PIBB 生物化学与生物物理进展
Progress in Biochemistry and Biophysics
2009, 36(12): 1613~1616
www.pibb.ac.cn

PNmerger: a Cytoscape Plugin to Merge Biological Pathways and Protein Interaction Networks*

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Abstract PNmerger (a biological Pathway and protein Network merger) is a java based plugin for the widely used open source Cytoscape molecular interaction viewer. For a protein interaction network, PNmerger can automatically annotate the network proteins with the KEGG pathway information, find the known pathway elements in protein network, and predict the possible pathway elements. To present the pathway information for the protein network, PNmerger illustrates the clusters of the nodes with the same biological pathway, and also presents the potential crosstalk elements between different pathways. This information will be helpful for the users to find the important clues for knowledge discovery and experimental design. PNmerger is available online at http://www.hupo.org.cn/PNmerger.

Key words systems biology, biological pathway, protein-protein interactions, crosstalk elements, pathway expanding, cytoscape plugin
DOI: 10.3724/SP.J.1206.2009.00236

High-throughput screens have generated high volume of protein interaction data, which has been the focus of “systems biology”, because protein interaction network can present not only the bimolecular involved in a particular biological system or process, but also the relationships between these components. With the deposition of protein interaction datasets, it has become a big challenge to discover the knowledge underlying the protein interaction network. Various visualization tools have been developed for visualizing and understanding these interactions, interpreting high-throughput experimental data, generating hypotheses and sharing results[1]. These visualization tools uncover interesting stories that can not be directly found “by eye”, and facilitate a shift from the study of individual genes to the level of pathways and complexes.

However, there are two main limitations in the current bioinformatics visualization tools. First, the main motivation of the protein interaction experiment is to expand the known biological pathways, but few of the current visualization tools meet such request. Second, few current network tools are designed for both the visualization of biological networks and the analysis of them. Consequently, users have to switch between tools, resulting in the need to continually import/export and reformat data. Apparently, a more optimal choice would be a network tool that supports both visualization and analysis, with a seamless integration between these two procedures.

To address these two challenges, we develop PNmerger, a novel Cytoscape plugin that automatically analyzes the protein interaction network with the biology pathway information. Cytoscape[2] is an outstanding visualization platform for systems biology and has many excellent features. It is an open source software project that can integrate many types’ biomolecular data. Cytoscape’s core only provides

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*This work was supported by grants from National Basic Research Program of China(2006CB910803, 2006CB910706), Hi-Tech Research and Development Program of China (2006AA02A312), National S&T Major Project (2008ZX10002-016, 2009ZX09301-002), The National Natural Science Foundation of China (30621063 , 30800200) and State Key Laboratory of Proteomics (SKLP-Y200811).

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Received: April 14, 2009 Accepted: May 12, 2009

basic functions such as layout, query and visualization. The analysis functions are extended through a straightforward plugin architecture. Many Cytoscape plug-in have been developed to support the extension, such as BiNGO[3], BioNetBuilder[4], Cerebral[5], CABIN[6], DrugViz[7], NetAtlas[8] and MiML[9].

For an interaction network, our PNmerger plugin can automatically annotate the network proteins with the KEGG [10~12] pathway information, to identify the known pathway in protein network, and to predict the potential pathway components. PNmerger can also allow present the potential crosstalks between different pathways. This information will be helpful for the users to find the important clues for knowledge discovery and experimental design. Interacting with a large network is facilitated by panning and zooming, intelligent labeling at multiple zoom levels, highlighting a node's first neighbors upon mouse over, category-based highlighting, automatically navigation that frames node neighbors in the view, and the grouping of edges into bundles to reduce clutter.

1 Implementation and usage

PNmerger is developed by java 6.0 and implemented with the Eclipse toolkit. PNmerger runs well in Cytoscape version 2.6.0 on Windows XP platform and Linux platform (Ubuntu 7.10). Using the PNmerger plugin is very simple. The user is asked to provide the properly formatted protein interaction data, which are pairs of gene or protein identifiers (Entrez gene name pairs, blank or tab separated, and each interaction takes up a line). Then the users are required to select their desired biological features and appropriate parameters. Finally, users will be presented with the figures and tables for the analytical results (Figure 1 a~ d).

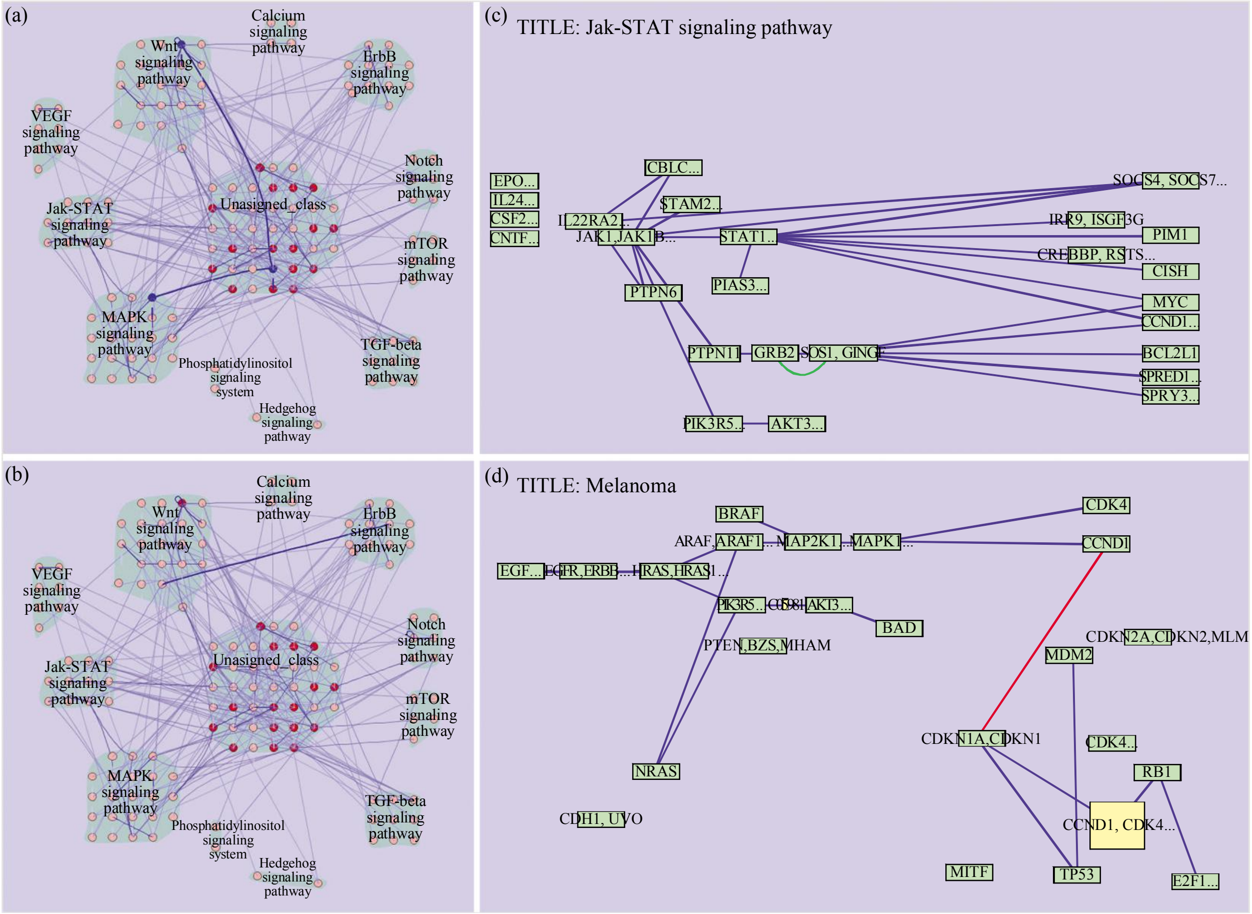

Fig. 1 A sample result of PNmerger for the analyses of human liver protein interaction network and biological pathway
(a) Crosstalk proteins in protein interaction network. Here the green shadows represent functional modules in a protein interaction network, and the red points are crosstalk proteins, which connect different modules *via* protein interactions (blue edges). (b) Crosstalk interactions in protein interaction network. Here the blue edge is a protein interaction that connects two pathways directly. (c) The known protein-protein interactions in Jak-STAT pathway. The green arc represents the protein-protein interaction which appears both in users'input protein-protein interaction network and a biological pathway. (d) A potential protein-protein interaction in Melanoma. The red arc represents the protein-protein interaction which appears only in users' input protein-protein interaction network and absent from the KEGG pathways. Such an interaction may extend this pathway and provide the novel regulatory interactions.

2 Availability and requirements

Before installing the PNmerger plugin, please download the latest version of Cytoscape from the Cytoscape project website http://www.cytoscape.org/. PNmerger is freely available under the BSD license. The non-commercial user can download the PNmerger software and source code freely from our website: http://www.hupo.org.cn/PNmerger. Please download both PNmerger.jar and prefuse.jar and place them into the local Cytoscape/plugins directory. If PNmerger installation is successful, you will find that “PNmerger” appears in the “Plugins” menu of Cytoscape. Otherwise, you may place the jar files in the wrong directory or your java environment is lower than Java SE 6.0. After verifying that you have placed the two jar files into the correct directory, please restart Cytoscape to reload the plugin.

3 Results and discussion

3.1 Illustrating the functional modules and crosstalk elements

Functional modules perform an important role in understanding organization of biological systems and dynamics of cell functions. Here, functional module is defined as those proteins that act together in network performing some discrete physiological function that is semi-autonomous in relation to other functional modules, such as biological pathway. Lots of methods have been presented to identify functional modules in protein-protein interaction networks, but few of them are used to visualize such functional modules in protein-protein interaction networks. Meanwhile, crosstalk elements are helpful to extend biological pathways, and finding out crosstalk elements in protein-protein interaction networks is significant for the research of biological pathways [13]. So it is necessary to develop a tool which can not only identify but also visualize the functional modules in PPI networks. Furthermore, the tool is required to find out the crosstalk elements, which would be helpful to find the novel regulatory molecules or interactions for biological hypothesis.

Our Cytoscape plugin PNmerger perfectly meets such requirements. According to KEGG pathways information, the proteins in the users’ protein-protein interaction network can be assigned to different pathways. PNmerger considers each pathway as distinct functional module. Meanwhile， PNmerger can visualize the functional modules in network. PNmerger can also find out the crosstalk elements (crosstalk proteins and crosstalk interactions) between these functional modules: crosstalk proteins connect different functional modules *via* multi-interactions (Figure 1a), while crosstalk interactions connect two functional modules directly (Figure 1b).

3.2 Identifying the known and potential interactions in biological pathways

Biological pathways provide deep insights into the signaling mechanisms of molecules. Presently, many essential pathways still remain unknown or incomplete even for many well-known model organisms, such as yeast and mouse. Thus, there is a need for tools to help scientists complete the pathways with the molecular interaction data.

Both the protein interaction network and biological pathways can be regarded as the set of vertices (proteins) and edges (interactions). By comparing the interaction network with KEGG biological pathways, PNmerger can extract some useful information for further analyses. First, PNmerger can find the interactions that appear both in protein-protein interaction network and KEGG pathways. These interactions are known elements in pathways (Figure 1c), indicating that these interactions had already been reported. These findings may be evidences for identified protein interactions. Second, PNmerger can find the submitted interactions that linking two proteins in the same KEGG pathway. These interactions are potential protein-protein interactions (Figure 1d), which can be considered as a resource to extend biological pathways.

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PNmerger: 一个整合生物学通路和蛋白质相互作用网络的 Cytoscape 插件 *

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摘要 Cytoscape 是一个广泛应用于分子相互作用网络可视化的软件．发展了一个基于 java 的 Cytoscape 插件 PNmerger．对于一个蛋白质相互作用网络，PNmerger 能够使用 KEGG 数据库中的通路信息自动注释网络中的蛋白质．并通过网络和通路的比较发现网络中已知的通路元件，预测可能的通路元件及通路交联元件．该软件可以可视化网络中存在的通路模块，并将连接不同通路间的潜在交联元件显示出来．PNmerger 软件能够有效地帮助实验人员发现网络中重要的功能线索，帮助实验人员进行实验设计．用户可以通过网站 http://www.hupo.org.cn/PNmerger 下载 PNmerger 插件．

关键词 系统生物学，生物学通路，蛋白质 - 蛋白质相互作用，交联元件，通路扩展，cytoscape 插件

学科分类号 Q61 **DOI:** 10.3724/SP.J.1206.2009.00236

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* 国家重点基础研究发展计划(973)资助项目(2006CB910803, 2006CB910706), 国家高技术研究发展计划(863)资助项目(2006AA02A312), 国家科技重大专项(2008ZX10002-016, 2009ZX09301-002), 国家自然科学基金(30621063, 30800200)和蛋白质组学国家重点实验室课题(SKLP-Y200811)资助项目.

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收稿日期：2009-04-14，接受日期：2009-05-12