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Computational Prediction of Protein–Protein Interaction Networks: Algorithms and Resources

Javad Zahiri, Joseph Hannon Bozorgmehr and Ali Masoudi-Nejad*

Laboratory of Systems Biology and Bioinformatics (LBB), Institute of Biochemistry and Biophysics, University of Tehran, Iran

Abstract: Protein interactions play an important role in the discovery of protein functions and pathways in biological processes. This is especially true in case of the diseases caused by the loss of specific protein-protein interactions in the organism. The accuracy of experimental results in finding protein-protein interactions, however, is rather dubious and high throughput experimental results have shown both high false positive beside false negative information for protein interaction. Computational methods have attracted tremendous attention among biologists because of the ability to predict protein-protein interactions and validate the obtained experimental results. In this study, we have reviewed several computational methods for protein-protein interaction prediction as well as describing major databases, which store both predicted and detected protein-protein interactions, and the tools used for analyzing protein interaction networks and improving protein-protein interaction reliability.

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1. INTRODUCTION

Protein–protein interactions (PPIs) are of interest in biology because they regulate roughly all cellular processes, including metabolic cycles, DNA transcription and replication, different signaling cascades and many additional processes. Proteins carry out their cellular functions through concerted interactions with other proteins, so it is important to know the specific nature of these relationships. Indeed, the importance of understanding these interactions has prompted the development of various experimental methods used in measuring them**.** While the amount of genomic sequence information continues to increase exponentially, the annotation of protein sequences appears to be somewhat lagging behind, both in terms of quality and quantity. Multi-pronged, high-throughput functional genomics approaches are needed to bridge the gap between raw sequence information and the relevant biochemical and medical information. Therefore, computational methods are required for discovering interactions that are not accessible to high throughput methods. These computational predictions can then be verified by using more labor-intensive methods. A number of computational approaches for protein interaction discovery have been developed over recent years. These methods differ in feature information used for protein interaction prediction. Many studies have demonstrated that knowing the tools and being familiar with the databases is important for new research in protein-protein interaction analysis to be conducted [1-7]. The scope of this review focuses on describing these resources.

*Address correspondence to this author at the Laboratory of Systems Biology and Bioinformatics (LBB), Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran; Tel: +98-21-6695-9256; Fax: +98-21-6640-4680; E-mail: amasoudin@ibb.ut.ac.ir

2. DATABASES

Through recent rapid advances in high-throughput technologies, massive protein-protein interaction data of various organisms have become available and are currently stored in several databases. More than 100 PPI related repositories have been published and are available online [8], these databases can be used as the major data for evaluating prediction methods. Many of these PPI data providers are independently funded and do their works in isolation and often contain redundant data from overlapping sets of publications. The issue of the integrating data from PPI disparate repositories began with the efforts of the Human Proteome Organization Proteomics Standards Initiative (HUPO-PSI) and International Molecular Exchange (IMEx) consortium and followed by publishing the 'minimum information about a molecular interaction experiment' (MIMIX) guidelines [9]. The HUPO-PSI has developed the PSI-MI XML format to establish a single, unified format for PPI data. Additionally, a simplified tabular format, MITAB has been developed [10]. The IMEx is an international collaboration between a group of major public interaction data providers who have agreed to share literature-curation efforts and make a nonredundant set of PPI available in a single search interface on a common website (http://www.imexconsortium.org/) [8]. IMEx defines three types of membership: Active: IMEx partner commits to producing relevant numbers of records curated to IMEx standard and providing these via a Proteomics Standards Initiative common query interface (PSICQUIC) service. Observer: Prospective IMEx consortium member. Inactive:

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former IMEx partner that contributed to the establishment of the IMEx curation rules. The PSICQUIC is a web service aimed at enabling users to access multiple interaction databases with a single query and standardizing the programmatic access to molecular interaction databases [11].

(Supplementary table **S1**) shows almost all active databases on the PPI, but in the following we focus on the most popular repository (which has more than 1000 citations according to Google scolar at the time of writing this manuscript, May 2013) in more detail, (see Table **1**) for feature by feature comparesion of these databases.

BioGRID [12, 13], the General Repository for Interaction Database, is one of the most comprehensive databases of experimentally determined protein-protein interactions. It has continuously been updating the source of protein and genetic interactions from major model organisms (by the time of writing this manuscript, Feb-2012, contains 27 different organisms) compiled through comprehensive curation efforts, it comprises more than 460000 interactions and all interaction data are freely available for download in a wide variety of standardized formats, more over, this repository supplies information about the experimental methods used for interaction detection. This database does not contain information about multi-protein complexes larger than dimers and lists any interaction as pairwise interactions.

The Database of Interacting Proteins (***DIP***^{TM})[14] developed at the University of California, Los Angeles has combined data from a variety of sources to create a single, consistent set of PPI. In addition to the primary sources, DIP drives its data from a number of other databases such as Yeast Protein Database (YPD) [15], EcoCyc [16], and FlyNet [17], Kyoto Encyclopedia of Genes and Genomes (KEGG)[18]. The complete DIP dataset are freely available for download as well as specialized DIP subsets and additional data (free registration required), the database contains more than 460 organisms.

The Biomolecular Interaction Network Database (***BIND)*** [19, 20], is a component of BOND (the Biomolecular Object Network Databank). This repository was created at the University of Toronto. It contains more than 200,000 interactions of more than 1500 organisms and it holds a large variety of interaction data including those curated by a team of curators. Although, the majority of BIND is the protein interactions data, BIND also contains many other types of interactions involving RNA, DNA, genes, complexes and small molecules. Although BIND curation stopped in 2005, BIND still remains a highly cited publicly available interaction database, because the BIND data is not available in a standard format from the official source, recently [21] a translation of BIND in the Proteomics Standard Initiative-MI (PSI-MI) 2.0 format was publicly available which makes the BIND data compatible with current software tools.

The Molecular Interaction Database (***MINT***) [22, 23] developed by the University of Rome Tor Vergata, interaction data and various experimental details are mined from published literature by using a literature-mining program, the MINT assistant, then expert curators establish the putative interactions. Currently MINT contains more than 230,000 interactions and more than 34,000 proteins and focused on the model organisms, this database provides confidence scores for experimentally detected PPIs, which show the reliability of the interactions. MINT is an active partner of IMEx and shares curation efforts and supports the Protein Standard Initiative (PSI) recommendation.

The Human Protein Reference Database (***HPRD*** [24-26]) was built as a cooperative effort between Johns Hopkins University and the Institute of Bioinformatics, this resource provides a collection of human protein-protein interaction. Data are manually extracted from the literature, and each record is linked to a detailed piece of information including post-translational modifications, disease associations via OMIM for each protein in the human proteome, subcellular localizations, enzyme–substrate relationships, protein isoforms and domain architectures. This database currently contains more than 30,000 proteins and more than 39,000 protein-protein interactions.

IntAct [27-29] is a molecular interaction database that its data come from the literature or from direct data depositions, IntAct source code and data are freely available for download. Currently this resource contains more than 60,000 proteins and more than 290,000 binary interaction evidences abstracted from more than 5000 scientific publications. IntAct is an active partner of the IMEx consortium, and the majority of its protein-protein interaction data is annotated to IMEx standards. In addition to protein-protein interaction data, IntAct also includes information on DNA, RNA, and small-molecule interactions.

3. COMPUTATIONAL METHODS FOR PROTEIN-PROTEIN INTERACTION PREDICTION

In general, the available methods for predicting protein-protein interaction can be divided into four main categories: methods based on genomic context and structural information, methods that use network topology to predict protein-protein interaction, methods that detect protein-protein interaction by using text mining and literature mining (or database search) and, finally, methods based on machine learning algorithms utilizing heterogeneous genomic/proteomic features (see Table **2** for a general overview). In the following section we describe each of these methods and their application.

3.1. Methods Based on Genomic Context and Structure Information

3.1.1. Gene Neighboring

Gene neighboring or co-localization of genes is one of the first and simplest methods for protein–protein interaction prediction methods based on the genomic context [45-47]. The main idea is that related genes are located close to one another in the genome (Fig. **1**). Like many other genome-context approaches, the predictions of this method become more confident with larger numbers of genomes [48]. Contrary to prokaryotic organisms, the tendency of being located at a close genomic distance is not evident regarding related genes in eukaryotes, so a major limitation of this method is that it is not applicable in the eukaryote genomes without a doubt especially when there are no homologues in prokaryotes. While its simplicity is a benefit, this method may

Table 1. The Most Popular Repository (Which Have More Than 1000 Citations According to Google Scolar at the Time of Writing this Manuscript, May 2013) on the PPI, for Detailed Description About These Repository Refer to the Text

Acronym	Organisms	Number of Interactions	Curated to IMEx/MIMIx standards	IMEx Partner	Accept submis-sion in PSI-MI format	Avail-ability	PSIC-QUIC service	Last Content Update	URL	References
BioGrid (IMEx partner)	Model organisms	279409	IMEx	Yes (Observer)	No	Free to aca-demic users	Yes	2013	http:// www.thebiogrid.org	[30-32]
BIND/BOND (IMEx partner)	H. sapiens, S.cerevisiae, M. musculus, H. pylori	198,905	No	Yes (Inactiv)	Yes (submis-sion by email)	Free to all users	Yes	2004	http://download.baderlab.org/ BINDTranslation/	[21, 33-35]
DIP/ LiveDIP (IMEx partner)	Model organisms	73268	IMEx	Yes (Active)	Yes (submis-sion by email)	Free to aca-demic users	Yes	2005	http://dip.doe-mbi.ucla.edu	[36-40]
HPRD	Human	30,047	No	No	Yes (submis-sion by email)	Free to aca-demic users	No	2009	http:// www.hprd.org	[24-26, 41]
IntAct (IMEx partner)	Model organisms	290,891	IMEx/MIMIx	Yes (Active)	Yes (submis-sion by web-based tool)	Free to all users	Yes	2011	http:// www.ebi.ac.uk/intact/	[28, 29, 42, 43]
MINT (IMEx partner)	Model organisms	241458	IMEx	Yes (Active)	Yes (submis-sion by email)	Free to all users	Yes	2011	http://mint.bio.uniroma2.it/mint	[22, 23, 43, 44]

Table 2. A General Overview of Computational Methods for Protein-Protein Interaction Prediction with Their References, for Description About Methods Refer to the Text

Method		Features	References
Methods based on genomic context and structure infor-mation	**Gene fusion**	• Usually used for small scale proteome. • Is not generally applicable to all genes. • Fusion event not abundant, especially in prokaryotes. • It is very reliable.	[54, 55]
	Gene neighboring	• Usually used for small scale proteome. • Relatively simple. • Prone to produce false negatives. • Results dependent on the number and distribution of used genomes.	[46, 47, 123]
	Phylogenetic similarity	• Needs complete genome • Results are dependent on the number and distribution of used genomes. • Cannot be applied to essential proteins	[50-52, 124-126]

(Table 2) contd….

Method		Features	References
	Sequence and primary structure	• Relatively simple. • Can be used for large scale proteome. • Need to interpret the features importance.	[65-74]
	Structure based	• Tend to be more limited in terms of scale. • Allow a detailed analysis of PPI.	[56-64, 127-129]
Methods based on machine learning algorithms with utilizing multiple genomic/proteomic features	**Decision tree and random forest**	• Copes well with high-dimensional data. • Copes well with missing values. • The pattern in the data can be easily explained.	[73, 121, 122, 130, 131]
	KNN	• Simple to understand. • Requires no training. • The computational cost and memory requirement grows rapidly with increasing feature vectors dimension.	[118].
	MLP	• Good generalization capabilities. • It looks like a black box.	[110, 111]
	Naïve Bays	• Assumption for independence between features. • Simple and easy to interpret. • Copes well with missing values.	[71, 74, 115-117]
	SVM	• Copes well with high-dimensional data. • It is very powerful. • The parameters can greatly affects the results.	[70, 104-106]
Other methods	**Using network topology for predicting protein-protein interaction**	• Results can be affected by false positives and network completeness.	[78-85]
	Text mining methods	• Results may not be reliable as manually curated data, but the fast growth of published biomedical literature can make these methods more confident.	[90-97, 99, 100]

produce some false negative results because fails to recognize the interaction between related but distantly located genes. Another drawback of gene neighbouring method is that the choice of reference genomes can affect the performance of the method [49].

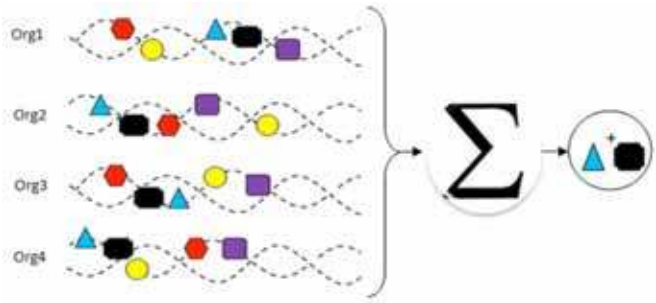

Fig. (1). Gene neighboring method for protein–protein interaction prediction, the main idea is that related genes are located close to one another in the genome. For example the black and blue proteins predict to interact (plus sign indicates the interaction between proteins).

3.1.2. Phylogenetic Relationship

In this method, the interaction of proteins will be detected based on "phylogenic profile" similarity [50-52], phylogenetic profile for a given protein is a binary vector that reflects the presence or absence of that protein across a set of organisms (Fig. **2**), this method is a flexible version of the gene neighboring method which can detect some interaction that gene neighboring method fails to detect. The basic idea is that functionally related genes remain together across many distant species for playing a role in a biological process. However, this powerful method has three important drawbacks. The first is that the number and distribution of the genomes that used can influence the results dramatically [49]. The second is that it cannot be applied to essential proteins that presents in almost all organisms, and third drawback is that this method only can run on the complete genomes [48].

3.1.3. Gene Fusion

It has seen that separate related genes, probably to reduce the regulatory load of multiple interacting gene products, can

be fused into a single multi-functional gene, a so-called "Rosetta Stone" protein. For example, topoisomerase II is a fusion result of Gyr A and Gyr B subunits of Escherichia coli DNA gyrase [53]. The gene fusion method uses comparative genomics and evolutionary information [54, 55] and so can be considered as complement of gene neighboring and phylogenetic profile methods (Fig. **3**). A major advantage of this method is its reliability, because the existing gene fusion events are very informative about functional relationship. One of the drawbacks of this method is that fusion event not abundant, especially in prokaryotes [48].

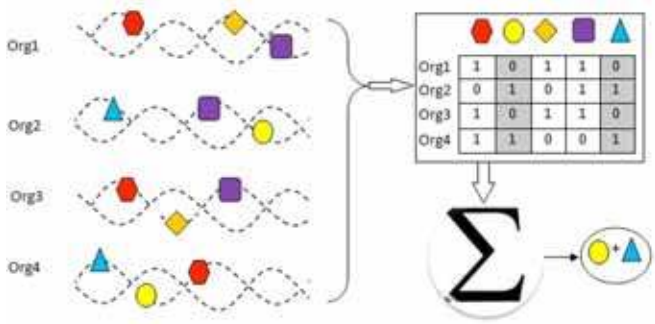

Fig. (2). Protein-protein interaction detection based on phylogenic profile similarity. Phylogenetic profile for every protein is a binary vector that reflects the presence or absence of that protein across a set of organisms. (plus sign indicates the interaction between proteins).

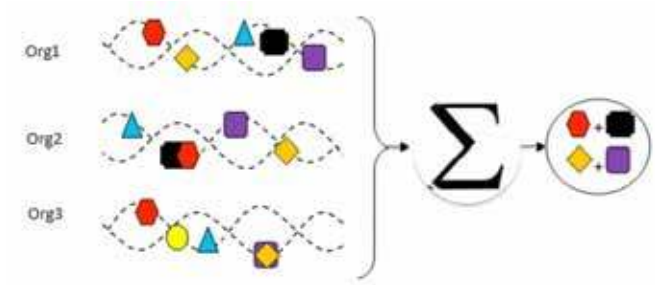

Fig. (3). Gene fusion method for protein-protein interaction detection. In this method, the complete genome comparison must be done across multiple organisms: if two separate proteins in one organism fused in another organism then one can conclude they interact. (plus sign indicates the interaction between proteins).

3.1.4. 3D Structure Based

This method uses three-dimensional (3D) structure information to predict interactions, the information from predicted interactions also can be used for predicting interaction between new proteins that are homologous with previously predicted interacting proteins [56-63]. This method need accurate dimensional structures (Fig. **4**) and so cannot be used for a large number of proteins, because the number of known 3D structures in the Protein Databank (PDB) is limited, recently a genome-wide scale method based on structure information for PPI prediction that have used homology models when three dimensional structures were asbsent [64]. In comparison to other methods the results of this method have more details such as interacting residue and biophysical characteristics of the interaction.

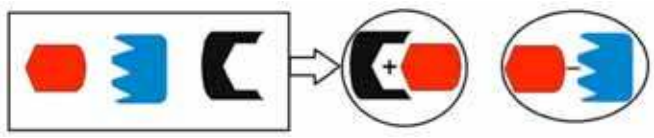

Fig. (4). Use three-dimensional (3D) structure information to predict interactions, this method need accurate dimensional structures.

3.1.5. Primary Structure

The information gained from protein sequences have been used in a number of Bioinformatics researches such as protein subcellular localization or protein recognition, in recent year sequence information also used for protein-protein interaction prediction [65-74]. Primary protein structure approaches predict protein-protein interaction typically based on the short conserved polypeptide such as signatures [66, 67, 69] or sequence similarity and k-let count (subsequences with length k) [70, 74-77].

3.2. Methods Based on Network Topology

Like in many real-world networks, protein-protein interaction networks in various organisms share common topological features which make these networks different from random networks. These topological features have been used as evidence to discern the difference between interactions that represent true positives and those that are false positives. These have allowed researchers to assign an improved confidence score to each interaction [78].

Analyzing the PPI networks from topological perspective is crucial for a better understanding of the underlying evolutionary mechanisms and network dynamics that shape the network. Because the network theory is a relatively new field, so for determining the significance of topological properties in a given PPI network, the properties are compared against those in random networks and then confidence scores are assigned to PPIs. Finally based on these scores some of intearctions can be eliminate and some other can be added to the network [79-85]. One problem is how to create random networks for comparison, usually the number of vertices and edges are held constant so that we can determine which properties are significant.

A random graph model is a model for generating graphs by random process that uses graph theory and probability theory. Random graph was defined in 1959 in two independent studies for the first time [86, 87]. ErdÖs-Rényi model is a model for a random graph generation, in this model the number of vertices in the random network is equals the number of vertices in the original protein-protein interaction network and the probability of an edge existing between any two vertices is equal to the edge density and is independent of other edges, so roughly speaking this model generates a network with the same number of edges and vertices. But this model is not a suitable random model for determining the significance of protein-protein interaction network properties, because many topological properties of these networks are different from protein-protein interaction networks.

Some of the most important topological concepts of protein-protein interaction networks are as follows: (in this section we consider the protein-protein interaction network as a

graph G=(V, E) in which V and E are vertex set and edge set of the graph respectively, we also suppose that the number of vertices are *n* and the number of edges are *e*)

Degree: for a vertex *v* shows the number of its interactions and represent as *deg(v)*

Degree Distribution: indicate the number of vertices whit different degree.

Hub: nodes with high degree called hub which suggested having an important role in cellular processes.

k-core: A subgraph of the network where every vertex in the subgraph has degree greater than k-1 within that subgraph.

Edge Density: is the ratio of the number of network edges to the maximum possible number of edges that can be computed as equation 1:

$$1.\ ED = \frac{\sum_{v \in V} deg(v)}{n(n-1)}$$

Clustering Coefficient (CC): for a vertex such as *v* if E_v shows the maximum number of possible interactions between neighbors of *v* and F_v shows the number of neighbors of *v* that interact with each other then clustering coefficient for *v* is defined as follows:

$$2.\ cc(v) = \frac{F_v}{E_v}$$

For a network clustering coefficient define as the average clustering coefficient over all vertices:

$$3.\ CC = \frac{1}{n} \sum_{v \in V} cc(v)$$

Path length: the least number of edges needed to reach from one vertex to another called the path length between them.

Average path length: the average path length over all possible vertex pairs in the network.

Diameter: the maximum path length in the network.

Centrality: in general centrality is a structural attribute of nodes or edges that shows the importance of those nodes or edges in the network. There are many centrality measures, however, we describe three of the most popular centrality measures below:

Degree centrality: it is the simplest centrality measure, which is defined as the number of edges incidences with that node, in the normalized version the degree is divided by the maximum possible degree.

Closeness centrality: this measure is based on the distance of a node to all other nodes in the graph and is precisely defined as follows:

$$4.\ C_c(v) = \frac{1}{\sum_{u \in V} dist(u, v)}$$

Betweenness centrality: betweenness centrality for a node *v* is defined as the number of shortest paths passing through *v*, this measure can be defined for an edge in the same way. A protein with high betweenness centrality value has great influence over information flows in the whole network. In spite of closeness centrality, betweenness centrality can be used for disconnected networks.

Motif: A subgraph of the network which its occurrences are significantly high (more than expected at random).

Protein-protein interaction networks of different species interestingly have many common topological features. PPI networks are also said to have a *power-law* degree distribution, which means there are a few nodes with many connections and many nodes with few connections and so the degree distribution of the PPI networks is heavy-tailed (*power-law* degree distribution)[88, 89]. Another feature in protein-protein interaction networks compared to random networks is having a high clustering coefficient: the interaction probability of the neighbors of two interacting proteins is significantly high. Unlike the high clustering, the average path length in the PPI networks is short. Protein-protein interaction networks are referred to as *small-world* networks because of having a high clustering coefficient and a short average path length.

In addition to being used to predict protein-protein interaction, topological properties of protein-protein interaction networks have been used to predict proteins function, finding protein complexes and finding functional modules.

3.3. Methods Based on Text Mining and Literature Mining

PubMed is expanding at the rate of approximately one paper every thirty seconds; this fact shows the importance of the biomedical literature mining approaches. Some methods use text mining and literature mining algorithms and use the information of co-occurrence of the proteins in the PubMed abstracts approaches for protein-protein interaction prediction [90-100]. In general, each literature mining system consists of three steps (Fig. **5**):

Named Entity Recognition or *NER* step, it does the identification task of protein names which is a crucial step for further analyzing. *Zoning* step, in which the text is split into basic building blocks and sentences are extracted from the text. *Protein–protein interaction extraction* step that uses various algorithms to infer protein-protein interaction. Current biomedical literature mining approaches for detecting protein-protein interactions can be divided into three categories:

Computational natural language processing (NLP) and linguistics-based methods, which define a grammar and use parsers to detect protein-protein interaction. Rule-based methods, these methods infer protein-protein interaction using a set of context specific rules or patterns. Machine learning approaches which don't need rules or grammar but some classifiers learn the pattern that enables them to identify protein-protein interaction from a training set.

This automated data mining results may not be as reliable as manually curated data, but the fast growth of published biomedical literature can make these methods more confident. (Supplementary Table **2**) shows literature and text mining tools for protein-protein interaction.

3.4. Methods Based on Machine Learning Algorithms with Utilizing Heterogeneous Genomic/Proteomic Features

Some other methods use heterogeneous biological data such as gene expression, codon usage [71, 101], k-let count (subsequences with length k) [70, 74-77] and physicochemical properties of amino acids [77, 102] to learn a model for predicting PPI. These methods integrate biological data sources provided by high-throughput technologies to feature vectors and use machine learning approaches to learn and predict PPI from these feature vectors (some of these methods mentioned previously as another method specially as sequence based methods, but now we focus on machine learning algorithms that were used in those studies). Generally speaking, a machine learning algorithm (classifier) for protein-protein interaction prediction uses a set of various features (or descriptors) of the proteins or protein pairs with known interaction and non-interaction as learning set to learn which proteins interact and which do not interact, and then the algorithm can classify new protein pairs to interacting or non-interacting classes. There are particular machine learning algorithms used to address protein-protein interaction prediction problem, we shall briefly describe these methods in the following context.

Support vector machines (SVM) or kernel machines are widely used in bioinformatics and computational biology for classifying biological data [103] as well as protein-protein interaction prediction [70, 104-106]. The support vector machine (SVM) classifier is underpinned by the idea of maximizing the margins. Intuitively, the margin for an object is related to the certainty of its classification (see Fig. **6**). Objects for which the assigned label is correct and highly certain will have large margins and objects with uncertain classification are likely to have small margins [107]. An SVM can be trained using a labeled training dataset, each data marked as belonging to one of two classes, to build a model that could predict class labels for new examples. SVM is extremely powerful and can classify problems with arbitrary complexity, but it is complex and has large memory requirements also it is a little slow to train and evaluate. Another drawback of this classifier is that the parameters can greatly impact the results [103]. For more details, we refer the interested reader to [108, 109].

Artificial neural networks (ANNs or simply NNs) originated from the idea to model mathematically human intellectual abilities by biologically plausible engineering designs. One of the most popular NN models is the multilayer perceptron (MLP) [107], MLP is a tool used for modeling PPI with good performance [110, 111]. However, MLP has been criticised as being a black-box classifier because it is difficult to know what the model parameters mean [112]. An MLP is a feedforward artificial neural network, which consists of multiple layers and each layer is fully connected to the next layer with weighted edges. Typically there are three layers: input layer, hidden layer (intermediate layer) and output layer, each node at the hidden and output layer is a neuron with an activation function, this node contains the processing units of an MLP. The weights of the edges are optimized and adjusted on the training dataset to minimize classification error using a supervised learning approach. (Fig. **7**) shows a schematic representation of a MLP for protein-protein interaction prediction. For more details, we refer the interested reader to [113].

Naïve Bayes is a probabilistic classifier that is based on Bayes' theorem and it is a popular algorithm owing to its simplicity (the source of simplicity is the assumption that the independent variables are statistically independent.), computational efficiency and easy to interpret. In spite of the simplicity of this classifier, it turns out that Naïve Bayse works quite well in problems involving normal distributions, which are very common in real-world problems. Naive Bayes classifiers can be trained efficiently on a small training dataset in a supervised learning approach using maximum likelihood, but in the more complex classification problem it may work not well [114]. This method has been widly used in PPI prediction problem [71, 74, 115-117].

K-Nearest neighbors (K-NN) is one of the simplest machine learning classifiers that is a prototype method for classifying objects, which assign labels to each object based on the K closest objects (parameter K must be set by user) in the feature space according to majority vote, in contrast to other statistical methods, K-NN requires no explicit training (because the choice of K is very crucial in this method, optimizing K can be considered as a kind of learning). In spite of its simplicity to implement, when a large data set or numerous features are used the computational cost and memory requirement grows rapidly. This method has been used (not widely) in PPI prediction problem [118]. For more details, we refer the interested reader to [119].

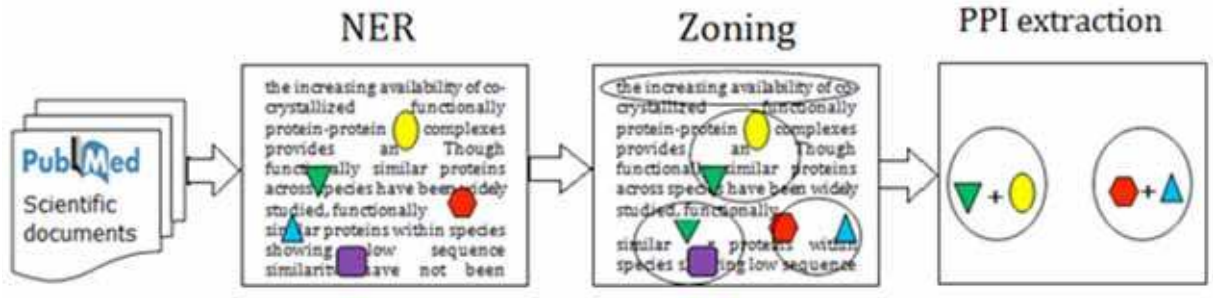

Fig. (5). The schematic text mining approaches for protein-protein interaction prediction, In general, each literature mining system consists of three steps: *Named Entity Recognition* or *NER* step, it does the identification task of protein. *Zoning* step, in this step the text split into basic building blocks and extract sentences from the text. PPI step that uses various algorithms to infer protein-protein interaction.

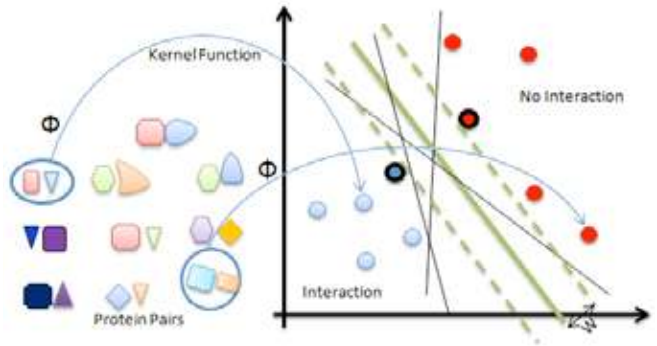

Fig. (6). Schematic view of SVM classifier: At the first step, using a function that is called "kernel function" (and is denoted by Φ) the protein pairs are transformed into points in a new space (presumably making the classification easier in this space). Then, the best separating hyperplane (separating line in this figure) is selected as the boundary of two classes, in this example each three thin black lines and the thick green line are separating lines. The margin for a separating hyperplane is the shortest distance from that hyperplane to the closest positive or negative example; in this figure the margin of thick green line is denoted by 'w'. The best separating hyperplane is the one with the maximum margin; in this example the thick green line is the best separating line (closest points to the best separating hyperplane are called support vectors, the support vectors are circled in the figure).

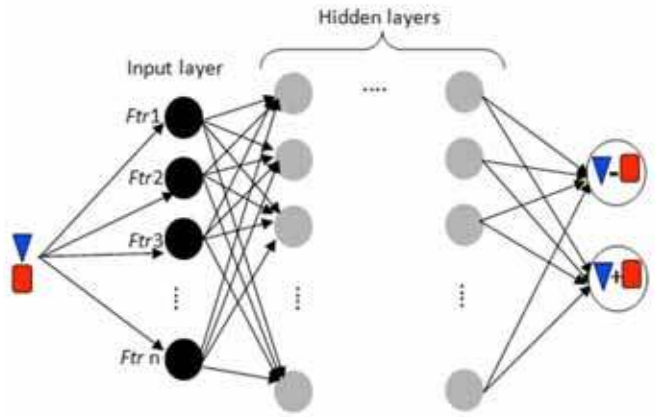

Fig. (7). A Multilayer Perceptron (MLP), which consists of multiple layers and each layer is fully connected to the next layer with weighted edges. Typically there are three layers: input layer, hidden layer (intermediate layer) and output layer, the features (feature abbreviated as ftr in the figure) of every protein pairs is delivered to the input layer for classifying. Each node at the hidden and output layer is a neuron with an activation function, these nodes are the processing units of an MLP. Neuron at output layer classify input protein pair into interacting (which is denoted by a '+' sign between two proteins) or non-interacting (which is denoted by a '-' sign between two proteins) class. The weights of the edges are optimized and adjusted on the training dataset to minimize classification error using a supervised learning approach.

Decision tree or classification tree is a popular machine learning classifier, which has great applications in bioinformatics and computational biology and has shown to be one of the best classifier for protein-protein interaction prediction. In these trees, internal node test features, each branch correspond to feature value and finally leaves assigns a class label (Fig. **8**). In the training phase, training dataset is partitioned into the subsets according to the feature values and this process is recursively done on the subsets until splitting no effect on the classification. Concerning various aspects of optimality, constructing the optimal decision tree is an NP-complete problem and so practical decision tree construction algorithms such as ID3, C4.5 and CART employ a heuristic search [114]. In addition it is efficient from computational cost and memory requirements points of view. This classifier is prone to overfitting and in some applications it may not have good generalization, but compared with other classifiers such MLP the pattern in the data can be easily explained with classification trees [112].

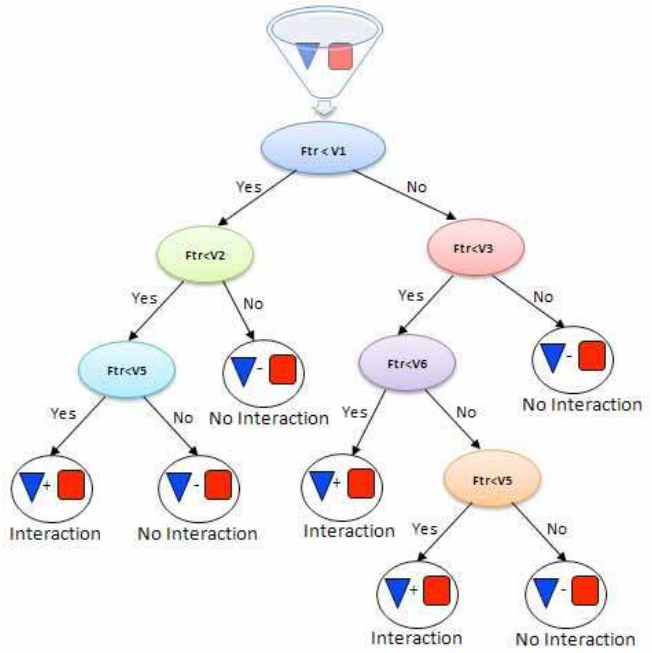

Fig. (8). Decision tree or classification tree, in these trees internal nodes tests features (in each internal node corresponding feature is compared with a value), each branch corresponds to features value and finally leaves assigns a class label (positive or negative for interacting and non-interacting respectively).

Random forest (RF) algorithm is a classification method that consists of many decision trees (Fig. **9**), in training phase each tree is constructed based on random feature vectors sampled from a data set independently and for every node in a tree, a small fraction of the variables are randomly selected and then each classification tree is completely grown. To classify a new object, put the input vector down each of the trees in the forest, and finally according to the majority voting one class is assigned to the object. The RF is a practical classifier when there are a large dataset and large number of features and no need to feature selection or feature deletion, also it can rank features according to importance for classification. In addition RF can be used for recovering missing data, but in some databases containing noisy data RF may be overfit [114]. Decision trees and random forest are widely used in bioinformatics and computational biology for classifying biological data [120] especially for PPI prediction [73, 121, 122].

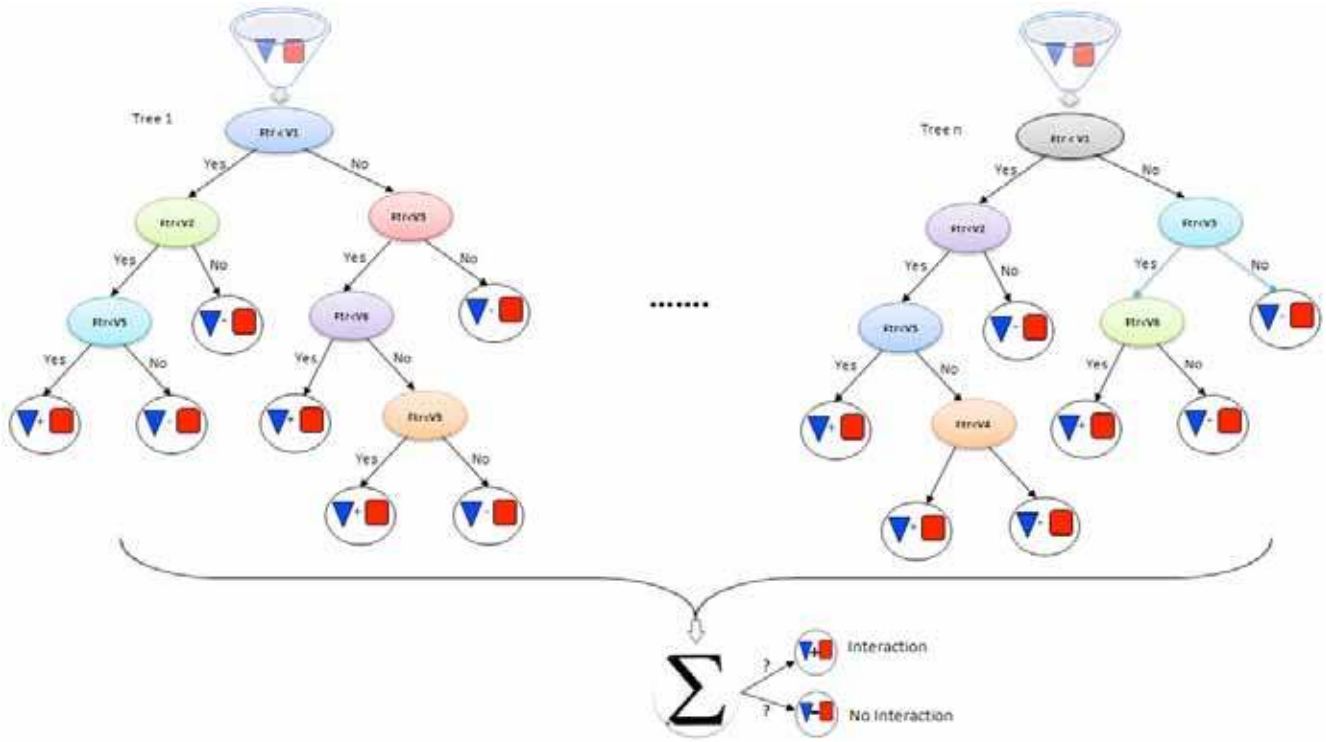

Fig. (9). The random forest (RF) classifier, which consists of many decision trees. To classify a new object, put the input vector down each of the trees in the forest, and finally according to the majority voting one class assign to the protein pair.

4. RESULTS ASSESSMENT

The need for gold standard data sets, which contain both positive and negative interactions, to evaluate performance of methods for PPI prediction is a critical problem in protein-protein interaction prediction. Each available database of protein-protein interaction contains positive interactions which may also include many false positives (interactions that are not biologically real and are produced due to tools biases and errors). The most complex part is in selecting negative examples (non-interacting proteins), benchmark data can affect the performance results and may lead to over-estimating the prediction performance [132, 133]. Recently two web based systems have been developed for constructing benchmark protein-protein interaction data [134, 135] and some high quality PPI data sets have been published for model organisms [136-138]but researches about constructing gold standard datasets for PPI prediction had conflicting results [132, 133, 139] and it seems there is need for more efforts. After constructing a gold standard dataset, the prediction performance could be assessed with different measures based on four following basic parameters:

TP (True Positive or hit): the number of interactions predicted correctly.

TN (True Negative or correct rejection): the number of non-interactions predicted correctly.

FP (False Positive or type I error): the number of non-interactions predicted incorrectly as interaction.

FN (False Negative or type II error): the number of interactions predicted incorrectly as non-interaction.

(Table **3**) lists the important measures for evaluating prediction methods. In addition to these measures, one popular graphical tool for assessing the classification performance is ROC (receiver operating characteristic) curve which plots sensitivity (true positive rate) vs. one minus the specificity (true negative rate), which each of them changes between 0 and 1. The ROC curve shows the tradeoff between sensitivity and specificity (see Fig. **10**), and the closer the curve follows the left-hand border and then the top border of the ROC space, the more accurate the classifier, and the closer the curve comes to the diagonal of the ROC space, the less accurate the classifier and closer to the random classifier. The area under the ROC curve (AUC or "Area Under Curve"), is another measure of classification accuracy, the closer the AUC to one the more accurate the classification. It is argued that reporting accuracy and precision can be misleading but AUC has proved to be a reliable performance measure for imbalanced problems like PPI prediction [140, 141] there are many tools for evaluating and visualizing the performance of classifiers [142, 143].

5. TOOLS FOR ANALYZING AND VISUALIZING PROTEIN-PROTEIN INTERACTION

After constructing the protein-protein interaction, researchers need to visualize and analyze the networks. In recent years, many tools and software tools have been developed for this purpose; (Table **4**) briefly discusses some of the popular tools used for the analysis and visualization of biological networks. In the following section, some of the most popular instances of these tools are described in detail.

Cytoscape [144-146] is a free software package, which is one of the most popular protein-protein interaction visualiza-

Table 3. Important Measures to Evaluate Prediction Methods with Brief Descriptions

Measure	Description	Formula
Precision	Measures what fraction of the positive interaction prediction is correct.	$\frac{TP}{TP+FP}$
Accuracy	Measures the accuracy of the predictor with assigning the same weight to positive and negative interactions.	$\frac{TP+TN}{TP+FP+TN+FN}$
Error rate	Measures the error rate of the predictor with assigning the same weight to positive and negative interactions.	$\frac{FP+FN}{TP+FP+TN+FN}$
Sensitivity (recall or coverage) or TPR (true positive rate)	Measures what fraction of the real positive interactions was correctly identified by the predictor.	$\frac{TP}{TP+FN}$
Specificity (True Negative Rate)	Measures what fraction of the real negative interactions was correctly identified by the predictor.	$\frac{TN}{TN+FP}$
Matthews Correlation coefficient (MCC)	Measures correlation between the actual and predicted interactions.	$\frac{TP\times TN - FP\times FN}{\sqrt{(TP+FP)(TP+FN)(TN+FP)(TN+FN)}}$

tion and data integration tools. It has many interesting features such as custom node graphics and attribute equations, with these features the user can project images onto nodes and use spreadsheet-like functionality capability for more enhanced network visualization (supplementary Fig. **S1**). This software provides complex network searches, filtering operations and many other analysis options.

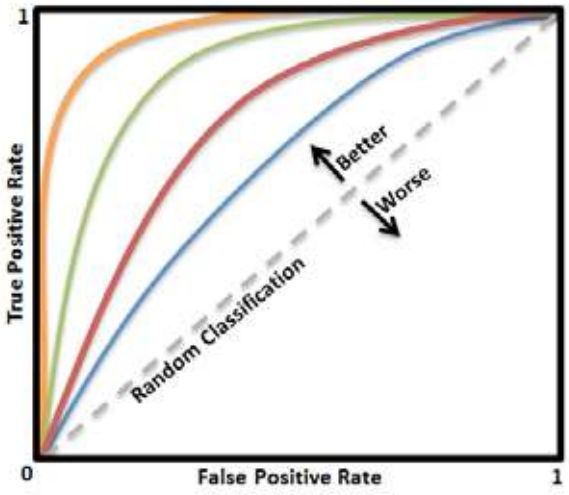

Fig. (10). The ROC curve is a plot of the true positive rate against the false positive rate, it shows the tradeoff between sensitivity and specificity. The closer the curve follows the left-hand border and then the top border of the ROC space, the more accurate the classifier, and the closer the curve comes to the diagonal of the ROC space, the less accurate the classifier and closer to the random classifier. If two ROC curves do not intersect, the upper one dominates the other (in this example the orange curve is the best and the blue curve is the worst).

Medusa is a powerful Java standalone application for visualization of large-scale biological networks in 2D, it also implements various clustering algorithms: k-Means, spectral, predefined clustering and affinity propagation. It is very interactive and uses a variety of layout and methods (Grid, random, circular, hierarchical, fruchterman-reingold, spring embedding, distance geometry and parallel coordinates) for more intuitive visualizations. It also supports varieties of graphs such as weighted and unweighted multi-edged directed and undirected graphs. Medusa has some other interesting features: it is compatible with many other tools, have up to10 types of connections, have search functionality, the user can collapse/expand nodes and provides color schemes. This software allows users to load an arbitrary image as a background for more descriptive visualizations (supplementary Fig. **S2**).

NAViGaTOR is a graphing tool for the 2D and 3D visualization of biological networks which has been implemented in Java and is freely available for researchers, it can be installed on Windows, Mac, Linux and Unix. (Supplementary Fig. **S3**) shows NAViGaTOR interface and one rendered network. This software uses hardware acceleration to facilitate the visualization of large networks. It supports some popular data interchange formats, such as PSI-MI, BioPAX and GML makes it compatible with other tools. NAViGaTOR includes many functions for network analysis and visualizing options and allows the user to generate high quality images, it also can be extended through an application programming interface (API).

6. FUTURE DIRECTION AND CONCERNS: EVOLUTION OF PROTEIN-PROTEIN INTERACTION NETWORKS

Protein-protein interaction network is highly dynamic [168] and studying the evolution of protein-protein

Table 4. The Most Popular Available Tools for Analyzing and Visualizing Protein-Protein Interaction Networks with Brief Descriptions and References. OS Column Shows Operating System(s) Including Linux (Lin), Macintosh (Mac) and Windows (Win) that the Tools Can Run on it (Them). The Popularity of Tools Range from One Star to Five Stars Based on the Numbers of Corresponding Publications' Citations (According to Google Scholar at the Time of Writing this Manuscript, May 2013): One Star Means Less than 50 Citations; Two Stars Mean Between 50 and 100 Citations; Three Stars Mean Between 100 and 200 Citations; Four Stars Mean Between 200 and 500 Citations, and Four Stars Mean Greater Than 500 Citations

Acronym	Description	OS	Availability	Popularity	Stand-alone/Web-based/Plug-in	URL and References
APID (*Cancer Research Center*)	(Agile Protein Interaction DataAnalyzer) it's an interactive web-tool that allow exploration and analysis of protein-protein interaction	Lin/Mac/Win	Free	***	Web-based	http://bioinfow.dep.usal.es/apid/index.htm [147]
BiNoM	It developed to facilitate the manipulation of biological networks represented in standard systems biology formats (SBML, SBGN, BioPAX) and to carry out studies on the network structure.	Lin/Mac/Win	Free	**	Cytoscape plug-in	https://binom.curie.fr/ [148]
BioLayout	BioLayout is a tool for visualization and clustering of biological networks in both 3D and 2D, it is compatible with Cytoscape. It also includes analytical approaches to microarray data analysis.	Lin/Mac/Win	Free	*	Stand-alone	http://www.biolayout.org. [149, 150]
Cerebral	It enhances Cytoscape's functionality by using extra annotation provided by the user to both automatically generate a more pathway-like representation of a network and to provide an environment for the visualization, comparison, and clustering of expression data from multiple conditions.	Lin/Mac/Win	Free	*	Cytoscape plug-in	http://www.pathogenomics.ca/cerebral/ [151]
Cytoscape	A powerful interactive open source network visualization tool	Lin/Mac/Win	Free	*****	Stand-alone	http://cytoscapeweb.cytoscape.org/ [144, 146]
InterProSurf *(University of Texas Medical Branch)*	wWeb server for predicting the functional sites on a protein surface	Lin/Mac/Win	Free	*	Web-based	http://curie.utmb.edu/prosurf.html [152]

(Table 4) contd….

Acronym	Description	OS	Availability	Popularity	Stand-alone/Web-based/Plug-in	URL and References
InterViewer *(Inha University)*	Produces a molecular interaction network of good quality without computing force between every pair of nodes	Win	Free	*	Stand-alone	http://interviewer.inha.ac.kr/ [153]
iSPOT *(Universita di Roma)*	SPOT (Sequence Prediction Of Target) infer the peptide binding specificity of any member of a family of protein binding domains.	Lin/Mac/Win	Free	*	Web-based	http://cbm.bio.uniroma2.it/ispot/ [154]
MCODE	It finds clusters (highly interconnected regions) in a network. It can also be used to lay out any graph that requires stratification according to some characteristic and thus can be used by researchers in a variety of fields	Lin/Mac/Win	Free	*****	Cytoscape plug-in	http://baderlab.org/Software/MCODE [155]
Medusa	An powerful interactive tool for visualization and clustering analysis of biological networks.	Lin/Mac/Win	Free	*	Stand-alone	https://sites.google.com/site/medusa3visualization [156]
meta-PPISP *(Florida State University)*	A web server for protein-protein interaction site prediction (this tool is built on three individual web servers: cons-PPISP, PINUP, and Promate).	Lin/Mac/Win	Free	**	Web-based	http://pipe.scs.fsu.edu/meta-ppisp.html [157]
NAViGaTOR (University of Toronto)	Software package for visualizing and analyzing protein-protein interaction networks	Lin/Mac/Win	Free	**	Stand-alone	http://ophid.utoronto.ca/navigator/ [158]
NOXclass *(Max-Planck-Institut für Informatik)*	A classifier identifying protein-protein interaction types implemented using a SVM algorithm.	Lin/Mac/Win	Free	***	Web-based	http://noxclass.bioinf.mpi-inf.mpg.de/ [159]
Osprey	a A tool for visualization and manipulation of complex interaction networks	Lin/Mac/Win	Free (registeration is needed)	****	Stand-alone	http://biodata.mshri.on.ca/osprey/servlet/Index [160]
Pajek	is a standalone application, iIt can use for analyzing large networks with up to million of nodes and vertices.	Win	Free	*****	Stand-alone	http://vlado.fmf.uni-lj.si/pub/networks/pajek/ [161, 162]

(Table 4) contd….

Acronym	Description	OS	Availability	Popularity	Stand-alone/Web-based/Plug-in	URL and References
PathBLAST *(Whitehead Institute)*	It ssearches the protein-protein interaction network of the target organism to extract all protein interaction pathways that align with a pathway query.	Lin/Mac/Win	Free	****	Web-based	http://www.pathblast.org/ [163]
SCOWLP *(TU Dresden)*	Structural classification of protein binding regions for atomic comparative analysis of protein interactions allow individual and comparative analysis of protein interactions.	Lin/Mac/Win	Free	*	Web-based	http://www.scowlp.org/scowlp/ [164, 165]
UVCLUSTER	Iterative cluster analysis of protein interaction data.	Lin/Win	Free for academic users (fulfillment of software license agreement is needed)	***	Stand-alone	http://www.uv.es/genomica/UVCLUSTER/ [166]
VisANT	It designed specifically for the integrative visual data-mining of multi-scale Bio-Network/Pathways. It also can find the over-represented GO terms in network modules.	Lin/Mac/Win	Free	**	Cytoscape plug-in	http://visant.bu.edu/ [167]

interaction networks is one of the central problems of systems biology, the results of such researches are crucial for a better understanding of the evolution of living systems and could be used for protein interaction and function prediction.

Statistics Versus Comparative Approaches

Generally, it is possible to categorize studies on protein-protein interaction network evolution in two ways: those based on a statistical and mathematical models, and those based on a comparative network analysis. In approaches based on statistical and mathematical models after analyzing protein-protein interaction networks (by focusing on the topological features) mathematical and statistical models of evolving networks is produced and then by tuning parameters we proceed to reproducing properties observed in experimentally produced networks. In approaches based on comparative network analysis protein-protein interaction networks of species with different levels of complexity are analyzed and then by comparing networks we try to find the evolutionary processes that generally shaped these networks [169-171]. In both of these approaches, three main evolutionary events are considered as the main processes that have shaped the structure of the protein-protein interaction network.

Addition of New Nodes

Gene duplication is an important evolutionary mechanism that naturally increases the number of proteins in the protein-protein interaction networks. A gene duplication event therefore corresponds to the addition of a node and with links identical to the original node, followed by the divergence of some of the initially redundant links between the two duplicate nodes [172]. After gene duplication, a protein product that has the ability to bind strongly to its partner will be better able to explore mutations that allow it to co-evolve, or to dimerize with other, existing, homologues using the ancestral binding mode. This duplicating effect should, therefore lead to an enhanced ability to create homologous interacting pairs of proteins, and could have played a role in the early emergence of protein-protein interaction networks. This should allow for an increased resistance to environmental change, or adaptability However, single gene duplica-

tions may lead to an immediate stoichiometric imbalance, which would therefore tend to be counter selected [173]. In smaller gene family sizes, especially for genes encoding protein complex components, there is less potential for paralogs to evolve new interaction partners through mutation and selection.

Addition and Elimination of Edges

There are two reasons for the loss and gain of new interactions, namely neofunctionalization and subfunctionalization. After gene duplication, the second copy of the gene is relatively free from selective pressure and is able to diverge and accumulate mutations faster than a functional single-copy gene because these mutations often have no deleterious effects [174, 175]. If these mutations are solely degenerative in nature then this will lead to a nonfunctional gene product, but if instead they are innovative, then this can lead to neofunctionalization and the acquisition of novel features. In another possible trajectory, some of the functions of the original gene are assigned to the new copy and both copies accumulate degenerative mutations leading to a differentiation of function and division of labor (i.e. subfunctionalization). The result of these processes is the divergence at interaction pattern of the original gene and its copy (ie. the addition and elimination of edges).

Elimination of Nodes

After gene duplication the mutation that takes place on the new copy of a gene could convert it to a nonfunctional gene, consequently it is deleted from the network because it does not have any interaction (gene lost).

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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SUPPLEMENTARY MATERIALS

Supplementary material is available on the publisher's web site along with the published article.

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