

Systems biology

GLay: community structure analysis of biological networksGang Su^{1,6,*}, Allan Kuchinsky², John H. Morris³, David J. States⁴ and Fan Meng^{5,6}¹Bioinformatics Program, University of Michigan, Ann Arbor, MI, ²Agilent Technologies, Santa Clara, CA,³Department of Pharmaceutical Chemistry, University of California San Francisco, San Francisco, CA, ⁴School of Health Information Sciences, Brown Foundation Institute of Molecular Medicine, University of Texas Health Science Center at Houston, TX, ⁵Psychiatry Department and Molecular Behavioral Neuroscience Institute and ⁶National Center for Integrative Biomedical Informatics, University of Michigan, Ann Arbor, MI, USA

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ABSTRACT

Summary: GLay provides Cytoscape users an assorted collection of versatile community structure algorithms and graph layout functions for network clustering and structured visualization. High performance is achieved by dynamically linking highly optimized C functions to the Cytoscape JAVA program, which makes GLay especially suitable for decomposition, display and exploratory analysis of large biological networks.

Availability: <http://brainarray.mbni.med.umich.edu/glay/>

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1 INTRODUCTION

With the rapid development in experimental and computational technology, the scale and dimension of accumulated molecular interaction data have increased dramatically. Many online repositories, such as Michigan molecular interaction (MiMI; Tarcea *et al.*, 2009), have made extensive gene-wise interaction data readily available. The challenge is then how to systematically explore and visualize such large and complex datasets for biological inferences. One solution is to decompose such an interaction network into communities of densely interacting nodes and imply functional modules. A variety of community detection algorithms have been developed to tackle similar challenges in social networks and they have been successfully extended to the biological context (Schwarz *et al.*, 2008; Viana *et al.*, 2009). Recently, Ruan *et al.* (2010) proposed an interesting generic method combing association networks with community structure detection algorithms to infer network modules from microarray data.

Cytoscape is a well-established open source software foundation for analysis and visualization of biological networks. Currently there are several plugins developed for clustering and functional module detection, such as MCode (Bader and Hogue, 2003), NeMo (Rivera *et al.*, 2010) and ClusterMaker (<http://www.cgl.ucsf.edu/cytoscape/cluster/clusterMaker.html>). However, some algorithms in ClusterMaker, such as kmeans or hierarchical, require the network to have numerical attributes to compute a distance matrix for clustering. MCode and NeMo are engineered to identify small and highly intra-connected clusters in a network, without clustering all the nodes. For example, when executed on a MiMI human

interactome network of 11 884 nodes and 88 134 edges using the default parameters, MCODE produced 105 clusters, in which 52 clusters contain less than five nodes. Therefore, it may not be suitable for global subdividing large networks for exploratory analysis. In addition, some of these plugins were not tailored for large networks. For example, NeMo failed when executing on the same MiMI network on a 2.67 GHz Intel Core i7 machine. So far, no plugin offers a comprehensive collection of highly efficient community detection algorithms, which could profoundly improve cluster analysis if added to Cytoscape.

The increasing size and complexity of networks also bring significant challenges to visualization. Generating a layout on such a network not only consumes considerable time and computational resources, but also rarely produces any informative outcome. A typical case is a massive hairball as a result of applying force-based layout to a large network (>500 nodes) with many edges (Merico *et al.*, 2009). Visual separation of clusters in a network can be improved by overlaying community structure on a graphic layout addressing specific topology.

We therefore developed this Cytoscape GLay plugin to make commonly used community structure detection algorithms available. GLay also provides layout algorithms optimized for large networks. GLay not only supplements existing clustering functions, but also provides structured and informative visualization for more efficient exploration and analysis of large biological networks.

2 IMPLEMENTATION

The core of GLay was developed as a Cytoscape plugin with high-performance community analysis and graph layout functions ported from igraph C library (Csardi and Nepusz, 2006). The bridging is built via Java native access (JNA, <https://jna.dev.java.net>) interface. The functions ported from igraph C library are currently only compiled under Windows 32/64 bit platform but will be extended to other platforms in the near future.

Before performing any community analysis, GLay automatically transforms the input network into a simplified model, with edge directionality, duplication and self-looping removed. Such a network standardization step will make the resultant community structures from different community structure detection algorithms comparable as well as improving performance. Upon completion of an analysis, the user may browse the resultant community structure with the built-in GLay navigator panel.

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Table 1. GLayer community algorithms

Connected components	Find connected clusters from a network
Edge betweenness (Newman and Girvan, 2004)	Optimization of modularity score utilizing edge betweenness score
Fast-greedy (Original, HE, HN, HEN) (Clauset <i>et al.</i> , 2004; Wakita and Tsurumi, 2007)	Greedy optimization of modularity score, with different corrections on edge density and cluster size
Label propagation (Raghavan <i>et al.</i> , 2007)	Determine community membership by iterative neighbor votes
Leading eigenvector (Newman, 2006)	Find communities using eigenvector of matrices
Spin glass (Global, Single) (Reichardt and Bornholdt, 2006)	Using spin glass model and simulated annealing. The single mode allows finding communities only surrounding selected nodes
Walk trap (Pons and Latapy, 2005)	Determine community membership via short random walks

Table 1 summarizes the incorporated community detection algorithms. Because of the distinct heuristics of algorithms, running speed and the resultant community structures vary. Some algorithms, such as the leading eigenvector algorithm, works well on a small network of a few hundred nodes but may not be scalable for large networks. Others are optimized for large datasets but may be less accurate. For example, the fast greedy algorithm may produce communities with skewed community size distribution because of the greedy optimization of the modularity score (Wakita and Tsurumi, 2007). Users may test different algorithms and evaluate performance by various benchmarks such as modularity, number of communities and community size distribution.

Table 2 lists GLayer layout algorithms. These algorithms are able to efficiently layout very large networks or generate hierarchical trees. A key advantage of GLayer layout is that it allows the layout calculations of various algorithms to initiate from the current network layout state. This adds significant flexibility since it enables the user to progressively improve the layout by either fine-tuning parameters or using different layout algorithms together. For example, for a very large network, the user may specify a small number of iterations to obtain a draft layout, and then gradually refine the layout by adding more iterations or tuning the parameters. Once done, the user may superimpose the community structure on the layout to investigate network topology. For more information, please refer to the plugin homepage and igraph library documentation (Csardi and Nepusz, 2006).

3 RESULTS AND CONCLUSION

We have tested GLayer on datasets of various size and structure. GLayer demonstrated substantial performance gain in both network decomposition and layout over existing Cytoscape solutions. For example, using GLayer to subdivide the MiMI human Interactome—which contains 11 884 nodes and 88 134 edges—takes 0.7 s using the label propagation algorithm and 20 s using the fast greedy algorithm on the same 2.67 GHz Intel Core i7 machine. MCODE takes 198 s to find clusters. Generating layout on this network using the Fruchterman Reingold grid algorithm takes about 20 s,

Table 2. GLayer layout algorithms

Fruchterman Reingold (original, grid) (Fruchterman and Reingold, 1991)	Efficient force-based algorithms, with the grid version optimized for large networks
graphopt (GraphOPT http://www.schmuhl.org/graphopt/)	Force-based algorithm with optimization
Kamada kawai	Force-based spring layout
Large graph layout (Adai <i>et al.</i> , 2004)	Large graph layout algorithms for connected graphs
Multidimensional scaling (MDS) (Brandes and Pich, 2007)	Layout based on multidimensional scaling based on shortest distances
reingold tilford (hierarchical, circular) (Reingold and Tilford, 1981)	Tree-like layout for connected networks, can be hierarchical or circular from any node as root

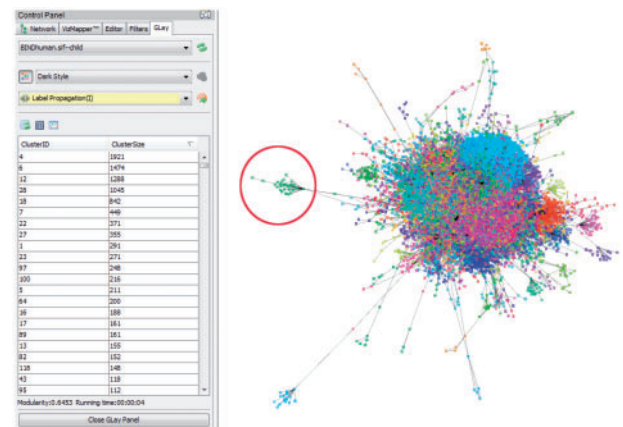


Fig. 1. Fast-greedy community structure superimposed on Fruchterman Reingold grid layout from the largest component of Cytoscape human BIND dataset, consists of 17 961 nodes and 30 156 edges. Note that nodes belong to the same community tend to aggregate spatially, which resulted in clusters with good visual separation. The red circle indicates a group of highly interacting immunoglobulins.

whereas the Cytoscape built-in force directed and spring embedded algorithms both reported error during execution both with default setup and 1.5 G heap space. This demonstrates that Java-C hybrid model has dramatic performance advantage handling large networks in Cytoscape.

GLayer also enables easy navigation of clustering results. Figure 1 shows a screenshot of overlaying fast greedy community structure on Fruchterman Reingold grid layout on the Cytoscape built-in BIND human dataset. Users may navigate and explore communities of genes with the GLayer browser. For example, clicking the cluster entry in the browser table will select all nodes within a cluster. The user will then be able to create a new subnetwork or nested network from the selected nodes, extract gene lists from attribute browser or incorporate other experimental data for various research interests.

In addition, GLayer can provide qualitative different results from existing solutions. Figure 2 shows a side-by-side comparison of MCODE at default parameters and GLayer using fast greedy algorithm. It can be seen that by using the default parameters, MCODE produces much smaller clusters than GLayer, leaving majority of the nodes unclustered. Therefore, GLayer outperforms

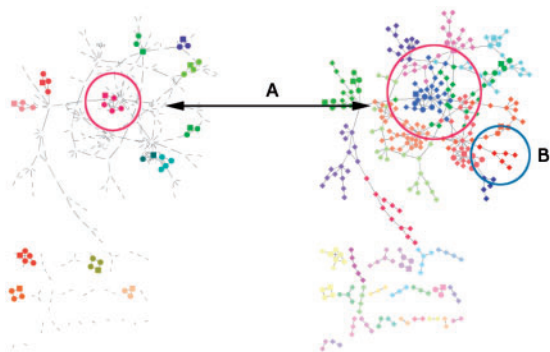


Fig. 2. Comparison between clusters produced by MCODE with default parameters (left) and GLay using fast-greedy algorithm (right) on Cytoscape bundled galFiltered (Ideker *et al.*, 2001) dataset. The node color is determined by the corresponding cluster membership. Left: MCODE clusters. The unclustered genes are hidden. Right: GLay fast-greedy clusters. **(A)** A MCODE cluster, in which four out of five genes are associated with MAPK pathway. The corresponding cluster in GLay contains 25 genes, including more genes in MAPK pathway, cell cycle and ion binding. **(B)** A GLay cluster not identifiable by MCODE. This cluster consists of six genes, with four are related to RNA process.

MCODE in terms of structural partitioning of the original network. In addition, overall GLay has higher sensitivity than MCODE at the trade-off of specificity, which made it more suitable for functional interpretation. For example, in Figure 2, one cluster in MCODE contains five genes, with four genes function in MAPK pathway. The equivalent GLay cluster contains 25 genes. Submitting these genes to DAVID (Dennis *et al.*, 2003) reveals one enriched functional cluster for the MCODE cluster and nine enriched functional cluster for the GLay cluster. As some of the genes such as *cdc28* and *ste12* are involved in multiple regulation processes, the GLay cluster recovered more biological-relevant information than the equivalent MCODE cluster.

In summary, GLay capitalizes on the power of highly optimized C code from several social network analysis and network layout algorithms to improve scalability of Cytoscape for large networks. We hope GLay can help to address the increasing needs for analysis and visualization of large-scale networks. We are committed to add cross-platform support for Linux and Mac environments as well as to integrate novel network analysis and layout functions in GLay.

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Conflict of Interest: none declared.

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