Dominating Sets in Protein-Protein Interaction Networks

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Abstract. Protein-Protein interactions (PPIs) are vital for explaining the structural and functional architecture of the cell. To have a wider comprehension of the mechanisms, finding driver proteins that are vital for the control of the said network is a pertinent task in systems biology. Lately, it has become a strategy to find the smallest set of driver nodes to control the whole network. To apply on networks that are undirected, Nacher and Akutsu viewed this problem from the point of view of finding the smallest dominating set. Dominating sets are widely enriched with genes that are biologically central. Nacher and Akutsu found that the speculated driver proteins using the smallest dominating set model not only pass pertinent functional features but also control the whole network They classified the vertices into three types such as critical vertices that belong to every configuration, unnecessary vertices that do not belong to any configuration and intermediary vertices that belong to some configurations but not all. In this paper we explain the above and probe how various centrality measures such as degree centrality, betweenness centrality, subgraph centrality etc., help us to understand PPI networks.

Keywords: Smallest dominating sets · Centrality measures · Protein-protein interaction · Networks

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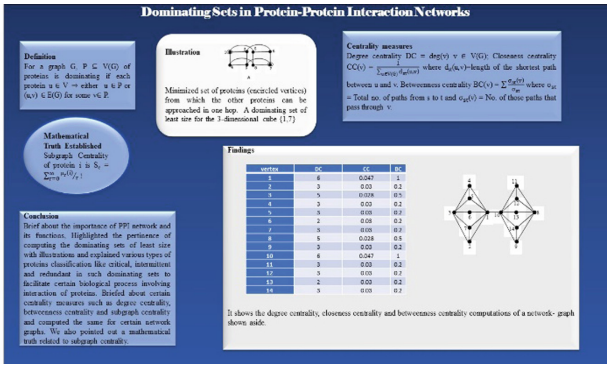
1 Introduction



PPI networks assumes huge participation in comprehending disease propagations and associated mechanisms [1]. Several techniques are proposed to spell the underlying structure in various organisms, like yeast [2–5]. Advances in biotechnology has played a major role in the creation of various databases explaining them [6, 7]. So it is inevitable to look for an apt representation at system level to pick a subset of genes deeming crucial part in viability of cells, like the one in cancer genes [8]. The probe of the dominating set with minimum number of elements is the need of the hour. It has the attribute that each other vertex in the network must be adjacent to at least one vertex of it [8–10]. It reveals the correlation among structural pattern and biological significance [8, 9, 11–20]. It is interesting to find that vital set which includes as many common vertices of all such dominating sets with minimum size [12, 20]. Finding such a dominating set with minimum size is computationally hard [10], and further no procedure developed so far can find it in polynomial time [21]. Nacher and Akutsu [22] proposed an integer based LP model to find an optimal solution for such a task. Zhang and others in [13] considered the degree measure and the betweenness centrality measures of proteins and expressed that topological attributes alone is not sufficient to speculate the protein functions [17]. In [23] the authors underlined the vitality of enrichment affect probe as no algorithm could find the best dominating set in real time [13, 24, 25]. In [26] it was observed that determining two or more dominating sets with least intersection belongs to class NP-hard. In [23] the authors gave a new framework called maximization of interaction make up, to produce for a given PPI network multiple dominating sets with least size. They made use of techniques said in [27–29] to identify the shared vertices among these two dominating sets of least size whose elements are essential vertices to hold tightly the critical set of the PPI network under consideration. Then, they generalized to produce k dominating sets of least size. In [30], the authors studied another extension of the dominating set of least size model to account for the degree heterogeneity and betweenness among proteins. Depending on the knowhow that high-degree and high-betweenness among proteins could act as controllers they developed a degree and betweenness centrality-corrected dominating set of least size model. They tested both the models standard on three different human networks that are PPI based. The results obtained by them

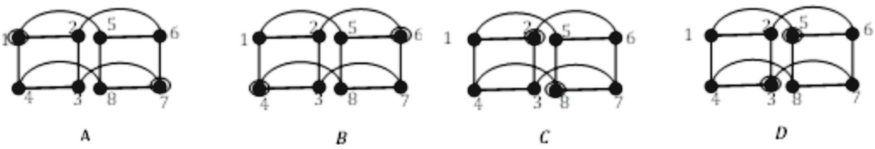


Fig. 1. An instance that stimulates our attention: It describes the concept of dominating sets of least size. It is a minimized set of proteins (encircled vertices) from which the other proteins can be approached in one hop. Four distinct dominating sets of least size for the 3-dimensional cube are shown. A) {1,7}, B) {4,6}, C) {2,8}, D) {3,5}.

showed that centrality-corrected dominating set of least size proteins guessed by three optimization methods are the same closely; but the overlap among dominating set of least size proteins guessed by three optimization methods is quite insignificant. So it is evident that such results means the high-degree/high-betweenness proteins deems a vital part in controlling the said network.

2 Dominating Sets of Least Size

Denote a PPI network by a graph G = (V, E), where V is the set of n vertices and E is the set of edges. Defined by an adjacency matrix A = (a_{ij}) with $a_{ij} = 1$ if there exists an interaction between proteins i and j and 0 in the case of the other. We also deem $a_{ii} = 1$ if G has self-loop at protein i.

We call a set P ⊆ V of proteins a dominating set if each protein u ∈ V is either a member of P or is joined by means of an edge to a member of P [8, 22]. A dominating set of least size for a given network can be seen in Fig. 1. To determine a dominating set P of minimum size, we assign to each protein i an integer variable y_i, that assumes the value 1 if protein i ∈ P and the value 0 if protein i ∉ P. Clearly a dominating set should satisfy: $y_i + \sum y_j \geq 1$where j ∈ N(i), the set of neighbours of protein i for i = 1,…,n. By making use of the adjacency matrix A, we can express it as $\sum A_{ij} y_j \geq 1$ for i = 1,…,n. In view of this the task of finding a dominating set of least size is equivalent to finding an integer valued solution of: Minimize $\sum y_j$ j = 1,…,n subject to $\sum A_{ij} y_j \geq 1$ for i,j = 1,…,n and $y_j \in \{0,1\}$ ---(1).

As said in [20], more than one optimal solution to (1) may exist for a given PPI network. So dominating set least size determined by various optimization techniques may be distinct. See Fig. 1A–D). There are instances where there is only one dominating set of least size. See Fig. 2. Figure 3 shows an instance where the degree of the vertices differ with different dominating sets of least size.

In view of this it is hard to declare the real set to control the whole network. To offset this one can consider degree and betweenness measures. Latest probes have demonstrated that network attributes of central genes reveal certain topological centrality when matched to the remaining set of proteins and moreover these measures are discriminate in bringing out central genes [8]. It would be appropriate to select those members of the collection of dominating sets of least size that have the highest degree and betweenness. However, if the network has the fantastic attribute of equal degree for all vertices then no technique could reveal which one would be better. So there are advantages and

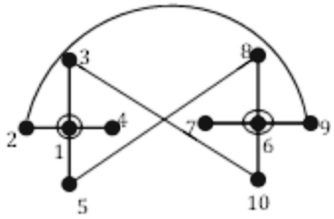


Fig. 2. It shows a network instance where there is only one dominating set of least size A = {1,6} encircled.

disadvantages for a network to be regular or otherwise. To add the heterogeneity factor in centrality one can use in the objective function of Eq. (1), the term $\sum y_j$ j = 1 to n to find the cardinality of the dominating set of least size, where each vertex of the network gets equal importance. To introduce heterogeneity factor of the centrality, a centrality-corrected form $\sum \alpha_j y_j$ is employed as a substitute for the original term, where $\alpha_1, \alpha_2, \cdots, \alpha_n$ are positive weights associated to vertex centralities. This gives raise to a centrality-corrected dominating set of least size as follows. Minimize $\sum \alpha_j y_j$ j = 1,…,n subject to $\sum A_{ij} y_j \geq 1$ for i, j = 1,…,n and $y_j \in \{0,1\}$---(2). This approach finds proteins with small weights as driver proteins. To determine the apt weights to recognize high-degree and high-betweenness proteins we pick the weights that varies as the reciprocal to the degrees and betweenness of proteins, i.e., $\alpha_j = (e_j c_j)^{-\beta}$--- (3) where e_j and c_j are the degree centrality and betweenness centrality of protein j, respectively; β (≥ 0) is a parameter that controls the weights. When $\beta = 0$, the dominating set of least size got from (2) points to the version given in (1); when $\beta > 0$, it selects high-degree and high-betweenness proteins.

2.1 Formulae for Centrality Measures

We deem degree centrality as the number among the proteins interacting partners. Degree centrality DC means DC = deg(v) v ∈ V(G). Closeness centrality CC means $CC(v) = \frac{1}{\sum_{u \in V(G)} d_{st}(u,v)}$ where $d_{st}(u,v)$ = length of the shortest path between u and v. Betweenness centrality BC means $BC(v) = \sum \frac{\sigma_{st}(v)}{\sigma_{st}}$ where σ_{st} = Total no. of paths from s to t and σ_{st} (v) = No. of those paths that pass through v. One can also find betweenness centrality with "MatlabBGL" [31].

2.2 Subgraph Centrality Measures

The subgraph centrality measure characterizes the role of every vertex in all subgraphs in a network. Subgraphs with lesser size are given more weight than the ones with larger size. This attribute is apt for describing network motifs. It can be obtained mathematically from the spectrum of the adjacency matrix of the network. This measure is more sharper to characterize the vertices in comparison to measures like degree, betweenness centralities etc. Strong correlations are there between various measures of centrality [32]. The vertices with huge degree provide small average distance to the other vertices that gives rise to high correlations among vertex degree and other centrality measures.

They also take part in huge number of subgraphs. S_c in general gives for the vertices of huge degree the highest ranking although they differ for most of the vertices. In [32] the authors to probe the effect of variations in the ranking of vertices in real-situations, studied the drastic effect of proteins in *S*. cereviciae and demonstrated that the deletion of a protein from the to its vertex degree. They ranked all proteins as per degree centrality and subgraph centrality and counted the number of vulnerable proteins in the first p proteins of the ranking, with 10 step increase. It was noted that the ranking introduced by subgraph centrality has more essential proteins. S_c measure considers the number of triangles, squares and other subgraphs that play vital part in comprehending the evolution of the protein–protein interaction network [33, 34].

2.3 A Mathematical Truth of Subgraph Centrality

Let G be a simple graph with p vertices. It is known that graph spectrum is the collection of all those eigen values corresponding to the graph G's adjacency matrix A. Suppose that $\mu_r(i)$ is the number of closed walks of length r with i as start and end vertex. It is also called as local spectral moments, can be computed as the ith diagonal entry of the rth power of A. That is $\mu_r(i) = (A^k)_{ii}$. These closed walks are linked to the subgraphs of the network under consideration as subgraph centrality measure. That is, the sum of closed walks of distinct lengths with start and end vertex as i is the subgraph centrality of i. Note that in this sum we consider all cyclic and acyclic subgraphs. Also closed walks of lesser length has more effect on the vertex centrality than the measure with bigger lengths. This is in accordance with the fact that real life networks are small subgraphs. Mathematically, subgraph centrality of i is $S_c = \sum_{r=0}^{\infty} \mu_r(i)/r!$. Suppose that λ is the main eigen value of A. Then $\sum_{r=0}^{\infty} \mu_r(i)/r! \leq \sum_{r=0}^{\infty} \lambda^r/r! = e^{\lambda}$ as for any $r \in Z^+$ and $1 \leq i \leq n$, $\mu_r(i)$ is at most λ^r, the terms of the series are non-negative and $\sum \mu_r(i)/r!$ converges. Suppose that x_j for $1 \leq j \leq p$ is the orthonormal basis of R^p provided by eigen vectors of A corresponding to the eigen values λ_j, $1 \leq j \leq p$. If x_j^i is the i^{th} component of x_j then for all $i \in V(G)$ the vertex set of G, the S_c can be given as $S_c = \sum_{j=1}^{p} \left(x_j^i\right)^2 e^{\lambda_j}$ --(*). This is because, the orthogonal projection of the ith unit vector of the natural base of R^p on x_j is given by $pr_j(e_i) = \left(\langle e_i, x_j\rangle / \|x_j\|^2\right) x_j = < e_i, x_j > x_j = x_j^i x_j$. So $\mu_r(i) = (A^r)_{ii} = \langle A^r e_i, e_i\rangle = \langle A^r \sum_{j=1}^{p} pr_j(e_i), \sum_{j=1}^{p} pr_j(e_i)\rangle = \sum_{j=1}^{r} \lambda_j^r \left(x_j^i\right)^2$. Hence $S_c = \sum_{r=0}^{\infty} \left(\sum_{j=1}^{p} \frac{\lambda_j^r \left(x_j^i\right)^2}{r!} \right)$. As the righthand side of S_c converges absolutely due to proper reordering and the fact that $\sum_{j=1}^{p} \left(x_j(i)^2 \sum_{r=0}^{\infty} \lambda_j^i / r!\right) = \sum_{j=1}^{p} \left(\left(x_j(i)\right)^2 e^{\lambda_j}\right)$ converges to S_c we get (*).

3 Protein-Protein Networks

In [27, 28] the authors suggested maximization of interaction convenience, to produce multiple dominating sets of least size for a given PPI network. The notion is conceived from the minimization of adjustment and linear step by procedures adopted in networks

that are metabolic. They created two dominating sets of least size with the maximum differences among their vertices. The shared vertices are viewed as the essential ones that closely contain the critical set of the network. So by calling once the optimisation procedure, the critical set is defined as the intersection among the created dominating sets of least size. Then, it was further generalized to create k- dominating sets of least size with large differences among all of them, where k is the number of dominating sets of least size. Using these k- dominating sets of least size, all vertices in the PPI network can be described and the critical set exactly defined, as the k-critical set. Further, a new set of proteins appearing in (k – 1) dominating sets of least size was collected and this set was identified as the (k − 1) critical set. They found that the (k – 1)-critical set is equally as pertinent as the k-critical set and can be employed to generalize the search for drug target proteins. The authors used this approach to find the minimum dominating set. It can also be employed to rank the vertices in the PPI data network. Nacher and Akutsu [20] grouped into three the vertices of the underlying graph of a PPI network, depending on the created dominating sets of least size as critical vertices belonging to every dominating sets of least size, intermittent vertices that belong to at least one dominating sets of least size, and redundant vertices that do not belong to any dominating sets of least size. In Fig. 3 we have explained this concept. It is an uphill task to find and isolate pertinent critical proteins in the network. Figure 4 shows a network instance with critical vertex.

Consider the graph shown in Fig. 3. Note that there are only two vertices of maximum degree 6 namely 1and 10. A set P = {1} or P = {10} cannot be a dominating set. So a dominating set P of G should contain at least two elements. Suppose we form $P_{revised}$ by adding both 1and10 and set $P_{revised}$ = {1,10} then also P is not a dominating set as both 1and 10 cannot dominate 3 and 8. So we form a $P_{revised}$ with one 6 degree vertex and one five degree vertex. There are two choices for the second element of P namely 3 and 8. So let $P_{revised}$ = {1,8}. But even now 1 and 8 cannot together dominate 3. Also $P_{revised}$ cannot be {1,3} or {10,8} or {10,3} for obvious reasons. So a dominating set P of G must contains at least three elements For the third element position in $P_{revised}$ there are five choices namely 2,4,5,6,7. So we get P_1 = {1,8,2}, P_2 = {1,8,4}, P_3 = {1,8,5}, P_4 = {1,8,6}, P_5 = {1,8,7}. Similarly, if we choose $P^*_{revised}$ = {3,10} there five choices for the third element position namely 9, 11,12,13,14 and these vertices are either two degree or three degree vertices. So we get P_6 = {3,10,9}, P_7 = {3,10,11}, P_8 = {3,10,12}, P_9 = {3,10,13}, P_{10} = {3,10,14}. Also two five degree vertices and one 6 degree vertex form a dominating set. So we get two more dominating set of least size, namely P_{11} = {3,8,10}, P_{12} = {3,8,1}. Thus these are only 12 dominating set of least size. Interesting we find that no vertex in G is a critical vertex.

Now, $d_{st}(1,1) = 0$, $d_{st}(2,1) = 1$, $d_{st}(3,1) = 2$, $d_{st}(4,1) = 1$, $d_{st}(5,1) = 1$, $d_{st}(6,1) = 1$, $d_{st}(7,1) = 1$, $d_{st}(8,1) = 3$, $d_{st}(9,1) = 2$, $d_{st}(10,1) = 1$, $d_{st}(11,1) = 2$, $d_{st}(12,1) = 2$, $d_{st}(13,1) = 2$, $d_{st}(14,1) = 2$. So CC(1) = 1/21 = 0.047. $\sigma_{3,1}$ = {3 4 1; 3 5 1; 3 6 1; 3 7 1; 3 2 1} and σ_{st} (4) = 1. So BC(4) = $\sum \frac{\sigma_{st}(4)}{\sigma_{st}} = \frac{1}{5} = 0.2$ (Table 1).

Consider the network graph G in Fig. 4. Note that there are only two vertices of maximum degree 5 in G namely 3 and 10. A minimum dominating set P of G should therefore contain either 3 or10. Suppose P = {3} then it cannot dominate 1, 8 to14. By Symmetry P = {10} also cannot dominates 8, 1 to 7. This implies a dominating

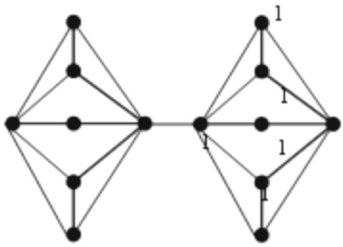


Fig. 3. It shows a network instance G where the vertices have different degree and with different dominating sets at least size. The dominating sets are {3,9,10}, {3,10,11}, {3,10,12}, {3,10,13}, {3,10,14}, {1,2,8}, {1,4,8}, {1,5,8}, {1,6,8}, {1,7,8}, {1,3,8}, {3,8,10}. Interestingly, the network has no critical vertices, 1,3, and 8 are the Intermittent vertices and 2,4,5,6,7,9,10,11,12,13,14 are the redundant vertices.

Table 1. It shows the degree centrality, closeness centrality and betweenness centrality computations of a network- graph shown in Fig. 3.

vertex	DC	CC	BC
1	6	0.047	1
2	3	0.03	0.2
3	5	0.028	0.5
4	3	0.03	0.2
5	3	0.03	0.2
6	2	0.03	0.2
7	3	0.03	0.2
8	5	0.028	0.5
9	3	0.03	0.2
10	6	0.047	1
11	3	0.03	0.2
12	3	0.03	0.2
13	2	0.03	0.2
14	3	0.03	0.2

set P of G must contain at least two elements. As we are looking for a dominating set with minimum cardinality, let us build a set P with both 3 and 10. That is, $P_{revised} = \{3,10\}$. But then even now P falls of being a dominating set as they both do not dominate 8. Hence a dominating set P of G must have at least three elements. Now the obvious choices for the third element of $P_{revised}$ are 8, 9, 11,12,14. Hence there are five different dominating sets $P_1 = \{3,10,8\}$ $P_2 = \{3,10,9\}$, $P_3 = \{3,10,11\}$, $P_4 = \{3,10,12\}$, $P_1 = \{3,10,14\}$. These are the only dominating sets of least size for G. Clearly we find u_4 and $u_4^{'}$ in all dominating sets of least size. Therefore 3 and 10 are critical vertices. However

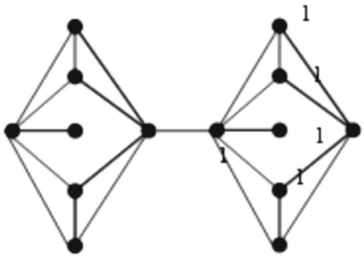


Fig. 4. It shows an instance of a network-graph G with critical vertex. This graph is a subgraph of the graph shown in Fig. 3 by omitting the edges (1,6) and (8,13).

we do not find an intermittent vertex for this network. The remaining left over vertices of G are dubbed as redundant vertices.

Researchers try hard to decrease the cost factor associated with the computation in recognizing and isolating the above said three types of proteins as the already available strategies determine such proteins after p repetitions of a specific procedure where p is the PPI network. Also the new sets we intend to find should have distinct criticalness degrees and the dominating set of least should be filled with the highest number of targeted proteins and provision for validation of notion of the dominating set of least size powered with the necessary genes and biological functions. In [35] the authors discussed three stages solution for the same. At the initial stage the data set is refined through apt data pre-processing methods that includes data collection, selection of protein, and implementation through graph representation. The next stage concerns with apt model selection from the two very distinct dominating sets of least size, the iterative way of building dominating sets of least size, and the user-friendly dominating sets of least size model. Finally stage deals with analysis and interpretation of the derived results. Such results spell out various dominating sets of least size produced under distinct criteria to be employed for finding the three different types of proteins such as critical, intermittent and redundant.

4 Conclusion

While giving a brief about the importance of PPI network and its functions, we have highlighted the pertinence of computing the dominating sets of least size with illustrations and explained various types of proteins classification like critical, intermittent and redundant in such dominating sets to facilitate certain biological process involving interaction of proteins. We also briefed about certain centrality measures such as degree centrality, betweenness centrality and subgraph centrality and computed the same for certain network graphs. We also pointed a mathematical truth related to subgraph centrality.

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