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Comparison of Computational Tools for Protein-Protein Interaction (PPI) Mapping and Analysis

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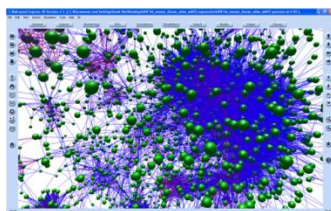
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Graphical abstract

Abstract

Several visualization tools for the mapping of protein-protein interactions have been developed in recent years. However, a systematic comparison of the virtues and limitations of different PPI visualization tools has not been carried out so far. In this study, we compare seven commonly used visualization tools, based on input and output file format, layout algorithm, database integration, Gene Ontology annotation and accessibility of each tool. The assessment was carried out based on brain disease datasets. Our suggested tools, NAViGaTOR, Cytoscape and Gephi perform competitively as PPI network visualization tools, can be a reference for future researches on PPI mapping and analysis.

Keywords: Visualization tools; protein-protein interaction network; system biology; proteomic database; protein mining; protein mapping

Abstrak

Pelbagai perisian untuk pemetaan interaksi antara protein telah dibangunkan sejak kebelakangan ini. Walau bagaimanapun, satu perbandingan yang sistematik mengenai keupayaan dan kekangan perisian-perisian ini belum dijalankan setakat ini. Di dalam kajian ini, kami membandingkan tujuh perisian yang digunakan sebagai alat paparan dari segi format fail input dan output, susun atur algoritma, pemaduan pangkalan maklumat, anotasi Gene Ontology dan ketercapaian setiap perisian dengan menggunakan data dari penyakit otak. Keputusan menunjukkan bahawa perisian NAViGaTOR, Cytoscape dan Gephi adalah amat berguna sebagai alat pemaparan rangkaian interaksi antara protein dan kami mencadangkan bahawa ia menjadi rujukan bagi penyelidik pemetaan protein pada masa hadapan.

Kata kunci: Perisian; pemetaan interaksi; biolosi sistem; pangkalan data proteomik; pelombongan data

1.0 INTRODUCTION

In this post-genomic era, the development of high-throughput technologies such as yeast two-hybrid screening, mass spectrometry screening and different types of microarrays has been generating massive proteomics and genomics data and these data is increasing exponentially every year [1, 2]. Users and researchers are often overwhelmed by these data and thus find it difficult to organize and analyze them. Representing the data in a visual format therefore is useful in the interpretation of these data sets. Thus, visualization and analysis of high throughput data using visualization tools has been an important step in helping researchers to generate new insights that contribute to our society.

Nowadays, there are several biological network visualization tools which can be obtained freely via the World Wide Web. For instance, Pajek [3], Cytoscape [4], BioLayout Express3D [5] and NAViGaTOR [6] are visualization tools that can be used to visualize biological networks and pathways. Reasons for researchers to use a particular visualization tool are varied. Some of the tools are able to extract data from online databases, while other tools import data in simple format and allow changes to be made. To choose the most suitable visualization tool in analyzing data, researchers need to understand the function of the tools, as well as their virtues and limitations. For example, Medusa is not a suitable tool if the input biological network is large. In this study, commonly used visualization tools were examined and analyzed so that in future researchers are able to choose a suitable tool for their specific purposes. Every visualization tool has its strengths and limitations. Several tools have been reviewed for the task of protein-protein interaction mapping [7-9].

■2.0 SOFTWARE COMPARISON

2.1 Cytoscape

2.1.1 Background and Strengths

Cytoscape [4] is one of the most familiar tools which has the highest number of citations (refer Table 1) and is generally used to analyze protein interaction data, expression profiles and metabolic profiles [7]. This fast developing freeware is downloadable from Cytoscape homepage and is available for three operating systems: Windows, Mac and Linux. It contains a variety of functions and plug-ins, which make the software approachable and suiting diverse task demands. Another competitive advantage of Cytoscape is the integration with several well-known databases such as IntAct, NCBI and cPath. This allows users to mine protein network data easily using search tools integrated into Cytoscape.

One of the important features of protein interactions analysis is the annotation and attributes of proteins. Cytoscape allows users to download annotations such as Gene Ontology (GO) [10]. Proteins can be grouped according to the GO info. APID2NET [11] is a user friendly plug-in which integrates several databases including IntAct[12], BIND [13], MINT [14], BioGrid [15, 16], DIP [17] and HPRD[18]. Annotated proteins can be colored automatically according to GO info by a simple click.
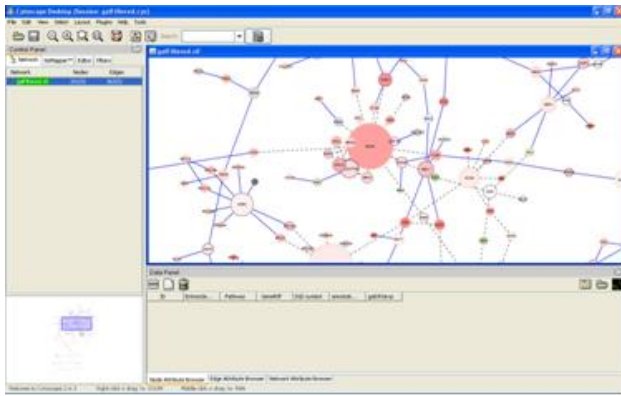
Figure 1   Cytoscape 2.6.3, an open source platform for complex network analysis and visualization
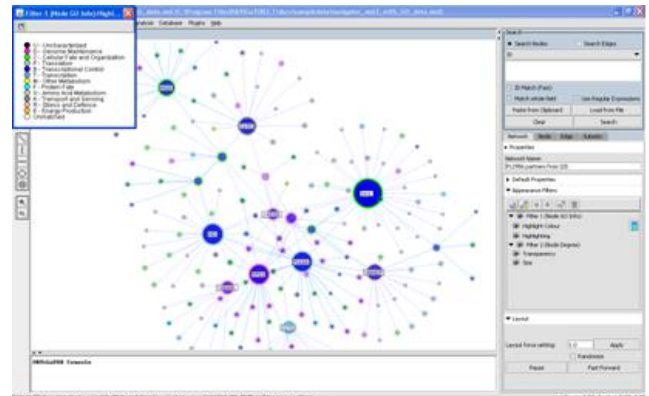
2.1.2 Limitations

Cytoscape does not provide 3D layout. Besides, databases integrated in Cytoscape are using different searching methods. Certain databases for instance "IntAct Web Service Client" and "Pathway Commons Web Service Client" allow users to search by key words such as disease name or species name. However, some databases only allow users to search by the specific protein name (or ID) or gene name (or ID) instead of keywords. The output would be the network of the query protein and its neighboring proteins, which are not necessarily related to the disease or organism of interest. This drawback places users in a dilemma when facing the task of comparing data sets from different databases.

2.2 Navigator

2.2.1 Background and Strengths

NAViGaTOR (Network Analysis, Visualization and Graphing Toronto) is implemented by members of Jurisica Lab at IBM Life Sciences Discovery Center, Ontario Cancer Institute [6]. It is a free software tools which supports Windows, Linux, Mac and Unix. The software tool enables visualization of large data sets in 2D and 3D view.

Its particular use is due to its ability to extract data directly from I2D and cPATH. Besides, it allows data to be imported in PSI-MI, XML, BIOPAX, GML and tab-delimited text format, which are the formats usually used to process protein data. It can also export the interaction network in PDF, BMP, JPEG, Pajek, SVG and TIFF format. The protein-protein interactions which displayed in the network panel can be differentiated by color or shape of the nodes. NAViGaTOR enables the execution of multiple network panels at the same time so that comparison of multiple interaction networks can be done. Furthermore, nodes can be copied from one interaction network and pasted into another interaction network. NAViGaTOR extracts protein information from Gene Ontology and the data can be saved within the biological network. Different molecular functions of the proteins will be classified and displayed in different colors. Proteins within a biological network can be group into subgroup based on different functions or characteristics.

Figure 2   NAViGaTOR 2.1 (Network Analysis, Visualization, & Graphing TORonto), a software package for visualizing and analyzing protein-protein interaction networks

2.2.2 Limitations

Public users cannot modify the functions and characteristics of this software. No plug-ins are available for NAViGaTOR.
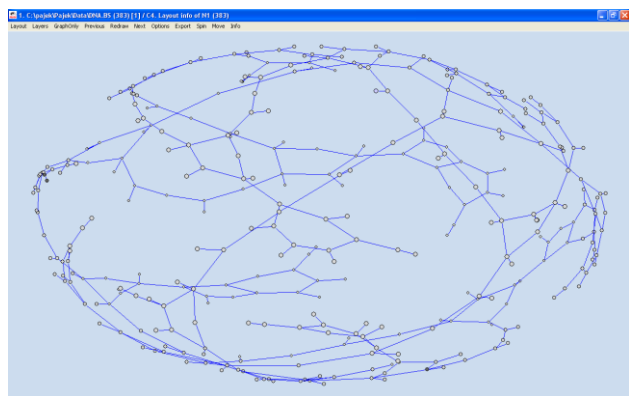
2.3 Pajek

2.3.1 Background and Strengths

Pajek is a non commercial free software which was invented thirteen years ago. Its functionality has been improved to make sure it is state-of-the-art and aesthetically pleasing. It generates 2D and pseudo 3D graph for viewing.

This is a powerful software tool since it allows the input of large data sets. Besides, it provides a variety of layout algorithm patterns such as circular, Fruchterman Reingold, Lanczos, Kamada-Kawai and so on. Pajek processes network interactions based on 6 data types namely network, partition, cluster, vector,

permutation, and hierarchy [3]. Apart from its own flat file format, it also supports UCINET, DL and GED format. Pajek supports several output graphic formats which can be examined by special 2D and 3D viewers. Those graphic formats include Encapsulated PostScript, VRML, MDLMOL, Chime and Kinemages. As for the tool itself, the Fruchterman Reingold layout algorithm provides 3D view for the graph and enables users to zoom around the network.

Figure 3 Pajek 1.28, Program for large network analysis

2.3.2 Limitations

Pajek does not integrate with any database and it only supports a flat file format which is not compatible to most of the XML formats nowadays. The data need to be converted into Pajek file format to visualize. These limitations have restricted the usage of Pajek by end users.
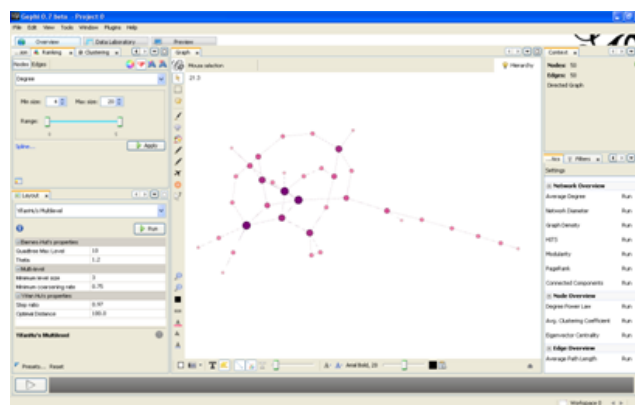
2.4 Gephi

2.4.1 Background and Strengths

Gephi is an open-source software which allows users to do modification to the characteristics and functions of the tool. It is one of the projects under Google Summer of Code in 2009 and 2010. A forum is generated for users and creators to communicate and improve the functionalities of Gephi.

Gephi is capable in processing huge data sets because it is built on a multi-task model and it provides a 3D render engine to visualize all kinds of interactions. Social networks, relationships among people or computer networks are the examples of visualized interactions. Besides, Gephi supports GEXF, GraphML, Pajek NET, GDF, GML, Tulip TLP, CSV, and Compressed ZIP format and it able to export the graph to SVG, PDF and graph file format. The plug-ins are implemented from programmers all over the world. There are some plug-ins which have been specifically designed for Gephi. For instance, the "overlap" plug-in prevents the round notes from overlapping with each other. Furthermore, the features of the nodes, edges, and the graph pattern can be adjusted by users.

2.4.2 Limitations

Gephi does not support the PSI-MI file format which is commonly used for protein-protein interaction data. As a result, the conversion of the file format to other formats which are supported by Gephi is necessary. Besides, Gephi does not integrate with any protein database. There might be some difficulties for users to export the data from a database to the

software. Also, Gephi is not specifically designed for protein-protein interaction network analysis.

Figure 4 Gephi 0.7 beta, the open graph viz platform

2.5 Biolayout Express 3D

2.5.1 Background and Strengths

Biolayout express 3D is a powerful network visualization tools that allows users to visualize interaction in 2D and 3D view. It is an open source application and freely available online.

Biolayout is useful in analyzing large data sets and it is easy to use. It supports a simple input file format which only requires a list of connections [8]. Additional nodes and edges can be easily created by typing their names and interactions in text format. It can also import SIF, XML, GraphML, OWL, Expession data input format, Matrix file, mEPN and ondex XML file format and export the data in PNG, JPG, and TGF format. By using Biolayout, weighted graphs can be created by users, too. Furthermore, the interaction can be viewed in both 2D and 3D depending on the users' choice. They can zoom in, rotate and move the network to view a particular node or interaction. The latest version of Biolayout (Version 2.1) can be used to create timecourse network and stochastic flow simulation which is very useful for visualization of signaling pathways.
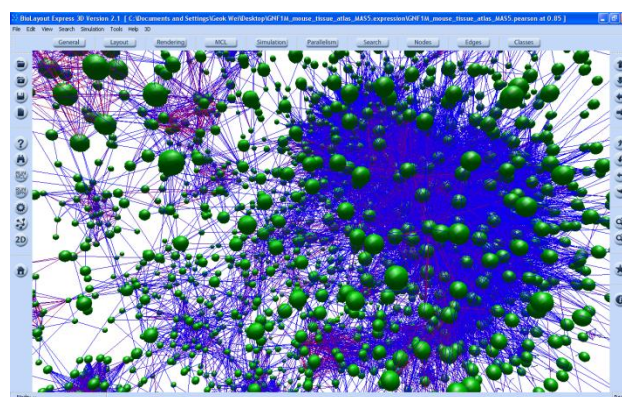
Figure 5 Biolayout Express3D 2.1, a powerful tool for the visualization and analysis of network graphs

2.5.2 Limitations

Biolayout express 3D does not integrate with protein databases and it has no supported plug-in. The nodes are colored according to user-defined classes and manual modification of the node's color is allowed but cannot be saved.

2.6 Medusa

2.6.1 Background and Strengths

Medusa is a simple, open source visualization tool that is designed to visualize protein-protein interactions from the STRING database. It provides 2D representation for biological network. It consists of a very useful feature, which other tools do not have is that background images can be inserted to the network. Besides, it possesses the ability to build multi-edge connections. It is a Java application and runs on any machine with Java 1.4.2 installed. It does not require installation onto an operating system. It runs as standalone and as an applet for use in web interfaces.

Figure 6 Medusa 1.5, a java standalone application for visualization and clustering analysis of biological networks in 2D

2.6.2 Limitations

Medusa is designed for the analysis of small datasets. Hence, it is not capable in analyzing interactions with large amount of nodes [8]. Furthermore, it possesses its own unique input file format. It requires users to possess basic knowledge of java programming to deploy the applet.
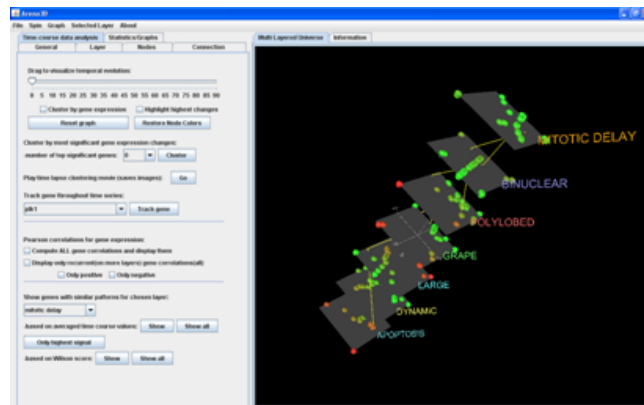
2.7 Arena3D

2.7.1 Background and Strengths

Arena3D is a Java application and runs on any platform with Java3D 1.5.1 API and Java JRE or JDK 1.5 installed. It is simple, open source and does not require installation onto an operating system. It is free for academic users.

Arena 3D can visualize different types of data such as proteins, structures, pathways and diseases in multilayers and in 3D space. It allows the users to navigate the order, location, and orientation of individual layers. With this feature, users can view biological networks in a reduced complexity and more comprehensible way. Basic interaction modes and general information will be displayed by clicking the nodes from the interaction network. It can export networks in Pajek and Medusa

format. Each node or edge can be linked to a user-defined URL (uniform resource location) link. New feature of the latest version of Arena 3D includes the visualization of time course data. The changes of gene expression now can be viewed through the changes in nodes' color. Also, it enables coloring according to gene pattern similarity.

Figure 7 Arena3D, a new, staggered multi layer concept that allows the analysis of big networks in a three dimensional space representation

2.7.2 Limitations

Similar to Medusa, Arena3D possesses its own input text file format which is complicated for biologists. Its strength to define each node or edge with an URL link is also its drawback because each URL link needs to be manually typed in the input text files prior visualizing the network in the software interface or via the information tab in the interface. It does not integrate with any proteomics database. It is also unable to make changes on the color, shape and size of the nodes and edges from the interaction network are displayed in the network panel.

Table 1 Commonly used visualization tools

Visualization Tools	No. of Citations	Date Retrieved
Cytoscape	1705	06/12/2010
NAViGaTOR	10	06/12/2010
Biolayout	111	06/12/2010
Medusa	57	06/12/2010
Pajek	596	06/12/2010
Gephi	5	06/12/2010
Arena3D	12	06/12/2010

■3.0 DATA SOURCES FOR PPI

There are various types of Proteomics databases available on World Wide Web. Most of the databases are non-profit and free for academic use. For instance, IntAct, UniProtKB, HPRD, PDB are free databases which are commonly used. There are universities or institutes which build their own proteomics databases too. However, the databases may not be as thorough and detailed compared to the proteomics databases mentioned. Generally, the databases are built for specific research purposes. For example, the JPSL Proteomics Database gathers the protein data related to cancer research.

To retrieve the data from those databases, bioinformaticians keep the data in various formats. This enables user to export the data to the desired destination. Examples of the file format are PSI-MI, BioPAX, text file, SBML, XML and SIF. Among the different file formats, PSI-MI (Proteomics Standards Initiative-Molecular Interaction) and text file formats are commonly used to keep the protein-protein interaction data. Databases such as IntAct, HPRD, BOND, BioGRID and MINT keep and export proteomics data in both PSI-MI and text file format. They are most frequently used because PSI MI allows the storage and

exchange of molecular interactions data from one database to another in a particular format to enhance the pace in comparing and analyzing data while the text file format is the simplest format which allows users to understand and modify the information easily.

The protein-protein interaction data for brain diseases were chosen to be mined and exported to visualization software for viewing. Data was gathered from different PPI databases by using different search methods. This is due to the different input queries required among the databases (Table 2).

Table 2 Databases related to protein-protein interaction

No.	PPI database	URL link	Search by
1	IntAct	http://www.ebi.ac.uk/intact/	keywords, protein name, protein ID
2	BOND	http://bond.unleashedinformatics.com/	keywords, protein name, protein ID
3	APID	http://bioinfow.dep.usal.es/apid/	keywords, protein name, protein ID
4	STRING	http://string-db.org/	keywords, protein name, protein ID
5	I2D	http://ophid.utoronto.ca/	protein name, protein ID
6	MINT	http://mint.bio.uniroma2.it/mint/	keywords, protein name, protein ID
7	HPRD	http://www.hprd.org/	protein name, protein ID
8	Reactome	http://www.reactome.org/	keywords, protein name, protein ID
9	iHOP	http://www.ihop-net.org/UniPub/iHOP/	keywords, protein name, protein ID
10	DIP	http://dip.doe-mbi.ucla.edu/dip/	protein ID, protein sequence
11	HAPPI	http://discern.uits.iu.edu:8340/HAPPI/	uniprot ID

Most of the databases such as IntAct, BOND and MINT use keywords as query. Nevertheless, some databases use unique input query instead of keyword. For example, DIP requires motif, protein sequence and article as input query while BioGRID requires gene name and information of publication as query.

3.1 Mining

There are few ways in exporting the data from databases to visualization tools. First, the data can be directly exported to the software if there is integration between the databases and software itself. For instance, NAViGaTOR integrates with I2D and cPath. Hence, it extracts the protein-protein interaction data from the two databases and displays it in its network panel. If there is no integration between the tool and databases, the data can be saved in certain file formats and exported into the visualization tools to be displayed. Also, users can create protein-protein interaction network by manually typing in the information in text file format and exporting it to the respective visualization tool. The interaction network can also be exported from a software tool to another. The advantage of exchanging data from one tool to the other allows overcoming limitations. For example, if one wants the map to be visualized in NAViGaTOR, he can mine the data from IntAct using Cytoscape and export to NAViGaTOR by compatible file formats (Figure 8).
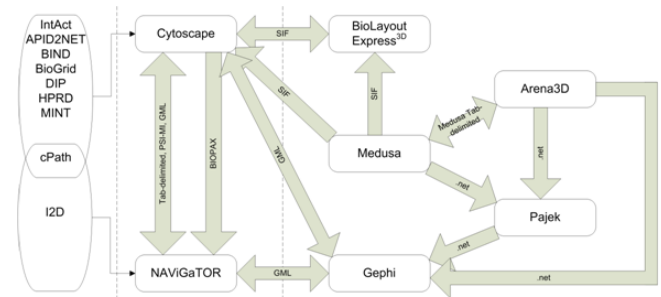
Figure 8 Interchangeable of data between softwares. Cytoscape is integrated with several databases includes IntAct, APID2NET, BIND, BioGrid, DIP, HPRD, MINT and cPath. NAViGaTOR is integrated with both cPath and I2D

For example, Cytoscape contains many plug-ins to assist users in network visualization. However, it only visualizes the networks in 2D view. As a result, the data can be exported from Cytoscape to another software tool which contains a 3D network interaction viewer. NAViGaTOR is a powerful 3D visualization tool. It supports file types exported from Cytoscape and is able to extract additional information from Gene Ontology. By using both visualization tools, their individual limitations are compensated.

Table 3 Comparisons in terms of features, database integration, data input format, export file format, and layout algorithm

	Arena3D	Biolayout	Cytoscape	Navigator	Pajek	Gephi	Medusa
URL	http://www.arena3d.org/	http://www.biolayout.org/	http://www.cytoscape.org/	http://ophid.utoronto.ca/navigator/	http://pajek.imfm.si/doku.php	http://gephi.org/	https://sites.google.com/site/medusa3visualization/
Features:							
2D	Y	Y	Y	Y	Y	Y	Y
3D	Y	Y	X	Y	Y	Y	X
3D (layers)	Y	X	X	X	X	X	X
Plug-ins	X	X	Y	X	X	Y	X
Auto merge numbers of networks (no modification on original input file)	X	X	Y	Y	X	X	X
Mark nodes according to GO annotations	X	X	Y (plug-ins)	X	X	X	X
GO annotations	X	X	Y (plug-ins)	Y	X	X	X
Ability of inserting background images	X	X	X	X	X	X	Y
Database Integration:							
IntAct	X	X	Y (plug-ins)	X	X	X	X
NCBI	X	X	Y (plug-ins)	X	X	X	X
APID2NET	X	X	Y (plug-ins)	X	X	X	X
cPath	X	X	Y (plug-ins)	Y	X	X	X
GO	X	X	Y (plug-ins)	Y	X	X	X
Data Input Format							
Text delimited data	X	Y	Y	Y	X	X	Y
GML	X	X	Y	Y	X	Y	X
PSI-MI XML	X	X	Y	Y	X	X	X
SIF	X	Y	Y	X	X	X	X
BIOPAX	X	X	Y	Y	X	X	X
XGMML	X	X	Y	X	X	X	X
Third Party Plugin	X	X	Y	Y	X	X	X
PAJEk file	X	X	X	X	Y	Y	X
Text	Y	Y	Y	Y	X	X	Y
Export File Format							
Image file	Y	Y	Y	Y	Y	Y	Y
xml	X	X	X	Y	X	X	X
Pajek	Y	X	X	X	Y	X	Y
gml	X	X	Y	Y	X	X	X
PSI-MI	X	X	Y	Y	X	X	X
Arena3D	Y	X	X	X	X	X	Y

text	Y	X	X	Y	X	X	X
sif	X	Y	Y	X	X	X	Y
svg	X	X	Y	Y	Y	Y	X
tiff	X	X	X	Y	X	X	X
pdf	X	X	Y	Y	X	Y	X
GraphViz	X	X	X	X	X	X	Y
Medusa format	Y	X	X	X	X	X	Y
VRML	Y	X	X	X	Y	X	X
Layout Algorithm							
Multi-threaded grid-variant layout algorithm	X	X	X	Y	X	X	X
Spring Embedded algorithms	X	X	Y	X	Y	X	Y
Fruchterman-Rheingold layout algorithm	Y	Y	X	X	Y	X	Y
Lanczos algorithm	X	X	X	X	Y	X	X
Force Atlas algorithm	X	X	X	X	X	Y	X
Distance Geometry layout	Y	X	X	X	X	X	Y
Simulated Annealing Algorithm	X	Y	Y	X	X	X	X
Circular layout	Y	X	Y	Y	Y	Y	Y
Hierarchiral layout	Y	X	Y	X	X	X	Y
Yifan's Hu Multilevel layout	X	X	X	X	X	Y	X

3.2 Mapping

To obtain a clear interaction network, several issues need to be considered during the selection of the visualization tool. The differences in mapping a process by various visualization tools represent the interaction networks in different ways and this is crucial in determining software selection.

Different layout algorithms have been developed. For example, force-directed layout [19] is one of the well-known layout algorithms, which is commonly employed in visualization software to view the interactions. The varieties in layout patterns make the graph aesthetically pleasing, accelerate the pace in generating the interaction network and allow users to view the interaction in different ways. Hence, the users can select the best layout for their own interaction networks.From Table 3, each of the visualization tools listed possesses different types of layout algorithms and the Circular layout algorithm is mostly applied in those tools, followed by a Fruchterman-Rheingold layout algorithm and a Hierarchiral layout.

If the protein-protein interaction network is large, some layouts may not be suitable as they slow down the generation time of the interaction network [20]. As a result, some of the visualization software is not suitable in viewing large protein-protein interaction map.

■4.0 CONCLUSION

System biology is a rapidly evolving field where the data as well as the software are developing continuously. Large amounts of data generated from high throughput methods require suitable tools to visualize and analyze. Visualization of protein–protein interactions into suitable maps provides valuable insight into the cellular and molecular function of the proteome, and may contribute to drug design. Each tool has its strengths and limitations. Thus, there is no best tool to fit different requirements.

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