Identifying edge clusters in networks via edge graphlet degree vectors (edge-GDVs) and edge-GDV-similarities

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ABSTRACT

Inference of new biological knowledge, e.g., prediction of protein function, from protein-protein interaction (PPI) networks has received attention in the post-genomic era. A popular strategy has been to cluster the network into functionally coherent groups of proteins and predict protein function from the clusters. Traditionally, network research has focused on clustering of nodes. However, why favor nodes over edges, when clustering of edges may be preferred? For example, nodes belong to multiple functional groups, but clustering of nodes typically cannot capture the group overlap, while clustering of edges can. Clustering of adjacent edges that share many neighbors was proposed recently, outperforming different node clustering methods. However, since some biological processes can have characteristic “signatures” throughout the network, not just locally, it may be of interest to consider edges that are not necessarily adjacent. Hence, we design a sensitive measure of the “topological similarity” of edges that can deal with edges that are not necessarily adjacent. We cluster edges that are similar according to our measure in different baker’s yeast PPI networks, outperforming existing node and edge clustering approaches.

In particular, PPI network analysis could help in suggesting top candidates for future experimental validation, since proteins aggregate to perform a function, and since PPI networks model these aggregations. Thus, it is no surprise that prediction of protein function [Sharan et al., 2007; Milenković & Pržulj, 2008] and the role of proteins in disease [Sharan & Ideker, 2008; Radivojac et al., 2008; Goh et al., 2007; Milenković et al., 2010; Vanunu et al., 2010] from PPI networks have received attention in the post-genomic era. For example, it has been argued that proteins which are close in the network are likely to be involved in similar biological processes [Sharan et al., 2007], that “topologically central” proteins correspond to “biologically central” (e.g., lethal, aging-, or cancer-related) proteins [Jeong et al., 2001; Sharan & Ideker, 2008; Jonsson & Bates, 2009; Milenković et al., 2011], or that proteins with similar topological neighborhoods have similar biological characteristics [Milenković & Pržulj, 2008; Ho et al., 2010].

A particularly popular strategy for functional characterization of proteins has been to cluster the network into functionally “coherent” groups of nodes and assign the entire cluster with a function based on functions of its annotated members [Sharan et al., 2007; Sharan & Ideker, 2008]. A variety of clustering approaches exist, each with its own (dis)advantages [Brohee & van Helden, 2006; Fortunato, 2010]. Typically, they aim to group nodes that are in a dense connected network region [Fortunato, 2010]. Also, approaches exist that cluster “topologically similar” nodes without the nodes necessarily being connected in the network. This is important, since a biological process can have characteristic topological “signatures” throughout the network, not just locally in close network proximity [Milenković & Pržulj, 2008; Milenković et al., 2010; Ho et al., 2010]. For example, we designed a measure that computes the topological similarity of the extended network neighborhoods of two nodes, without the nodes necessarily being close in the network [Milenković & Pržulj, 2008]. We found that 96% of known cancer gene pairs that are topologically similar according to our measure are actually not neighbours in the PPI network; instead, they are at the shortest path distance of up to six [Milenković et al., 2010]. As such, they may be missed by approaches that focus on connected nodes only. We clustered proteins in the human PPI network that are topologically similar and showed that function of a protein and its network position are closely related [Milenković & Pržulj, 2008] and that the topology around cancer and non-cancer genes is different [Milenković et al., 2010]. We used these observations to predict new cancer genes in melanogenesis-related pathways and our predictions were validated phenotypically [Ho et al., 2010].

Traditionally, network research has focused on clustering of nodes [Fortunato, 2010]. However, a network consists of nodes and edges. Hence, why favor nodes over edges, especially when clustering of edges may be preferred? For example, since nodes typically belong to multiple functional groups, and since clusters are

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expected to correspond to the functional groups, it may be desirable to allow for a node to belong to multiple clusters. Clustering of nodes typically cannot capture the group overlap, especially if the network is partitioned into disjoint node sets, as is the case with many (although not all) node clustering approaches (Fortunato, 2010; Ahn et al., 2010). However, clustering of edges can trivially capture the group overlap (Fig. 1). Edge clustering methods were proposed only recently (Ahn et al., 2010; Evans & Lambiotte, 2009). Adjacent (connected) edges that share many neighbors were defined as similar and were thus clustered together (see below), outperforming different node clustering methods, including a method which allows for the group overlap (Ahn et al., 2010). However, it may be of interest to consider edges that are not necessarily adjacent (see above).

Hence, we introduce a new measure of edge similarity that is not only capable of dealing with edges that are not necessarily adjacent, but is also a more sensitive measure of topology than the above shared-neighborhood measure (Ahn et al., 2010). For a fair evaluation of our measure, when grouping edges that are similar according to our measure, we precisely mimic the above edge clustering approach by (Ahn et al., 2010). We show that using our measure results in clusters of comparable or better quality.

2 APPROACH

We recently designed a graphlet-based measure of the topological position of a node in the network; graphlets are small induced subgraphs of a network (Fig. 2) (Pržulj, 2007). This measure generalizes the degree of a node that counts the number of edges that the node touches (where an edge is the only 2-node graphlet) into the node graphlet degree vector (node-GDV) that counts the number of different graphlets that the node touches, for all 2-5-node graphlets (Fig. 2, also, see Methods). Hence, node-GDV describes the topology of the node’s up to 4-deep neighborhood (Milenković & Pržulj, 2008). This is effective: going to distance of four around a node captures a large portion of the network due to the small-world nature of many real networks (Watts & Strogatz, 1998). For this reason, and since the number of graphlets on n nodes increases exponentially with n, using larger graphlets could unnecessarily increase the computational complexity of the method. Also, we designed node-GDV-similarity measure to compare node-GDVs of two nodes and hence quantify the topological similarity of their extended network neighborhoods (Milenković & Pržulj, 2008).

Since a graphlet consists of nodes and edges, we now design edge-GDV to count the number of different 3-5-node graphlets that an edge touches (Fig. 2). (We exclude the count for the only 2-node graphlet, an edge, as each edge touches exactly one 2-node graphlet, itself.) Also, we design edge-GDV-similarity to compare edge-GDVs of two edges and hence quantify the topological similarity of their extended network neighborhoods. Unlike the shared-neighborhood measure (Ahn et al., 2010), edge-GDV-similarity can measure similarity between edges independent on whether they are adjacent. Also, by counting the shared neighbors of end nodes of two (adjacent) edges, the shared-neighborhood measure actually counts the 3-node paths that the end nodes share (Ahn et al., 2010). Since edge-GDV counts the different 3-5-node graphlets that an edge touches, including a 3-node path, edge-GDV is a more constraining measure of topology. See Methods for details.

We evaluate our approach against existing clustering methods, as follows (also, see Methods). The existing edge clustering method mentioned above, henceforth denoted by edge - shared neighborhood (edge-SN), was already shown to be superior to different node clustering methods on four baker’s yeast PPI networks (Ahn et al., 2010). For a fair evaluation, we mimic edge-SN exactly, except that we use edge-GDV-similarity instead of the shared-neighborhood measure as the distance metric for the same clustering method, namely hierarchical clustering. Just as edge-SN, we (initially) cluster only adjacent edges, and of all partitions, we choose the one with the maximum density (see Methods). Just as edge-SN, we evaluate such partition with respect to four measures: cluster coverage (the portion of the network “covered” by “non-trivial” clusters), overlap coverage (the amount of node overlap between clusters), cluster quality (enrichment of clusters in Gene Ontology (GO) terms (Ashburner et al., 2000)), and overlap quality (the correlation between the number of clusters and the number of GO terms that nodes participate in). When applied to the same yeast networks, our approach in comparable or superior to edge-SN (and hence to the node clustering approaches that were outperformed by edge-SN on the same networks). Thus, we gain by using a more sensitive measure of topology compared to edge-SN. Furthermore, when we cluster both adjacent and non-adjacent edges, our method in general performs even better. Hence, we gain additionally by using a measure that can capture similarity of edges that are not necessarily adjacent. We note that we do not propose a new edge clustering method but a new edge similarity measure that can serve as a distance metric for existing clustering methods.

3 METHODS

3.1 Data sets

We cluster the same four baker’s yeast PPI networks that edge-SN was evaluated on (Ahn et al., 2010; Yu et al., 2008): 1) Y2H network, obtained by Y2H, with 1,647 proteins and 2,518 PPIs; 2) AP/MS network, obtained by AP/MS, with 1,004 proteins and 8,319 PPIs; 3) LC network, obtained by literature curation, with 1,213 proteins and 2,556 PPIs; and 4) ALL network, representing the union of Y2H, AP/MS, and LC, with 2,729 proteins and 12,174 PPIs. Using these different networks ensures that our method is robust to different types of experiments for PPI detection.

3.2 Related work

We compare our method to three popular node clustering methods: clique percolation (Palla et al., 2005), greedy modularity optimization (Newman, 2004), and InfoMap (Rosvall & Bergstrom, 2008). Also, we compare it to the existing edge clustering algorithm, edge-SN (Ahn et al., 2010). Briefly, clique percolation is the most prominent overlapping node clustering...
algorithm, greedy modularity optimization is the most popular modularity-based technique, and Infomap is often considered the most accurate method available. "Ahn et al. (2010) say Edge-SN hierarchically groups adjacent edges whose non-common end-nodes share many neighbors (see below). We did not run these algorithms on the yeast networks because the results were not reported by "Ahn et al. (2010) who ran the algorithms on the same networks. For details on how the methods were implemented, see "Ahn et al. (2010)."

3.3 New measures of network topology: edge graphlet degree vector (edge-GDV) and edge-GDV-similarity

A graphlet is an induced subgraph of graph X that contains all edges of X connecting its nodes (Fig. 2). We generalized the degree of node v that counts the number of edges that v touches (where an edge is the only 2-node graphlet, Go in Fig. 2) into node graphlet degree vector (node-GDV) of v that counts the number of 2-5-node graphlets (Go, G1, . . . , G29 in Fig. 2) that v touches (Milenković & Pržulj, 2008). We need to distinguish between v touching, e.g., a G1 at an end node or at the middle node, since G1 admits an automorphism that maps its end nodes to each other and the middle node to itself. To understand this, recall the following. An isomorphism f from graph X to graph Y is a bijection of nodes of X to nodes of Y such that xy is an edge of X if and only if f(x)f(y) is an edge of Y. An automorphism is an isomorphism from X to itself. The automorphisms of X form the automorphism group, Aut(X). If x is a node of X, then the automorphism node orbit of x is Orb(x) = {y ∈ V(X)|y = f(x) for some f ∈ Aut(X)}, where V(X) is the set of nodes of X. Thus, end nodes of a G1 belong to one node orbit, while its middle node belongs to another one. There are 73 node orbits for 2-5-node graphlets. Hence, node-GDV of v has 73 elements counting how many node orbits of each type touch v (v’s degree is the first element). It captures v’s up to 4-deep neighborhood and thus a large portion of real networks, as they are small-world (Watts & Strogatz, 1998).

Since a graphlet contains nodes and edges, we propose a new graphlet-based measure of the topological position of an edge in the network. We define edge-GDV to count the number of graphlets that an edge touches at a given “edge orbit” (Fig. 3). We define edge orbits are follows. Given the automorphism group of graph X, Aut(X), if xy is an edge of X, then the edge orbit of xy is Orb(xy) = {zw ∈ E(X)|z = f(x) and w = f(y) for some f ∈ Aut(X)}, where E(X) is the set of edges of X. For example, in Fig. 1 in a G1, both edges are in edge orbit 1. In a G2, all three edges are in edge orbit 2. In a G3, the two “outer” edges are in edge orbit 3, while the “middle” edge is in edge orbit 4. And so on. There are 69 edge orbits for 2-5-node graphlets. (We intentionally exclude orbit 0 in the only 2-node graphlet, Go, as each edge touches exactly one Go, namely itself.)

Comparing edge-GDV’s of two edges gives a sensitive measure of their topological similarity, since their extended network neighborhoods are compared. Using some existing measure, e.g., Euclidean distance, to compare edge-GDV’s might be inappropriate, as some edge orbits are not independent. Instead, we design edge-GDV-similarity measure as follows. For an edge e, ei is the ith element of its edge-GDV. The distance between the ith edge orbits of edges e and f is Di(e, f) = wi × log(Di(e, f) + 1)/log(n), where wi is the weight of edge orbit i that accounts for edge orbit dependencies. For example, the differences in counts of orbit 2 of two edges will imply the differences in counts of all other orbits that contain orbit 2, such as orbits 8-12 (Fig. 2). This is applied to all edge orbits: the smaller the number of orbits that affect orbit i (including itself), ai, the higher its weight wi, where wi = 1 − log(ai)/log(n). Clearly, wi is in (0,1] and the highest weight of 1 is assigned to orbit i with ai = 1. The log is used in the formula for Di because the ith elements of two edge-GDVs can differ by several orders of magnitude and we do not want the distance between edge-GDVs to be dominated by large values; also, we want to account for the relative difference between ei and fi and that is why we divide by the value of the denominator, which also scales Di to [0, 1]. The constants are added to prevent Di to be infinite. The total distance is D(e, f) = ∑n−1i=0 Di(e, f). Finally, edge-GDV-similarity is S(e, f) = 1 − D(e, f). It is in [0, 1]. The higher the edge-GDV-similarity, the higher the topological similarity of edges’ extended network neighborhoods. We design edge-GDV-similarity as described because we already designed node-GDV-similarity, which compares node-GDVs, in a similar way (Milenković & Pržulj, 2008), and because we showed in different contexts that node-GDV-similarity successfully extracts function from network topology (Milenković et al., 2010, Mensimov et al., 2010). Kuchaiev et al. (2010) say, we expect edge-GDV-similarity to successfully extract function from topology as well.

3.4 Our clustering strategies

We cluster the yeast PPI networks in the same manner as edge-SN, except that we use edge-GDV-similarity as the distance metrics instead of using the shared-neighborhood measure. Initially, for a fair comparison with edge-SN, we cluster adjacent edges only, to test if and how much we gain by using our more sensitive measure of edge similarity. Later on, we cluster all
edges, to test if and how much we gain by taking into account edges that are not necessarily adjacent. Some further information is provided below, after defining measures of partition quality.

3.5 Quality of partitions

We evaluate a partition with respect to the same measures that were used by edge-SN: cluster coverage (CC), overlap coverage (OC), cluster quality (CQ), and overlap quality (OQ). CC is the fraction of nodes that belong to at least one “non-trivial” cluster of three or more nodes. OC is the average number of non-trivial clusters that nodes belong to. CQ is the ratio of the average Gene Ontology (GO) term similarity over all node pairs that are in at least one same cluster and the average GO terms similarity over all node pairs in the network. OQ is the mutual information between the number of GO terms and the number of non-trivial clusters that proteins are involved in. Raw values for the four measures do not necessarily fall in [0, 1]. Hence, just as Ahn et al. (2010), we normalize each measure such that the best method has a value of one. Then, the overall partition quality is the sum of these four normalized measures, such that the maximum achievable score is four.

We can now note the following. To mimic Ahn et al. (2010), we would report for a given network the partition with maximum partition density \( D \). However, we find that \( D \) is strongly negatively correlated with CQ and OC, and sometimes with CC, over all of our partitions (Fig. A). Thus, choosing the partition with low CC would result in high CQ and OQ (and sometimes OC), hence artificially increasing the overall partition quality. Since in three out of four yeast networks CC is lower for edge-SN than for the node clustering methods, it might not be surprising that edge-SN’s overall partition quality is the highest. Analogously, since edge-SN’s partitions with maximum \( D \) have lower CC than our partitions with maximum \( D \), our partitions may have lower overall partition quality simply because of the strong negative correlation between CC and other measures. Hence, we find the partition with maximum \( D \) among all partitions that have CC less than or equal to CC of edge-SN’s partition with maximum \( D \). Then, we report either the partition obtained in this way or the partition with maximum \( D \) (independent of its CC), whichever has better overall partition quality. Furthermore, when we cluster both adjacent and non-adjacent edges, selecting the partition based on its density, as just described, might be inappropriate (see above). Thus, when we cluster both adjacent and non-adjacent edges, we also report the partition with the best overall partition quality.

4 RESULTS

We evaluate our method against three node clustering methods (clique percolation – CliqPerc, greedy modularity optimization – GreedMod, and Infomap) and one edge clustering method (edge-SN) on four yeast PPI networks (Y2H, AP/MS, LC, and ALL), with respect to four measures of partition quality (cluster coverage – CC, overlap coverage - OC, cluster quality – CQ, and overlap quality – OQ) that are combined into the normalized overall partition quality; see Methods. We denote our method when clustering adjacent edges only and reporting the partition with the maximum density as eGDV-A-D. We denote our method when clustering both adjacent and non-adjacent edges and reporting the partition with the maximum density as eGDV-NA-D. We denote our method when clustering both adjacent and non-adjacent edges and reporting the partition with the best overall partition quality as eGDV-NA-B. See Methods for details. Results are shown in Fig. A. We gain by using edge-GDV-similarity for clustering: eGDV-A-D outperforms all node clustering approaches on all networks. (This includes node clustering by using node-GDV-similarity, as shown in Fig. B). Also, it outperforms edge-SN on Y2H and AP/MS. Although edge-SN is slightly better than and comparable to eGDV-A-D on LC and ALL networks, respectively, eGDV-NA-D outperforms edge-SN on these two networks, as well as on AP/MS. Hence, we gain further by clustering non-adjacent edges in addition to adjacent ones. The only exception is Y2H, for which edge-SN is slightly better than eGDV-NA-D. However, as already noted, eGDV-A-D outperforms edge-SN on Y2H network. Hence, we are always superior, with either eGDV-A-D or eGDV-NA-D or both eGDV-A-D and eGDV-NA-D. With eGDV-NA-B, we further demonstrate our superiority over all other methods on all networks.

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Fig. 3. Pairwise Pearson correlations for four measures of partition quality (cluster coverage – CC, overlap coverage - OC, overlap quality – OQ, and cluster quality – CQ) over all partitions for a given yeast PPI network (Y2H, AP/MS, LC, and ALL), when clustering adjacent edges only (Adjacent Edges; panels A-D) and when clustering both adjacent and non-adjacent edges (All Edges; panels E-H). In all eight panels, CC is strongly negatively correlated with OQ and CQ.
Fig. 4. Method comparison for (A) Y2H, (B) AP/MS, (C) LC, and (D) ALL yeast PPI networks. The following methods are compared: clique percolation (CliqPerc), greedy modularity optimization (GreedMod), Infomap, edge-SN, our method when clustering adjacent edges only and choosing the partition with the maximum density (eGDV-A-D), our method when hierarchically clustering both adjacent and non-adjacent edges and choosing the partition with the maximum density (eGDV-NA-PD), and our method when hierarchically clustering both adjacent and non-adjacent edges and choosing the partition with the best overall partition quality (eGDV-NA-B). Clustering methods are compared with respect to the following measures: cluster coverage (CC), overlap coverage (OC), cluster quality (CQ), and overlap quality (OQ). The overall partition quality score (y-axis) is the sum of these four measures after each is normalized to [0,1], such that the maximum achievable score is four.
Fig. 5. Comparison of our node and edge clustering methods on the four yeast PPI networks (Y2H, LC, AP/MS, and ALL). nGDV-A denotes the node clustering method when node-GDV-similarity is used as the distance metric for hierarchical clustering of adjacent nodes only and the partition with the maximum partition density is selected. nGDV-NA denotes the node clustering method when node-GDV-similarity is used as the distance metric for hierarchical clustering of both adjacent and non-adjacent nodes and the partition with the best overall partition quality is selected. eGDV-A denotes the edge clustering method when edge-GDV-similarity is used as the distance metric for hierarchical clustering of adjacent edges only and the partition with the maximum partition density is selected. eGDV-NA denotes the edge clustering method when edge-GDV-similarity is used as the distance metric for hierarchical clustering of both adjacent and non-adjacent edges and the partition with the best overall partition quality is selected. The clustering methods are compared with respect to the following measures: cluster coverage (CC), overlap coverage (OC), cluster quality (CQ), and overlap quality (OQ). The overall partition quality score (y-axis) is the sum of these four measures after each is normalized to [0,1], such that the maximum achievable score is four. We compare our approach when using edge-GDV-similarity as the distance metric for edge clustering against our approach when using node-GDV-similarity as the distance metric for node clustering since we want to answer if and how much we gain by clustering of edges compared to clustering of nodes. And to answer this, one should use conceptually similar edge and node clustering methods, such as these. The figure shows that in each network: 1) we gain by clustering both adjacent and non-adjacent nodes compared to clustering only adjacent nodes; 2) we gain further by clustering adjacent edges instead of clustering nodes; and 3) we gain the most by clustering both adjacent and non-adjacent edges.