An Iterative Model for Identifying Essential Proteins based on the Whole Process Network of Protein Evolution

Yaocan Zhu

Changsha University

Xin Liu

Changsha University

Zhiping Chen

Changsha University

Zhen Zhang

Changsha University

Lei Wang (✉ wanglei@xtu.edu.cn)

Changsha University

Research Article

Keywords: Essential protein recognition, The whole process network, Protein evolution, Computational methods, Entropy

Posted Date: February 24th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1362263/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

An Iterative Model for Identifying Essential Proteins based on the Whole Process Network of Protein Evolution

Yaocan Zhu^{1,2}, Xin Liu^{1,2}, Zhiping Chen^{1,2}, Zhen Zhang^{1,2}, Lei Wang^{1,2*}

¹Institute of Bioinformatics Complex Network Big Data, Changsha University, Changsha 410022, China

²Big Data Innovation and Entrepreneurship Education Center of Hunan Province, Changsha University, Changsha 410022, China

*Correspondence: wanglei@xtu.edu.cn

Abstract

Background: Essential proteins play important roles in cell growth and regulation. However, due to high cost and low efficiency of traditional biological experiments to identify essential proteins, in recent years, with the development of high-throughput technologies and bioinformatics, more and more computational models have been proposed to infer key proteins based on Protein-Protein Interaction (PPI) networks.

Result: In order to improve the predictive accuracy of computational methods, a novel prediction model named MWPNPE (Model based on the Whole Process Network of Protein Evolution) was proposed to infer potential basic proteins in this manuscript. In MWPNPE, known PPI data and gene expression data were first downloaded from benchmark databases and adopted to construct the whole process network of protein evolution. And then, considering that the interaction between proteins is a kind of dynamic process, a new measure was designed to estimate the relationships between proteins, based on which, an improved iterative algorithm was put forward to evaluate the importance of proteins. Finally, in order to verify the predictive performance of MWPNPE, we compared it with

24 state-of-the-art representative computational methods, and experimental results demonstrated that the
25 recognition accuracy of MWPNPE in the top 100, 200 and 300 candidate key proteins can reach 89,
26 166 and 233 respectively, which is significantly better than the predictive accuracies achieved by
27 these competitive methods.

28 **Conclusions:** Through combining a variety of data sources of proteins, a whole process network of
29 protein evolution was constructed first in this manuscript, which greatly reduced the noises and errors
30 existing in original PPI networks. Moreover, through considering the dynamic process of interactions
31 between proteins in the network, a new measure was designed to estimate the relationship between
32 proteins, which improved the predictive accuracy of the newly proposed model effectively. Hence, it
33 can be seen that MWPNPE may be a useful tool for the development of key protein recognition in the
34 future.

35 **Keywords:** Essential protein recognition, The whole process network, Protein evolution,
36 Computational methods, Entropy

37 **Background**

38 Essential proteins are the basis of cell and tissue structure [1]. However, it is time-consuming
39 and high-costly to infer essential proteins by traditional ways such as gene knockout [2] and RNA
40 interference (RNAi) [3-4], etc. In recent years, with the rapid accumulation of PPI data and other
41 biological data of proteins [5-6], a lot of computational models have been proposed to infer potential
42 key proteins and achieved great advances in the improvement of predictive performance. For
43 example, based on the concept of centrality, a series of different methods, including SC [7], EC [8],
44 DC [9] (degree centrality), BC [10] (better centrality), CC [11] (closeness centrality), NC [12]
45 (neighbor centrality) and IC [13] (information centrality), were proposed successively by adopting
46 different topological characteristics of the PPI networks. In addition, based on the local features of

PPI networks, Qi et al and Li et al proposed a calculative model named LID [14] (Local Interaction Density) and LAC [15] (Local Average Connection) respectively. Lin et al designed two kinds of prediction model named MNC (Maximum Neighborhood Connectivity) and DMNC (Maximum Neighborhood Connectivity of Density) separately [16]. Jeong et al introduced a central lethal rule to estimate the relationships between proteins as well [17]. However, due to a variety of noise data such as false positive and false negative existing in original PPI networks [18-19], satisfactory accuracy cannot be achieved by these methods based solely on PPI networks in the identification of essential proteins. Thus, in order to further improve the predictive accuracy of computational models, some new methods have been proposed by integrating PPI networks with biological information of proteins. For instance, Zhang et al put forward a calculation method by fusing dynamic PPI networks [20]. Lei et al designed a prediction model based on the artificial fish swarm optimization [21]. Zhao et al designed a model by combining the gene expression profiles of proteins and PPI networks [22]. Zhang et al proposed a detection model called CoEWC by integrating topological properties of PPI networks and the gene co-expression characteristics of proteins [23]. Ren et al introduced a method called ECC by integration of PPI network topology and protein complexes [24]. Li et al established a model called PEC based on the combination of protein–protein interaction and gene expression data [25]. Sun et al proposed an iterative method called IoMCD based on the cross entropy to fuse biological information [26]. Li et al presented an iterative method named CVIM based on the fusion of protein topology and functional features [27]. Peng et al designed an iterative method called ION by integrating biological information and PPI network characteristics [28]. Zhang et al defined a predictive method called TEGS based on the combination of subcellular location information and PPI network structure [29-30]. Lei et al designed a model named RSG by combining RNA SEQ data, go annotation and subcellular localization [31]. Zhao et al proposed an iterative calculation method called RWHN [32] through integrating protein domain information, subcellular localization information and protein homology information with topology features of PPI networks. Experimental

72 results show that these methods based on the combination of biological information of proteins and
73 topological characteristics of PPI networks can obtain much better prediction accuracy.

74 Inspired by above models, in this manuscript, a novel iterative method called MWPNPE was
75 designed based on a newly constructed whole process network of protein evolution to infer potential
76 essential proteins. In MWPNPE, through combining the original PPI network with the conservative
77 degrees and gene expression profiles of proteins, the whole process network of protein evolution was
78 first constructed. And then, through considering the dynamic process of interactions between
79 proteins, a new measure was designed to estimate the relationships between proteins, based on
80 which, an iterative algorithm was proposed to evaluate the importance of proteins. Finally, in order to
81 verify the predictive effects of MWPNPE, we compared it with state-of-the-art prediction models
82 such as SC [7], EC [8], DC [9], BC [10], CC [11], NC [12], IC [13], PEC [25], LAC [15], CoEWC
83 [23], POEM [22], ION [28], TEGS [30] and RWHN [32] simultaneously, and experimental results
84 demonstrated that MWPNPE outperformed all these competitive methods in terms of predictive
85 accuracy of essential proteins.

86 **Methods**

87 As shown in Figure 1, the flowchart of MWPNPE consists of the following four major steps:

88 Step 1: Based on the known PPI data and gene expression data of proteins downloaded from
89 benchmark databases, the whole process network of protein evolution will be constructed first.

90 Step 2: Through considering the dynamic process of interactions between proteins, a new
91 measure will be designed to estimate the relationships between proteins, based on which, topological
92 characteristics including the degrees of compactness, relevance and aggregation will be extracted for
93 proteins from the whole process network of protein evolution in succession.

Step 3: Based on the gene expression data and homologous information of proteins, biological characteristics including the homology fraction and the co-expression intensity will be extracted for proteins as well.

Step 4: Finally, based on the topological and biological characteristics extracted for proteins, an improved iterative method will be designed to estimate the importance of proteins.

Construction of the whole process network of protein evolution

Construction of original PPI networks and transient networks of proteins

Firstly, we will download three datasets of known PPIs from different databases such as Gavin [34], Krogan [35] and DIP [36] respectively. Based on each dataset Ω , let $N_p = \{p_1, p_2, \dots, p_N\}$ denote the set of proteins in Ω , E_p represent the edge set between proteins in N_p , then we can obtain an original PPI network $OppiN = \{N_p, E_p\}$ as follows: for any two given proteins p_i and p_j in N_p , there is $ed(p_i, p_j) = 1$ if and only if there is a known interaction between these two proteins in Ω , otherwise, there is $ed(p_i, p_j) = 0$.

107 Next, for any given protein p_i in N_p , if it has a gene expression sequence $g_i = <$
 108 $g_{i1}, g_{i2}, \dots, g_{iT} >$ with T ($=36$) different time points, where g_{it} represents the value of the gene
 109 expression level of p_i at the t -th time point, then we can respectively calculate the values of its
 110 average gene expression level $\bar{g}_i$, its standard deviation σ_i , and the average gene expression level $\bar{g}$
 111 of all these N proteins as follows:

$$112 \quad \bar{g}_i = \frac{1}{T} \sum_{t=1}^T g_{it} \quad (1)$$

$$113 \quad \sigma_i = \sqrt{\frac{1}{T} \sum_{t=1}^T (g_{it} - \bar{g}_i)^2} \quad (2)$$

$$114 \quad \bar{g} = \frac{1}{N} \sum_{i=1}^N \bar{g}_i \quad (3)$$

115 For any given protein p_i in N_p , it is obvious that there are fluctuations in concentration of its
 116 gene expression level at different time points. For simplicity, supposing that the gene expression
 117 value g_{it} of p_i obeys the pseudo normal distribution with a mean (i.e., the mathematical
 118 expectation) of $\bar{g}_i$ and a variance of σ_i^2 , then we can define the concentration F_i of its gene
 119 expression value as follow:

$$120 \quad F_i = \frac{T_i}{T} \quad (4)$$

121 Where T_i represents the number of gene expression value g_{it} in the horizontal axis interval
 122 $(\bar{g}_i - \sigma_i, \bar{g}_i + \sigma_i)$. Considering that the area in the horizontal axis interval $(\bar{g}_i - \sigma_i, \bar{g}_i + \sigma_i)$ in
 123 the standard normal distribution curve is 68.268949%, therefore, in this paper, we will set a threshold
 124 $\eta^{con} = 0.68$, based on which, for any given protein p_i at time point t , we will divide it into one of
 125 these three categories of proteins such as the completely conserved, semi completely conserved or
 126 incompletely conserved proteins as follows:

$$(p_i, t) = \begin{cases} \text{complete}; & \text{if } F_i \geq \eta^{con} \text{ and } \bar{g}_i \geq \bar{g} \\ \text{Semicomplete}; & \text{else if } F_i < \eta^{con} \text{ and } g_{it} \geq \bar{g}_i \\ \text{Incomplete}; & \text{otherwise} \end{cases} \quad (5)$$

According to above formula (5), it is easy to see that the completely conserved proteins refer to proteins with high activity in the whole T time points, the semi completely conserved proteins refer to proteins with high activity at a certain time point or at some time points, while the incompletely conserved proteins refer to proteins with low activity or no gene expression sequence in the whole T time points. It is reasonable to believe that proteins are qualified to interact with other proteins only at the time point of high activity. Hence, for any two given proteins p_i and p_j , the interaction between them can be defined as follows:

$$e_t(p_i, p_j) = \begin{cases} 0; & \text{if } incomplete(p_i) \text{ or } incomplete(p_j) \\ 1; & \text{otherwise} \end{cases} \quad (6)$$

Obviously, based on above formula (6), let $G_t = \{N_p, E_t\}$ represent the transient network of proteins at the time point t , and $E_t = \{e_{t1}, e_{t2}, \dots, e_{tm}\}$ denote the set of protein interactions at the time point t , then we can construct 36 different transient networks $\{G_1, G_2, \dots, G_t, \dots, G_T\}$ of proteins in final.

140 **Construction of the whole process network Net**

For any given transient network G_t , $\forall p_i \in N_p$, let $NG_t(p_i)$ represent the set of adjacent nodes in N_p interacting with p_i at time point t , then there is:

$$NG_t(p_i) = \{p_j | \exists e_t(p_i, p_j) \in E_t, p_j \in N_p\} \quad (7)$$

Moreover, assuming that $NG_t(p_i) = \{p_j, p_{j+1}, \dots, p_{j+k}\}$, let $THNG_t(p_i)$ represent the set of nodes in N_p interacting with p_i or adjacent nodes of p_i at the time point t , then there is:

$$THNG_t(p_i) = NG_t(p_i) \cup NG_t(p_j) \cup NG_t(p_{j+1}) \cup \dots \cup NG_t(p_{j+k}) \quad (8)$$

147 In the sequence of transient networks of the whole process of protein evolution, it is reasonable
 148 to believe that, with the passage of time, the data of proteins in the past time become less prominent,
 149 while the links between recently generated proteins will play a greater role. Therefore, considering
 150 that proteins will change with time in the process of evolution, it is obvious that the same edge will
 151 appear at different times in these transient networks, and the earlier this edge appears, the more its
 152 role in protein evolution will change over time. Hence, we can calculate the weight corresponding to
 153 each edge by the following way:

154 For any two given proteins p_i and p_j , assuming that the edge between them at the time point t is
 155 $e_t(p_i, p_j)$, then its weight $D_t(p_i, p_j)$ at the time point t can be defined as follows:

$$156 \quad D_t(p_i, p_j) = \begin{cases} ed(p_i, p_j) & ; \quad t = 0 \\ D_{t-1}(p_i, p_j) * \gamma + e_t(p_i, p_j) & ; \text{otherwise} \end{cases} \quad (9)$$

157 Where γ is a parameter with value between 0 and 1, and according to the literature [33], in this
 158 paper, we will set the value of the parameter γ to 0.9.

159 Based on above formula (9), for any given protein p_i , assuming that p_j is a neighbor of p_i , then
 160 we can define the weight $w_t(p_i, p_j)$ of p_j to p_i at the time point t as follows:

$$161 \quad w_t(p_i, p_j) = \frac{D_t(p_i, p_j)}{\sum_{p_k \in NG_t(p_i)} D_t(p_i, p_k)} \quad (10)$$

162 According to above formula (10), it is easy to see that there is $\sum_{p_k \in NG_t(p_i)} w_t(p_i, p_k) = 1$, and
 163 $w_t(p_j, p_i)$ may not equal to $w_t(p_i, p_j)$.

164 Obviously, we have reasons to believe that, for any two given proteins p_i and p_j , when the
 165 weight $w_t(p_i, p_j)$ between them reaches the maximum, the role of the link between them can best

166 reflect the current relationship between them. Hence, let $w_{max}(p_i, p_j)$ represent the maximum weight
 167 between p_i and p_j , then we can obtain a weight matrix $W = [w_{ij}]_{N \times N}$ as follows:

$$168 \quad w_{ij} = \frac{w_{max}(p_i, p_j)}{\sum_{j=1}^N w_{max}(p_i, p_j)} \quad (11)$$

169 Based on above formula (11), it is obvious that we can fuse those 36 transient networks
 170 $\{G_1, G_2, \dots, G_t, \dots, G_T\}$ of proteins into a whole process network $Net = \{N_p, W\}$ of protein evolution
 171 easily.

172 **Construction of the interaction matrix**

173 **Construction of the interaction matrix based on Net**

174 Considering the dynamic process of protein-protein interactions, for any two given proteins p_i
 175 and p_j , if there are more protein nodes interacting with both of them in Net , then we have reasons to
 176 think that the relationship between them will be more reliable. In this section, for any two given
 177 proteins p_i and p_j , we will introduce the following three kinds of network topological features such
 178 as DC (Degree of Compactness), DR (Degree of Relevance) and DA (Degree of Aggregation) to
 179 better reflect the reliability of the relationship between them:

$$180 \quad DC(p_i, p_j) = \begin{cases} \frac{|NG(p_i) \cap NG(p_j)| + 1}{|NG(p_i)|} : & p_j \in NG(p_i) \\ \frac{1}{|NG(p_i)|} : & otherwise \end{cases} \quad (12)$$

$$181 \quad DR(p_i, p_j) = \begin{cases} \frac{\sum_{p_k \in NG(p_j)} TP_1(p_j, p_k)}{\sum_{p_j \in NG(p_i)} |NG(p_j)|} : & p_j \in NG(p_i), p_k \in NG(p_j) \\ \frac{1}{\sum_{p_j \in NG(p_i)} |NG(p_j)|} : & otherwise \end{cases} \quad (13)$$

$$182 \quad DA(p_i, p_j) = \begin{cases} \frac{|THNG(p_i) \cap NG(p_j)| + 1}{|THNG(p_i)|} : & p_j \in NG(p_i) \\ \frac{1}{|THNG(p_i)|} : & otherwise \end{cases} \quad (14)$$

183 Where $NG(p_k)$ represents the set of adjacent nodes of p_k in Net , $THNG(p_k)$ denotes the set
 184 of nodes interacting with p_k or adjacent nodes of p_k in $OppiN$, while $|\Lambda|$ is the number of elements
 185 in the set of Λ . As can be seen from the above formulas (12), (13) and (14), for any two proteins p_i
 186 and p_j in Net , the more adjacent nodes between them, the greater the value of $|NG(p_i) \cap NG(p_j)|$
 187 will be. Therefore, to a certain extent, $DC(p_i, p_j)$ can effectively reflect the tightness between p_i and
 188 p_j . Similarly, $DR(p_i, p_j)$ can effectively reflect the degree of correlation between p_i and p_j , and
 189 $DA(p_i, p_j)$ can effectively reflect the degree of aggregation between p_i and p_j .

190 Hence, for any given protein p_i , assuming that p_j is a neighbor of p_i , then we can estimate the
 191 importance $R(p_i, p_j)$ of p_j to p_i as follows:

$$192 \quad R(p_i, p_j) = w_{ij} * (\alpha * DC(p_i, p_j) + \beta * DR(p_i, p_j) + \varphi * DA(p_i, p_j)) \quad (15)$$

193 Where, α , β and φ are parameters with values between 0 and 1, and there is $\alpha + \beta + \varphi = 1$.

194 Moreover, for any given protein node p_i in Net , we have reasons to believe that the more
 195 proteins interacting with p_i and the greater the importance of these proteins to p_i , the stronger the
 196 ability of p_i to positively affect its neighbors by interacting with other proteins, that is, the more
 197 critical p_i is. Thus, for any given protein p_i in Net , we can calculate its criticality as follows:

$$198 \quad K(p_i) = \sum_{j=1}^N R(p_i, p_j) \quad (16)$$

199 According to above formula (16), it is obvious that we can construct a protein-protein interaction
 200 matrix $H = [h_{ij}]_{N \times N}$ for all N proteins in Net as follows:

$$201 \quad h_{ij} = \begin{cases} \frac{K(p_i)}{\sum_{m=1}^N K(p_m)}: & \text{if } i = j \\ \frac{\min\{K(p_i), K(p_j)\}}{\sum_{m=1}^N K(p_m)}: & \text{otherwise} \end{cases} \quad (17)$$

202 Value setting for the parameters of α , β and φ

203 Based on above formulas (12), (13) and (14), for any given protein node p_i in Net , let TP_1 , TP_2
 204 and TP_3 represent the importance of p_i based on these three kinds of network topological features
 205 such as DC , DR and DA respectively, then we can calculate the values of TP_1 , TP_2 and TP_3 as
 206 follows:

$$207 \quad TP_1(p_i) = \sum_{p_j \in NG(p_i)} DC(p_i, p_j) \quad (18)$$

$$208 \quad TP_2(p_i) = \sum_{p_j \in NG(p_i)} DR(p_i, p_j) \quad (19)$$

$$209 \quad TP_3(p_i) = \sum_{p_j \in NG(p_i)} DA(p_i, p_j) \quad (20)$$

210 Based on these M ($=3$) different biological feature scores obtained above, for all N protein nodes
 211 in Net , it is obvious that we can construct a feature matrix Z as follows:

$$212 \quad Z = [TP_1 \cdots TP_M]_{1 \times M} = [z_{ij}]_{N \times M} \quad (21)$$

213 According to above formula (21), it is easy to see that, for any given protein node p_i , there are M
 214 different features $TP_1(p_i)$, $TP_2(p_i)$, ..., $TP_M(p_i)$. Hence, in order to estimate the stability of all
 215 these different features, for the j -th features TP_j of proteins, we will further calculate its weight μ_j
 216 based on its entropy en_j as follows:

$$217 \quad en_j = -\sum_{i=1}^N z_{ij} \ln z_{ij} / \ln N \quad (22)$$

$$218 \quad \mu_j = (1 - en_j) / \sum_{i=1}^M (1 - en_i) \quad (23)$$

219 Thereafter, for convenience, in this paper, we will set the values of α , β and φ in the formula
 220 (15) to μ_1 , μ_2 and μ_3 respectively.

221 Calculation of initial scores for proteins

222 Calculation of biological feature scores for proteins

223 The essentiality of protein has been proved to be closely related to the degree of protein
224 conservatism [28]. For any given protein p_i , let $os(p_i)$ represent the homology fraction of p_i , then its
225 degree of conservatism $FS_1(p_i)$ can be obtained as follows:

$$226 \quad FS_1(p_i) = \frac{os(p_i)}{\max_{p_j \in V\{os(p_j)\}}} \quad (24)$$

227 Obviously, the degree of conservatism $FS_1(p_i)$ obtained by above formula (24) can be
228 regarded as one biological feature score of p_i .

229 Moreover, based on the gene expression sequences of proteins, for any two given proteins p_i and
230 p_j , we can further obtain the intensity of co-expression between them by adopting the PCC [45] as
231 follows:

$$232 \quad PCC(p_i, p_j) = \frac{1}{T-1} \sum_{t=1}^T \left(\frac{g_{it} - \bar{g}_i}{\sigma_i^2} \right) \left(\frac{g_{jt} - \bar{g}_j}{\sigma_j^2} \right) \quad (25)$$

233 Based on above formula (25), for any given protein p_i , we can further obtain another biological
234 feature score $FS_2(p_i)$ of p_i as follows:

$$235 \quad FS_2(p_i) = \sum_{p_j \in NG(p_i)} PCC(p_i, p_j) \quad (26)$$

236 Calculation of initial scores based on biological feature scores

237 Obviously, based on these L ($=2$) different biological feature scores obtained above, for all N
238 protein nodes in Net , it is obvious that we can construct a feature matrix X as follows:

$$239 \quad X = [FS_1 \cdots FS_L]_{1 \times L} = [x_{ij}]_{N \times L} \quad (27)$$

240 According to above formula (27), it is easy to see that, for any given protein node p_i , there are M
 241 different features $FS_1(p_i), FS_2(p_i), \dots, FS_L(p_i)$. Hence, in order to estimate the stability of all
 242 these different features, for the j -th features FS_j of proteins, we will further calculate its weight θ_j
 243 based on its entropy ent_j as follows:

$$244 \quad ent_j = -\sum_{i=1}^N x_{ij} \ln x_{ij} / \ln N \quad (28)$$

$$245 \quad \theta_j = (1 - ent_j) / \sum_{i=1}^L (1 - ent_i) \quad (29)$$

246 Thus, based on above formulas, we can calculate initial scores for all these N proteins in *Net* as
 247 follows:

$$248 \quad F = \sum_{j=1}^L \theta_j * FS_{ij} \quad (30)$$

249 **Algorithm**

250 Finally, based on above formulas (17) and (30), let $Y^0 = F$, then we can calculate the criticality
 251 scores for all these N proteins in *Net* iteratively by the following way:

$$252 \quad Y^{t+1} = \tau H Y^t + (1 - \tau) Y^0 \quad (31)$$

253 Where the parameter τ ($0 \leq \tau \leq 1$) is utilized to adjust the proportion of initial score Y^0) and
 254 last iteration score Y^t .

255 Hence, based on above formula (31), we can present our predictive algorithm MWPENPE as
 256 follows:

257 _____

258 **Algorithm:** MWPENPE

259 _____

260 Input: the gene expression data, the original PPI network $OppiN = \{N_p, E_p\}$, the homologous
261 data, and the parameters $\delta (= 10^{-5})$ and K

262 Output: Top K percent of proteins sorted by the vector Y in descending order

263 Step1: Constructing 36 different transient networks $\{G_1, G_2, \dots, G_t, \dots, G_T\}$ of proteins according
264 to above formula (6).

265 Step2: Constructing the whole process network $Net = \{N_p, W\}$ of protein evolution according to
266 above formula (11).

267 Step3: Constructing the interaction matrix H according to above formula (17).

268 Step4: Let $t = 0$, calculating initial score vector Y^t for all proteins according to above formula
269 (30).

270 Step5 : Let $t = t + 1$; Calculating Y^{t+1} according to above formula (31).

271 Step6 : Repeat step 5 until $\|Y^{t+1} - Y^t\| < \delta$.

272 Step7 : Sorting the values of Y^{t+1} in descending order, and outputting the top K percent of sorted
273 proteins.

274 _____

275 **Results and analysis**

276 **Experimental data**

277 Considering that *Saccharomyces cerevisiae* contains rich biological information data and the
278 most complete PPI data, and is widely used in the prediction model for evaluating key proteins,
279 therefore, we will first download known PPIs from the Gavin [34], Krogan [35] and DIP [36]
280 databases respectively, and then, after filtering the repeated interactions and self-interactions from the
281 downloaded datasets, we finally obtain 7669 interactions including 1855 proteins from Gavin, 14317
282 interactions including 3672 proteins from Krogan and 24743 interactions including 5093 proteins

283 from DIP. Secondly, we will download a benchmark dataset containing 1293 essential proteins in
 284 *Saccharomyces cerevisiae* from the *Saccharomyces* Genome deletion project database (SGDP) [37],
 285 the *Saccharomyces* Genome Database (SGD) [38], the database of essential genes (DEG) [39] and
 286 MIPS [40] to compare predictive accuracy between different recognition models. Moreover, we will
 287 download direct homology information data from the Inparanoid database (version 7) [41], and a
 288 dataset containing 6776 gene products and 36 samples from the database provided by Tu et al. [42].
 289 Finally, based on above newly-downloaded datasets, we will compare MWPNPE with the 14
 290 advanced competitive models (as shown in the following Table 1) to estimate its predictive
 291 performance based on different measurement and verification methods such as accuracy, folding
 292 knife, ROC curve and PR curve, etc. Besides, the influence of parameters τ on predictive
 293 performance of MWPNPE has been evaluated as well.

Table 1. Brief description of 14 advanced competitive prediction models

Algorithm	Biological information	Network topology
SC [7]	NO	Subgraph Centrality
EC [8]	NO	Eigenvector Centrality
DC [9]	NO	Degree Centrality
BC [10]	NO	Betweenness Centrality
CC [11]	NO	Closeness Centrality

NC [12]	NO	Neighbor Centrality
IC [13]	NO	Information Centrality
PEC [25]	Gene expression data	Edge clustering coefficient
LAC [15]	NO	Degree Centrality, Common neighbor node
CoEWC [23]	Gene expression data	Clustering coefficient
POEM [22]	Gene expression data	Degree Centrality, Subgraph, Edge clustering coefficient, Closeness Centrality
ION [28]	Orthologous data	Edge clustering coefficient
TEGS [30]	subcellular localization data	Sub-network partition and prioritization
RWHN [32]	Orthologous data, subcellular localization	Degree Centrality, protein-domain

Comparison between MWPNPE and competitive methods

In this section, we first compared MWPNPE with 13 competitive methods including SC, EC, DC, BC, CC, NC, IC, PEC, LAC, CoEWC, POEM, ION and RWHN based on the Gavin database, and the experimental results were shown in Fig.2. From observing Fig.2, it is easy to see that, in the ranking of true essential proteins inferred by all these competitive prediction methods, MWPNPE can detect more essential proteins in the top 5%, 10%, 15%, 20% and 25% based on the Gavin database.

Especially, from the top 5% to the top 25% ranked proteins, the predictive accuracies of MWPNPPE are 10.8%, 8.6%, 12.9%, 11.9% and 11.6% higher than that of RWHN method respectively.

Fig.2. (a) Top 1% (19) ranked proteins. (b) Top 5% (93) ranked proteins. (c) Top 10% (186)

ranked proteins. (d) Top 15% (278) ranked proteins. (e) Top 20% (371) ranked proteins. (f) Top 25% (464) ranked proteins. The comparison of numbers of true essential proteins predicted by MWPNPE, SC, EC, DC, BC, CC, NC, IC, PeC, LAC, CoEWC, POEM, ION and RWHN based on the Gavin database.

Next, we compared MWPNPE with 13 competitive methods such as SC, EC, DC, BC, CC, NC, IC, PEC, LAC, CoEWC, POEM, ION and TEGS based on DIP database, and the experimental results were shown in Fig.3. As can be seen from Fig. 3, comparing with these competing methods such as SC, EC, DC, BC, CC, NC, IC, PEC, LAC, CoEWC, POEM, ION and TEGS, the predictive performances of MWPNPE in the top 1% to 10% predicted proteins are significantly higher than that of all these competing methods. Especially, the predictive performance of MWPNPE can reach 92.2% in the top 1% and 79.2% in the top 5% predicted proteins.

Fig.3. (a)Top 1% (51) ranked proteins. (b) Top 1% (255) ranked proteins. (c) Top 1% (510) ranked proteins. (d) Top 1% (764) ranked proteins. (e) Top 1% (1019) ranked proteins. (f) Top 1% (1274) ranked proteins. The comparison of numbers of true essential proteins predicted by MWPNE, SC, EC, DC, BC, CC, NC, IC, PEC, LAC, CoEWC, POEM, ION and TEGS based on the DIP database.

Moreover, we compared MWPNE with 10 competitive methods such as SC, EC, DC, BC, CC, IC, PEC, LAC, CoEWC and RWHN based on Krogan database as well, and the experimental results were shown in Table 2.

312 **Table 2** comparison of numbers of true essential proteins predicted by MWPNPE and 10 competing
 313 methods based on the Krogan database

Methods	Top1% (37)	Top5% (184)	Top10% (367)	Top15% (551)	Top20% (734)	Top25% (918)
SC	20	78	145	215	273	337
EC	20	78	145	215	273	337
DC	18	98	173	256	321	380
BC	17	83	152	226	286	337
CC	13	68	142	206	262	326
IC	20	91	173	251	317	378
Pec	24	123	200	275	333	388
LAC	28	119	214	288	344	392
CoEWC	24	123	215	291	345	401
RWHN	21	97	198	291	382	447
MWPNPE	35	140	245	336	410	481

314 From observing above table 2, it can be seen that MWPNPE can achieve satisfactory
315 predictive performance on the basis of Krogan database as well. Specifically, among the top 1%
316 predicted essential proteins, the predictive accuracy of MWPNPE is 42.9%, 42.9%, 48.6%, 51.4%,
317 62.9%, 42.9%, 31.4%, 20.0%, 31.4% and 40.0% higher than that of SC, EC, DC, BC, CC, IC, PEC,
318 LAC, CoEWC and RWHN separately. And besides, in the top 5% to 25% predicted essential
319 proteins, MWPNPE can achieve better predictive performance than all these competitive methods as
320 well.

321 **Validation with jackknife methodology**

322 In this section, we will further adopt validation with jackknife methodology [43] to verify the
323 performance of MWPNPE. Firstly, we extract the top 800 proteins predicted by MWPNPE based on
324 the DIP database to compare MWPNPE with 12 competitive methods including SC, EC, DC, BC,
325 CC, NC, IC, PEC, LAC, CoEWC, POEM and ION, and show the comparison results in Fig.(4). Next,
326 we extract the top 400 proteins predicted by MWPNPE based on the Krogan database to compare
327 MWPNPE with 10 competitive methods including SC, EC, DC, BC, CC, IC, PEC, LAC, CoEWC
328 and RWHN, and show the comparison results in Fig.(5). In both Fig.(4) and Fig.(5), the X-axis
329 represents the number of top ranked proteins, while the Y-axis denotes the number of predicted
330 essential proteins. From observing both Fig.(4) and Fig.(5), it can be clearly seen that the predictive
331 performance of MWPNPE is superior to all these competing models.

Fig.4 Comparison of folding knife curve between MWPnPE and 12 competitive methods under the DIP database. (a) Comparison of MWPnPE with SC, EC, DC, BC, CC and NC. (b) Comparison of MWPnPE with IC, PEC, LAC, CoEWC, POEM and ION.

Fig.5 Comparison of folding knife curve between MWPnPE and 10 competitive methods under the Krogan database. (a) Comparison of MWPnPE with SC, EC, DC, BC and CC. (b) Comparison of MWPnPE with IC, PEC, LAC, CoEWC, RVHN and MWPnPE.

1.1.1.1 5.4 Validation by precision–recall curves and ROC curves

Considering that the proportions of key proteins in databases of Gavin, Krogan and DIP are very small, and researches show that when processing highly sparse datasets, PR curve can provide more information about algorithm performance [44]. Hence, in this section, we will adopt PR (Precision-recall) curve and ROC (receiver operating characteristic) curve to further verify the performance of MWPNPE. Firstly, we will compare MWPNPE with SC, EC, DC, BC, CC, NC, IC, PEC, LAC, CoEWC, POEM and TEGS based on the DIP database. The comparison results are illustrated in Fig. 6 and table 3. From observing both Fig. 6 and table 3, it is easy to see that the performance of MWPNPE is significantly higher than that of these 12 competitive methods.

Next, we will further compare MWPNPE with RTSW, SC, EC, DC, BC, CC, NC, IC, PEC, LAC, CoEWC and RWHN based on the Krogan database. The comparison results are illustrated in Fig. 7 and table 4. From observing both Fig. 7 and table 4, it is easy to see that the performance of MWPNPE is significantly higher than all these 10 competitive methods as well.

346

347 Table 3. Comparison of AUC values between MWPNPE and 12 competitive methods based on the
348 DIP database

method	MWPNPE	SC	EC	DC	BC	CC	NC
AUC	0.7489	0.6384	0.6384	0.6704	0.6250	0.6291	0.6879
method	MWPNPE	IC	PeC	LAC	CoEWC	POEM	TEGS
AUC	0.7489	0.6657	0.6329	0.6816	0.6513	0.6662	0.7386

a

(a)

(b)

Fig.7 PR curves and ROC curves of MWPNPE and 10 competitive methods under the Krogan database. (a) Comparison of PR curves and ROC curves between MWPNPE and SC, EC, DC, BC, CC. (b) Comparison of PR curves and ROC curves between MWPNPE and IC, PEC, LAC, CoEWC, RWHN.

350

351 Table 4. Comparison of AUC values between MWPNPE and 10 competitive methods based on the
352 Krogan database

method	MWPNPE	SC	EC	DC	BC	CC
AUC	0.7450	0.6167	0.6167	0.6583	0.6248	0.6114

method	MWPNPE	IC	PeC	LAC	CoEWC	RWHN
AUC	0.7450	0.6573	0.6446	0.6505	0.6396	0.7202

353 **Effect of parameters on Performance of MWPNPE**

354 In MWPNPE, we set a parameter τ with value interval of (0, 1) to adjust the final predicted
355 criticality scores of proteins. During experiments, all possible values of τ will be used to try to obtain
356 the most effective and stable protein score. Among them, the setting value with the highest
357 prediction accuracy of essential protein will be selected as the final value of τ . For simplicity, we
358 will set τ to 0.1,...,0.8 and 0.9 under the Gavin database, the Krogan database and the DIP database
359 respectively to predict essential proteins, and illustrate the results in the following Table 5, Table 6
360 and Table 7 separately. From observing Table 5, it is easy to see that, under the Gavin database,
361 MWPNPE can achieve the maximum performance when τ is set to 0.8 or 0.9. From observing Table
362 6, based on the Krogan database, MWPNPE can achieve the maximum performance when τ is equal
363 to 0.9. From observing Table 7, it is easy to see that, based on the DIP database, MWPNPE can
364 achieve the maximum performance when τ is equal to 0.8 or 0.9. Thus, after comprehensive

365 consideration, we will respectively set τ to 0.8, 0.9 and 0.8 in the experiments based on the databases
366 of Gavin, Krogan and DIP to compare MWPNPE with those advanced competitive models.

367 Table 5. Effect of the parameters τ on MWPNPE under the Gavin database

α	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Rank									
Top50	42	44	44	44	44	45	45	45	44
Top100	80	83	87	89	88	86	86	84	85
Top200	149	152	157	160	164	166	165	166	165
Top300	209	215	218	228	230	233	232	232	232
Top400	263	271	277	284	286	281	290	290	291
Top500	320	326	324	329	332	335	338	339	341

368

369 Table 6. Effect of the parameters τ on MWPNPE under the Krogan database

α	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Rank									
Top50	40	42	42	43	43	44	44	45	45

Top100	73	74	75	76	78	80	80	80	82
Top200	142	145	147	147	146	146	149	148	148
Top300	202	203	204	208	212	210	211	209	208
Top400	257	261	262	264	263	265	266	262	266
Top500	305	308	310	313	315	316	316	317	314

370

371 Table 7. Effect of the parameters τ on MWPNPE under the DIP database

α	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Rank									
Top100	74	78	77	80	82	83	83	86	85
Top200	139	148	151	155	156	160	160	160	161
Top30	201	207	211	217	222	224	224	224	227
Top400	257	262	267	274	279	284	288	288	288
Top500	311	310	317	320	327	333	337	340	344
Top600	361	364	366	373	379	385	388	392	392

372

373 **Conclusions**

374 Essential proteins play an important role in the process of cell life. The loss of essential proteins
375 will lead to the loss of cell function, and even lead to the inability of cells to survive. In recent years,
376 many potential key protein prediction methods based only on PPI network structure have been
377 developed. With the increasing improvement of PPI data and biological data and the development of
378 high-throughput technology, more and more methods based on the combination of PPI network
379 topology and biological information have been designed. However, they simply use the data of PPI
380 combined with biological information, which is not conducive to the realization of prediction
381 accuracy. Inspired by this, in this study, an iterative model named MWPNPE was proposed for
382 identifying essential proteins based on the whole process network of protein evolution. Comparing
383 with traditional state-of-the-art predictive models, MWPNPE can achieve better performance in
384 prediction of potential essential proteins. In the future, we will introduce more biological information
385 of proteins such as the subcellular location information and domain interaction information of protein
386 into MWPNPE to further improve its recognition ability.

387 **Abbreviations**

388 SC: Subgraph Centrality; EC: Eigenvector Centrality; DC: Degree Centrality; BC: Betweenness
389 Centrality; CC: Closeness Centrality; NC: Neighbor Centrality; IC: Information Centrality; LAC:
390 Local Average Connection; CoEWC: Co-Expression Weighted by Clustering coefficient; RWHN:
391 Randomly Walking in the Heterogeneous Network; PPI: Protein–Protein Interaction

392

393 **Acknowledgements**

394 Not applicable

395 **Author Contributions**

396 YCZ and LW conceived the study. XL, ZZ and ZPC improved the study based on the original model.
397 ZPC, ZZ and LW supervised the study. YCZ and LW wrote the manuscript of the study. All authors
398 reviewed and improved the manuscript.

400 **Funding Information**

401 This work was supported by the National Natural Science Foundation of China under Grants
402 61873221.

404 **Availability of data and materials**

405 All data generated or analysed during this study are included in this published article and its supplem
406 entary information files.

408 **Declarations**

409 **Ethics approval and consent to participate**

410 Not applicable.

411 **Consent for publication**

412 Not applicable.

413 **Competing interests**

414 The authors declare that they have no competing interests.

416 **Author details**

417 ¹Institute of Bioinformatics Complex Network Big Data, Changsha University, Changsha 410022,
418 China. ²Big Data Innovation and Entrepreneurship Education Center of Hunan Province, Changsha
419 University, Changsha 410022, China

References

- [1] Divya M, Wise R P, Dickerson J A, et al. DiffSLC: A graph centrality method to detect essential proteins of a protein-protein interaction network[J]. Plos One, 2017, 12(11): e0187091.
- [2] Giaever G, Chu A M, Ni L, et al. Functional profiling of the *Saccharomyces cerevisiae* genome[J]. Nature, 2002, 418(6896): p.387-391.
- [3] Kamath RS, Fraser AG, Dong Y, Poulin G, Durbin R, Gotta M, Kanapin A, Le Bot N, Moreno S, Sohrmann M, et al. Systematic functional analysis of the *Caenorhabditis elegans* genome using RNAi. Nature. 2003;421(6920):231–7.
- [4] Cullen L M, Arndt G M. Genome-wide screening for gene function using RNAi in mammalian cells[J]. Immunology & Cell Biology, 2005, 83(3): 217.
- [5] Dai W, Chen B, Peng W, et al. A Novel Multi-Ensemble Method for Identifying Essential Proteins[J]. Journal of Computational Biology: a Journal of Computational Molecular Cell Biology, 2021, 28(7).
- [6] Zhang W, Xue X, Xie C, et al. CEGSO: Boosting Essential Proteins Prediction by Integrating Protein Complex, Gene Expression, Gene Ontology, Subcellular Localization and Orthology Information[J]. Interdisciplinary Sciences: Computational Life Sciences, 2021:1-13.
- [7] Estrada E, Rodriguez-Velazquez J A. Subgraph Centrality in Complex Networks[J]. Physical Review E Statistical Nonlinear & Soft Matter Physics, 2005, 71(5 Pt 2):056103.
- [8] Bonacich, Phillip. Power and Centrality: A Family of Measures[J]. American Journal of Sociology, 1987, 92(5):1170-1182.

440 [9] Hahn M W, Kern A D. Comparative Genomics of Centrality and Essentiality in Three Eukaryotic
 441 Protein-Interaction Networks[J]. Molecular Biology & Evolution, 2005(4):803-6.

442 [10] Poulo J M, Amy B, Ingber D E, et al. High-Betweenness Proteins in the Yeast Protein
 443 Interaction Network[J]. Journal of Biomedicine & Biotechnology, 2005.

444 [11] Wuchty S, Stadler P F. Centers of complex networks[J]. Journal of Theoretical Biology, 2003,
 445 223(1):45-53.

446 [12] Wang J, Li M, Wang H, et al. Identification of Essential Proteins Based on Edge Clustering
 447 Coefficient[J]. IEEE/ACM Transactions on Computational Biology & Bioinformatics, 2012,
 448 9(4):1070-1080.

449 [13] Zelen S M. Rethinking centrality: Methods and examples[J]. Social Networks, 1989.

450 [14] Qi Yi, Luo Jiawei. Prediction of Essential Proteins Based on Local Interaction Density [J].
 451 IEEE/ACM Trans on Computational Biology and Bioinformatics, 2016. 13 (6): 1170-1182.

452 [15] Li M, Lu Y, Wang J, et al. A Topology Potential-Based Method for Identifying Essential
 453 Proteins from PPI Networks[J]. IEEE/ACM Transactions on Computational Biology &
 454 Bioinformatics, 2015, 12(2):372.

455 [16] Chung-Yen L, Chia-Hao C, Hsin-Hung W, et al. Hubba: hub objects analyzer—a framework of
 456 interactome hubs identification for network biology[J]. Nucleic Acids Research, 2008, 36(suppl_2):
 457 W438.

458 [17] Jeong H M, Mason S P, AL Barabási, et al. Lethality and centrality in protein networks[J].
 459 Nature, 2001, 411(6833):41-2.

460 [18] Sprinzak E, Sattath S, Margalit H. How reliable are experimental protein–protein interaction
461 data? *J Mol Biol.* 2003;327(5):919–23.

462 [19] Kuchaiev O, Ra?Ajski M , Higham D J , et al. Geometric De-noising of Protein-Protein
463 Interaction Networks[J]. *Plos Computational Biology*, 2009, 5(8): e1000454.

464 [20] Fengyu Zhang, Wei Peng, Yunfei Yang, Wei Dai,Junrong Song. A Novel Method for
465 Identifying Essential Genes by Fusing Dynamic Protein–Protein Interactive Networks. *Genes.* 2019,
466 10(1), 31.

467 [21] Lei X, Yang X, Wu F-X. Artificial fish swarm optimization-based method to identify essential
468 proteins. *IEEE/ACM Trans Comput Biol Bioinform.* 2018;17(2):495–505.

469 [22] Zhao B, Wang J, Li M, Wu FX, Pan Y. Prediction of essential proteins based on overlapping
470 essential modules. *IEEE Trans NanoBiosci.* 2014;13(4):415–24.

471 [23] Xue Z, Xu J, Xiao WX. A new method for the discovery of essential proteins. *PLoS ONE.*
472 2013;8: e58763.

473 [24] Ren R, Wang J, Li M, et al. Prediction of essential proteins by integration of PPI network
474 topology and protein complexes. *Bioinformatics research and applications.* Berlin, Heidelberg:
475 Springer 2011; pp. 12-24. <http://dx.doi.org/10.1007/978-3-642-21260-4-6>.

476 [25] Min L, Zhang H, Wang JX, Yi P. A new essential protein discovery method based on the
477 integration of protein–protein interaction and gene expression data. *BMC Syst Biol.* 2012; 6:1–9

478 [26] Sun W, Wang L, Peng J, et al. A Cross-Entropy-based Method for Essential Protein
479 Identification in Yeast Protein–Protein Interaction Network[J]. *Current Bioinformatics*, 2020, 15.

480 [27] Li S, Chen Z, X He, et al. An Iteration Method for Identifying Yeast Essential Proteins from
481 Weighted PPI Network based on topological and functional features of proteins[J]. IEEE Access,
482 2020, PP (99):1-1.

483 [28] Peng W, Wang J, Wang W, Liu Q, Wu F-X, Pan Y. Iteration method for predicting essential
484 proteins based on orthology and protein–protein interaction networks. BMC Syst Biol. 2012;6(1):1–
485 17.

486 [29] Zhang W, Xu J, Li Y, Zou X. Detecting essential proteins based on network topology, gene
487 expression data, and gene ontology information. IEEE/ACM Trans Comput Biol Bioinform.
488 2016;15(1):109–16.

489 [30] Zhang W, Xu J, Zou X. Predicting essential proteins by integrating network topology,
490 subcellular localization information, gene expression profile and go annotation data. IEEE/ACM
491 Trans Comput Biol Bioinform. 2019;17(6):2053–61.

492 [31] Lei X, Zhao J, Fujita H, Zhang A. Predicting essential proteins based on RNA-seq, subcellular
493 localization and go annotation datasets. Knowl Based Syst. 2018; 151:136–48.

494 [32] B. Zhao, Y. Zhao, X. Zhang, Z. Zhang, F. Zhang, and L. Wang, “An iteration method for
495 identifying yeast essential proteins from heterogeneous network,” BMC Bioinf., vol. 20, no. 1, p.
496 355, Dec. 2019.

497 [33] Dai C, He J, Hu K, et al. Identifying essential proteins in dynamic protein networks based on an
498 improved h -index algorithm[J]. BMC Medical Informatics and Decision Making, 2020, 20(1):1-10.

499 [34] Gavin A-C, Aloy P, Grandi P, Krause R, Boesche M, Marzioch M, Rau C, Jensen LJ, Bastuck S,
500 Dimpelfeld B, et al. Proteome survey reveals modularity of the yeast cell machinery. Nature.
501 2006;440(7084):631–6.

502 [35] Zhong G, Guo X, Ignatchenko A, Li J, Pu S, Datta N, Tikuisis AP, Krogan NJ, Cagney G, Yu H.
503 Global landscape of protein complexes in the yeast *saccharomyces cerevisiae*. *Nature*.
504 2006;440(7084):637–43.

505 [36] Xenarios I, Salwinski L, Duan XJ, Higney P, Kim S-M, Eisenberg D. Dip, the database of
506 interacting proteins: a research tool for studying cellular networks of protein interactions. *Nucleic*
507 *Acids Res.* 2002;30(1):303–5.

508 [37] *Saccharomyces* Genome Deletion Project. [http:// yeast delet ion. stanf ord. edu/](http://yeast-deletion.stanford.edu/).

509 [38] Cherry JM, Adler C, Ball C, Chervitz SA, Dwight SS, Hester ET, Jia Y, Juvik G, Roe T,
510 Schroeder M, et al. Sgd: *saccharomyces* genome database. *Nucleic Acids Res.* 1998;26(1):73–9.

511 [39] Zhang R, Lin Y. Deg 5.0, a database of essential genes in both prokaryotes and eukaryotes.
512 *Nucleic Acids Res.* 2009;37(suppl_1):455–8.

513 [40] Mewes H-W, Frishman D, Mayer KF, Münsterkötter M, Noubibou O, Pagel P, Rattei T,
514 Oesterheld M, Ruepp A, Stümpflen V. Mips: analysis and annotation of proteins from whole
515 genomes in 2005. *Nucleic Acids Res.* 2006;34(suppl_1):169–72.

516 [41] Östlund G, Schmitt T, Forslund K, Köstler T, Messina DN, Roopra S, Frings O, Sonnhammer
517 EL. Inparanoid 7: new algorithms and tools for eukaryotic orthology analysis. *Nucleic Acids Res.*
518 2010;38(suppl_1):196–203.

519 [42] Tu BP, Kudlicki A, Rowicka M, McKnight SL. Logic of the yeast metabolic cycle: temporal
520 compartmentalization of cellular processes. *Science.* 2005;310(5751):1152–8.

521 [43] Holman AG, Davis PJ, Foster JM, Carlow CK, Kumar S. Computational prediction of essential
522 genes in an unculturable endosymbiotic bacterium, Wolbachia of Brugia malayi. BMC Microbiol.
523 2009;9(1):243.

524 [44] Davis J. The Relationship Between Precision-Recall and ROC Curves[C]// Proceedings of the
525 23th International Conference on Machine Learning, 2006. 2006.

526 [45] D. Horyu, T. Hayashi. Comparison between pearson correlation coefficient and mutual
527 information as a similarity measure of gene expression profiles, Jpn. J. Biometrics, vol. 33, no. 2, pp.
528 125–143, 2013.

529