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Applications Note

Systems biology

DyNetViewer: a Cytoscape app for dynamic network construction, analysis and visualization

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Abstract

Summary: The molecular interactions in a cell are varying with time and surrounded environmental cues. The construction and analysis of dynamic molecular networks can elucidate dynamic cellular mechanisms of different biological functions and provide a chance to understand complex diseases at the systems level. Here, we develop DyNetViewer, a Cytoscape application that provides a range of functionalities for the construction, analysis and visualization of dynamic protein–protein interaction networks. The current version of DyNetViewer consists of four different dynamic network construction methods, twelve topological variation analysis methods and four clustering algorithms. Moreover, visualization of different topological variation of nodes and clusters over time enables users to quickly identify the most variations across many network states.

Availability and implementation: DyNetViewer is freely available with tutorials at the Cytoscape (3.4+) App Store (http://apps.cytoscape.org/apps/dynetviewer).

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

The cellular organization has inherent dynamic characteristics to perform different biological functions. Comprehensive investigation of the dynamics of molecular interaction networks and the cell machinery could help predict particular protein functions, reveal important insights into human disease mechanisms, and support the development of new drugs. As such, it is indispensable to focus on the inherent temporal nature of protein-protein interaction (PPI) networks by analyzing and modeling dynamic interaction networks.

To understand the dynamic organization of biological networks, plenty of dynamic network toolkits have been developed, such as TVNViewer (Curtis *et al.*, 2011), KDDN (Tian *et al.*, 2015), and DyNet (Goenawan *et al.*, 2016). TVNViewer provides functions for analyzing how the degree of different nodes in a network changes over time and exploring the change of network structure. KDDN supports analysis of two sub-networks of dynamic networks. DyNet supports the identification of the most rewired nodes and the visualization of node/edge changes across multiple network states. However, current software systems have not incorporated multiple algorithms to construct dynamic networks.

In this study, we present DyNetViewer, a Cytoscape application that provides a range of functionalities for the construction of dynamic networks, node topological change analysis and cluster change analysis over time. DyNetViewer also provides various visualizations of dynamic networks and analysis results. A comprehensive comparison of DyNetViewer with other related tools is described in Supplementary File S1. Although DyNetViewer was developed to protein interaction networks in mind, it can also be used for any types of dynamic networks.

2 Implementation

2.1 Construction of dynamic networks

The process and functions of DyNetViewer are shown in Figure 1. DyNetViewer contains four different methods for constructing

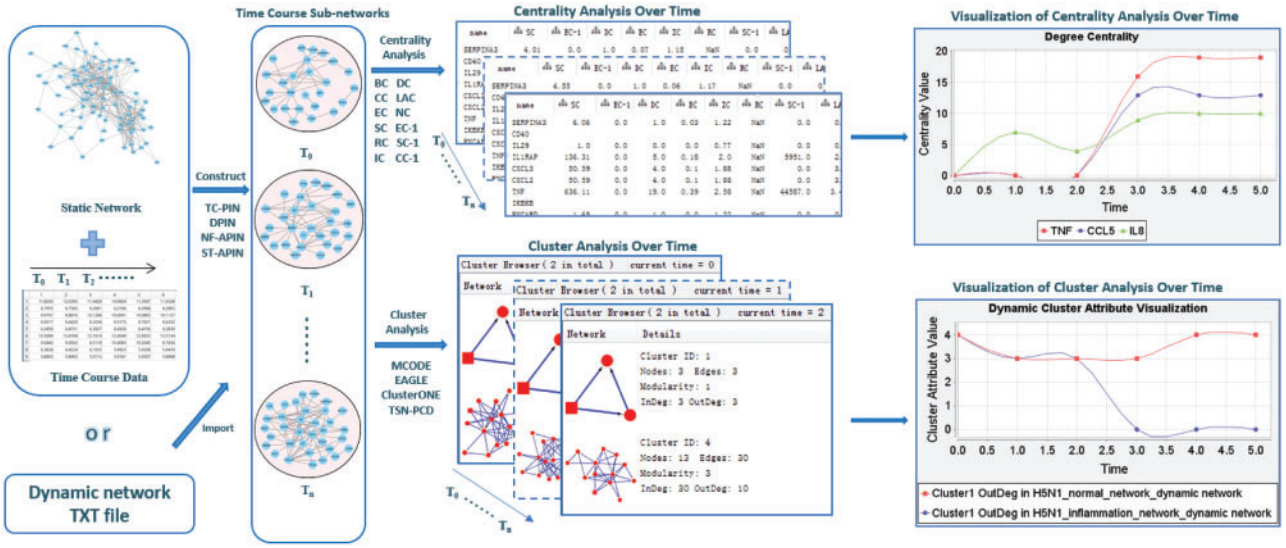

Fig. 1. The process and functions of DyNetViewer: dynamic network construction, analysis and visualization

dynamic PPI networks: TC-PIN (Tang *et al.*, 2011), DPIN (Wang *et al.*, 2013) and NF-APIN (Xiao et al., 2013), and ST-APIN (Li *et al.*, 2017). The detailed description of four algorithms and the difference on these methods is shown in Supplementary File S2. Moreover, DyNetViewer have implemented dynamic network construction methods in a modular way and allow users to freely select and combine these modules to obtain their own network construction method. In addition to constructing dynamic networks, users can import dynamic networks from a txt file directly and export dynamic networks to a txt file for further analysis.

2.2 Node centrality analysis of dynamic networks

DyNetViewer supports node centrality analysis of dynamic networks and integrates twelve typical centrality measures including Betweenness Centrality (BC), Closeness Centrality (CC), Degree Centrality (DC), Eigenvector Centrality (EC), Local Average Connectivity-based method (LAC), Network Centrality (NC), Subgraph Centrality (SC), Information Centrality (IC), Stress Centrality (SC-1), Radiality Centrality (RC), Eccentricity Centrality (EC-1) and Centroid Centrality (CC-1). The description of twelve algorithms is shown in Supplementary File S3. Again, multiple algorithms can be run simultaneously to analyze the centralities of nodes of dynamic networks. Once centralities are computed, a column for each centrality is added to the Node Table and centrality values are updated over time. Moreover, users can calculate the standard deviation for the centrality values across all sub-networks and the resulting scores are listed in order.

2.3 Cluster analysis of dynamic networks

Four graph clustering algorithms were implemented in DyNetViewer for analyzing clusters of dynamic networks: MCODE (Bader and Hogue, 2003), EAGLE (Shen *et al.*, 2009), ClusterONE (Nepusz *et al.*, 2012) and TSN-PCD (Li *et al.*, 2012). The features of these four clustering algorithms were depicted in the Supplementary File S4. The cluster results are intuitively presented in the form of a thumbnail list which can be updated against time. In addition, DyNetViewer can export results to a txt file and make detailed records of clusters.

2.4 Visualization

The dynamic network which is constructed with time-course data or imported from a txt file can be displayed dynamically. The user can animate a network forward or backward in time and update it over time. Again, the information on the number of currently displayed nodes and edges and the diameter of time-course subnetworks can be given. The dynamic display of network view can also be stopped at any time.

Additionally, the results of node centrality analysis and cluster's attributes (including number of nodes, number of edges, out-degree, in-degree and modularity) over time can also be visualized in a chart. Users may save the chart as jpg/png/svg file, save the chart data in a txt file and enlarge the chart by using the buttons provided for each one of them.

3 Case study

To demonstrate the performance of DyNetViewer, we present one case study. In this case, we obtain H5N1 normal network and H5N1 inflammatory network and their corresponding gene expression data from Jin's article (Jin et al., 2015). Then we apply DyNetViewer to construct the normal and inflammatory dynamic networks for H5N1 infections. Here, we select the TC-PIN algorithm and set the threshold to 6.5 to construct the dynamic network. Additionally, the further centrality analysis and cluster analysis can be implemented on the dynamic networks. The detail description about the case is shown in the Supplementary File S5.

4 Conclusion

DyNetViewer is a multifunctional Cytoscape app for constructing, analyzing, and visualizing dynamic molecular interaction networks. Through visualizing a dynamic network, users can observe that how the network changes over time. Additionally, node centrality analysis and cluster analysis can also be implemented for dynamic networks in DyNetViewer. The framework of DyNetViewer has high potential for extension, thus we can add new dynamic network construction algorithms, centrality analysis algorithms and cluster analysis algorithms to DyNetViewer.

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