data Files
Open file of A1 matrix (A1=(a1ij)N1*N1)
Open file of A2 matrix (A2=(a2ij)N2*N2)
Open file of F matrix (F=(fij)N2*N1)
Open file of H matrix (H=(hij)N1*K)
Run
Close

Fig. 1 The executable GUI software of the algorithm.

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