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Computational Approaches to Identify Key Therapeutic Targets in PPIN

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ABSTRACT

In recent years, the study of biological networks, particularly protein-protein interaction networks (PPINs) has gained attention due to their critical role in understanding disease mechanisms and therapeutic targeting. In this study, we apply computational graph theory and mathematical metrics to analyze the SARS-CoV-2 human PPIN with the goal of identifying novel therapeutic targets. This framework is based on domination theory, which identifies key proteins within the PPIN that could serve as crucial targets for drug delivery and therapeutic interventions. Our findings suggest that focusing on a refined subnetwork of these key proteins rather than the entire network could provide valuable insights for developing targeted therapies and efficient drug delivery systems. This study demonstrates the power of advanced computational techniques in solving complex biomedical challenges, particularly in the development of targeted medical therapies and drug delivery technologies.

Keywords: *PPIN, Domination, MCDS, Centrality, Rank correlation, Protein targets*

1. INTRODUCTION

Protein-protein interactions (PPIs) form networks driven by biochemical processes such as hydrophobic bonding, salt bridges, and van der Waals forces. These interactions are essential for many biological processes, including metabolic reactions, DNA replication, cellular responses to stimuli, and material transport. Understanding PPIs is crucial for explaining cellular functions, discovering disease mechanisms, and advancing therapeutic strategies.

Given the importance of PPIs in health and disease, researchers have focused on studying biological networks, particularly in the context of SARS-CoV-2 and human protein interactions. However, the complexity of these networks makes it difficult to identify key proteins that control the overall behavior of the system. While some PPIN analyses are straightforward, many protein-protein interactions are complex, which makes interaction studies challenging. In this context, graph theory offers valuable methods for analyzing these complex biological networks.

Graph-theoretical approaches have been widely used to explore the structure and dynamics of biological systems. [6] explored the application of domination theory in epidemiology, while Wuchty [11] and Nacher et al. [7] studied networks using the minimum dominating set (MCDS). Erciyes [2] provided an extensive review of graph methods for biological networks, highlighting their potential to identify functional components and active substructures. The study of SARS CoV-2 and human PPINs has also relied on graph theory, with basic concepts like degree and spanning trees being used to identify potential therapeutic targets [3, 12]. More sophisticated approaches, however, are gaining attention. Liu et al. [5] showed that network controllability depends not only on high-degree nodes but also on nodes identified through metrics such as betweenness and closeness centrality. Cheng et al. [1] focused on network-based biomarkers for predicting drug responses, emphasizing the role of centrality measures in identifying key nodes for therapeutic intervention.

After getting enough motivation from the literature survey, we optimize the original PPIN using the minimum connected domination (MCD) concept. Then the local and global graph metrics are used to analyze the filtered nodes and edges. The local parameters focus on the network substructure and the global parameters focus on the centralities. Finally, the characteristics of the network and the target proteins are explored. The targets obtained from the MCDS are compared with the targets obtained from the whole network. A short preview of our work is presented in the following figure 1.

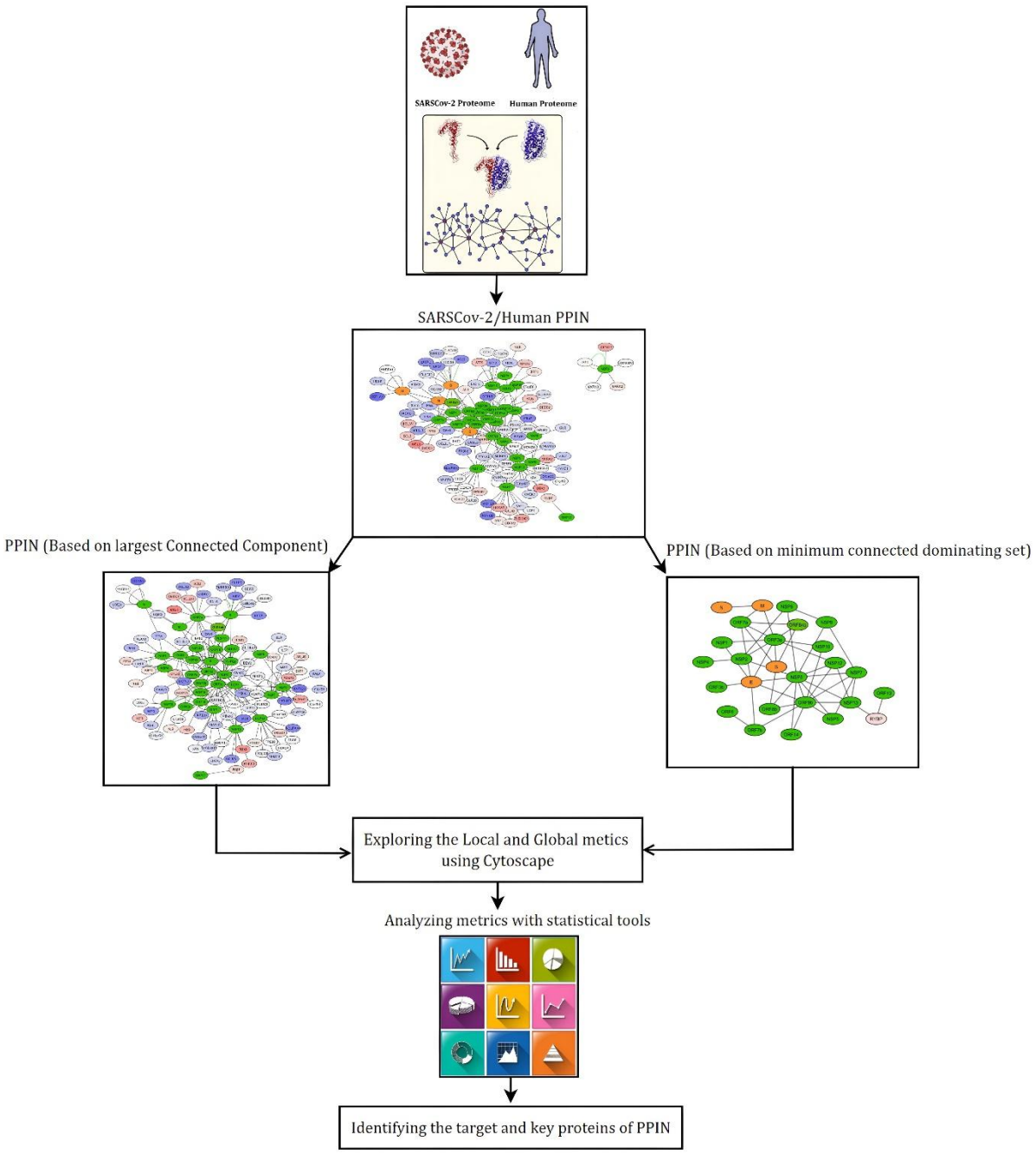

Figure 1: Flow chart for a brief outline

2. A BRIEF OVERVIEW OF PROTEINS

Viruses infect humans by interacting with specific proteins in the host's body. These interactions involve different types of proteins, which play distinct roles in the infection process. Here's a breakdown of these proteins: **Structural proteins**, including the spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins, are responsible for forming the virus's structure. These proteins have unique sequences that allow them to create complex shapes through repeated patterns and hydrogen bonds; **Non structural proteins (NSP)** are produced by the virus but not a part of the virus particle itself. They are crucial for its ability to replicate and spread. Consequently, they are potential targets for antiviral treatments; **Accessory proteins (ORF)** support the virus by influencing host cell functions. They help the virus control processes like gene expression and cell death, which are important for the virus's ability to infect and damage cells; The **Human/Host proteins** are the anti-viral proteins produced by the host organism during the infection. They are involved in producing recombinant

therapeutic proteins. For a quick and better understanding, the overview of the SARS-CoV-2 viral proteins is illustrated in figure 2.

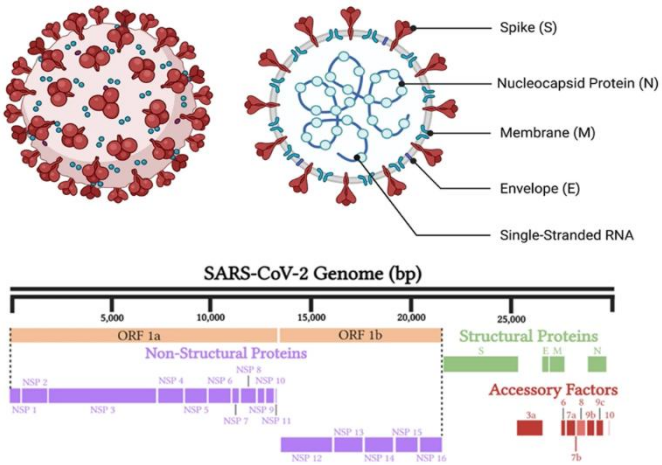

Figure 2: SARSCov-2 viral proteins

3. DATA ACQUISITION AND COMPONENT ANALYSIS

Based on the Guzzi et al.'s [4] research, the SARSCov-2 and human interaction network was created using Cytoscape https://cytoscape.org/. This network includes 125 proteins (31 viral proteins, 94 human proteins) and 206 interactions. In the network, nodes represent proteins, and edges indicate the interactions between them. The detailed network is illustrated in the Figure 3.

This network consists of two components, namely C_1 and C_2, where C_1 is a significant connected component, encompassing a large portion of the total nodes in the network and is call as Largest Connected Component (LCC). Consequently, the C_1 study is enough to explore the PPIN instead of a whole network study. Throughout this study, $H(V, E)$ indicates the LCC of PPIN with 199 proteins and 200 interactions.

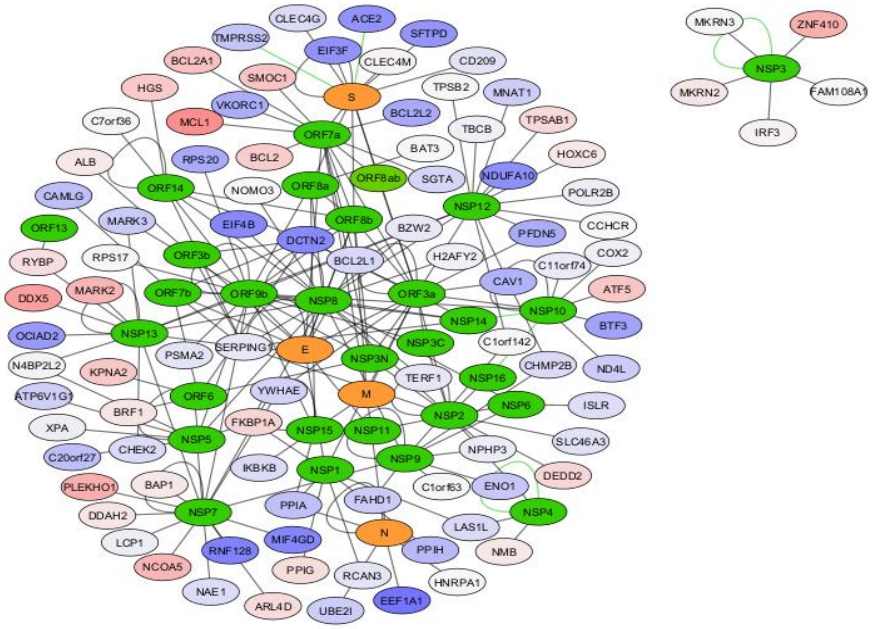

Figure 3: SARSCoV-2/Human interactome which contains 206 interactions among 125 proteins/nodes [download at http://korkinlab.org/wuhanDataset]. Network visualization was conducted using Cytoscape, an open-source software platform.

4. ANALYZING DISTINCT GRAPH METRICS OF PPIN

Analyzing distinct graph metrics of PPIN provides critical insights into the structural and functional roles of proteins within a biological system. By evaluating both local and global metrics researchers can identify key proteins, understand network dynamics and uncover potential therapeutic targets.

4.1 Local Metrics

Local metrics in graphs examine the characteristics and relationships that pertain to individual nodes and their direct neighbors. These metrics provide insights into the behavior and influence of specific nodes within their local context in a network. Here, the local metrics are calculated for the graph to analyze its substructures or sub network.

Definition 4.1.1 *The **degree distribution function** $P(k)$ gives the probability that a randomly chosen node has a degree k. Mathematically, it is expressed as*

$$P(k) = \frac{N_k}{N}$$

where, N_k is the node's count with degree.

*A network is described as a **scale-free network** if its degree distribution follows a power-law. This is defined as*

$$P(k) \sim k^{-\gamma}$$

where, γ is a parameter that typically lies in the range $2 < \gamma < 3$.

In biological networks, the scale-free properties imply that a few proteins (hubs) are involved in many interactions and they playing critical roles in cellular processes.

Definition 4.1.2 *A **graphlet** is an induced subgraph $H_I(V_I, E_I)$ of H such that: $V_I \subseteq V$, E_I contains all edges in H that connect pairs of vertices in V_I and H_I is connected.*

*In a graphlet H_I, an **orbit** is a classification of nodes based on their structural equivalence within the graphlet. Two nodes u and v are in the same orbit if there exists an automorphism of H_I that maps u to v while preserving the graphlet's structure.*

*For a node v in a graphlet H_I with orbits $O_1, O_2, \ldots, O_k$, the **orbit count** is the number of occurrences where v occupies orbit O_i within graphlets of type H_I.*

The orbit count gives insights into how the node contributes to different substructures. Nodes with high orbit counts in a PPIN are significant because they occupy key positions in many graphlets, that helps to identify the functional modules of the PPIN.

Definition 4.1.3 *A **maximal clique** in H is a subset $C \subseteq V$ such that: the subgraph induced by C ($H[C]$) is a complete graph and the clique C cannot be extended by including any additional vertex $w \in V \backslash C$ such that $H[C \cup \{w\}]$ is also a complete subgraph.*

In PPIN, a node involved in most maximal cliques is often a central protein. Its presence in many cliques suggests it plays a major role in various interactions and is important for maintaining network functionality.

4.2 Global Metrics

Global graph metrics assess the overall structure and connectivity of a network, evaluating how nodes interact across the entire graph. These metrics provide insights into a node's influence and importance within the broader network context. In this line, centralities are the major global metrics that quantify the significance of nodes within the graph. They provide insights into the role and influence of each node based on its position and connections.

Definition 4.2.1 *The **eccentricity** of a node v in a graph is defined as the maximum shortest path distance from v to any other node u in the graph. The eccentricity $e(v)$ of node v is given by:*

$$e(v) = \max_{u \in V} d(v, u)$$

where, $d(v, u)$ is the shortest path distance between nodes v and u and V is the set of all nodes in the graph.

Proteins with low eccentricity are centrally located in the network, indicating they are closer to all other proteins and likely play key roles in network connectivity and function. In contrast, proteins with high eccentricity are more peripheral, involved in specialized or isolated interactions and may have more specific, less central roles within the network.

Definition 4.2.2 *The **radiality** is a measure of a node's closeness to the center of the network and is normalized by the network's diameter. For a node v in a graph, the radiality $r(v)$ is defined as:*

$$r(v) = 1 - \frac{e(v)}{D - 1}$$

Here, $e(v)$ is the eccentricity of node v and D is the diameter of the network, which is the maximum eccentricity among all nodes.

The proteins with high radiality are central and being close to all other nodes. In contrast, the proteins with low radiality are peripheral and being farther from the most distant nodes.

Definition 4.2.3 *The **average shortest path length** (ASPL) of a graph measures the typical distance between pairs of nodes. It is calculated as:*

$$ASPL = \frac{1}{N(N-1)} \sum_{u \neq v} d(u, v)$$

Here, N is the total number of nodes in the graph, $d(u, v)$ represents the shortest path distance between nodes u and v and the sum is taken over all distinct pairs of nodes (u, v) where $u \neq v$.

In PPIN, a lower average shortest path length indicates that proteins are generally more closely connected, which can enhance the efficiency of interactions within the network. Conversely, a higher average shortest path length suggests that proteins are more distant from each other, potentially leading to less efficient communication.

Definition 4.2.4 *If A is the adjacency matrix of a graph, the **eigenvector centrality** ($\mathcal{EC}$) x_i of a node i is given by the solution to the following eigenvector equation:*

$$A\boldsymbol{x} = \lambda \boldsymbol{x}$$

where $\boldsymbol{x}$ is the eigenvector associated with the largest eigenvalue λ of the matrix A. The centrality score for node i is the i-th component of the eigenvector $\boldsymbol{x}$.

Definition 4.2.5 *The **betweenness centrality** ($\mathcal{BC}$) of a node v_i in a graph is defined as*

$$\mathcal{BC}(v_i) = \sum_{s \neq v_i \neq t} \frac{\sigma_{sp}(v_i)}{\sigma_{sp}}$$

where σ_{sp} is the number of shortest paths between nodes s and t and $\sigma_{sp}(v_i)$ is the number of those shortest paths that pass through node v_i.

Definition 4.2.6 *The **closeness centrality** ($\mathcal{CC}$) of a node v_i in a graph is defined as:*

$$\mathcal{CC}(v_i) = \frac{1}{\sum_{j \neq v_i} d(v_i, j)}$$

where $d(v_i, j)$ is the shortest path distance between nodes v_i and j.

This measure indicates how quickly a node can reach all other nodes in the network, with higher values representing nodes that are more centrally located and can access other nodes more efficiently.

Thus, eigenvector centrality identifies proteins that are connected to other highly influential proteins. Betweenness centrality highlights proteins that serve as important intermediaries or bridges within the network, controlling the flow of interactions between different nodes and maintaining network connectivity. Closeness centrality measures how efficiently a protein can interact with all other proteins in the PPIN.

Choosing proteins with high centralities as target proteins and developing drugs against them can lead to significant changes in the network, such as altering its structure, disrupting crucial pathways and modifying information flow. This strategic targeting can effectively influence the behavior of the network, potentially controlling disease progression or cellular dysfunction by impacting key nodes and interactions within the network.

4.3 Graph Reduction through Dominating Set Analysis

In complex networks, graph domination is a powerful technique used to identify a minimal set of nodes that can collectively cover or reach all other nodes in the network. This approach is valuable for various applications, including efficient placement of monitoring devices, simplifying network analysis and identifying crucial drug targets.

There are plenty of domination parameters available [9]. Here, the Minimum Connected Domination is preferred since it balances minimal size with essential connectivity [10]. It ensures that a small, strategically chosen subset of proteins covers the entire network while remaining connected, which is crucial for maintaining functional interactions. Consequently, MCDS naturally includes hubs or central nodes, which are often key targets in therapeutic interventions. Therefore, focusing on networks derived from MCDS is sufficient.

Definition 4.3.1 *A set $D \subseteq V$ is a **dominating set** if every vertex $v \in V$ is either in D or adjacent to at least one vertex in D. In other words, for every vertex $v \notin D$, there exists a vertex $u \in D$ such that $(u, v) \in E$. The set D is a **connected dominating***

set *if the subgraph induced by D is connected.*

A connected dominating set D is a ***minimum connected dominating set*** *if it has the smallest possible cardinality among all connected dominating sets in the graph. This means that there is no other connected dominating set in H with fewer vertices than D.*

The MCDS was derived from the LCC of the PPIN using 26 key proteins. These proteins are linked by 49 interactions, forming a connected structure illustrated in **Figure 4**.

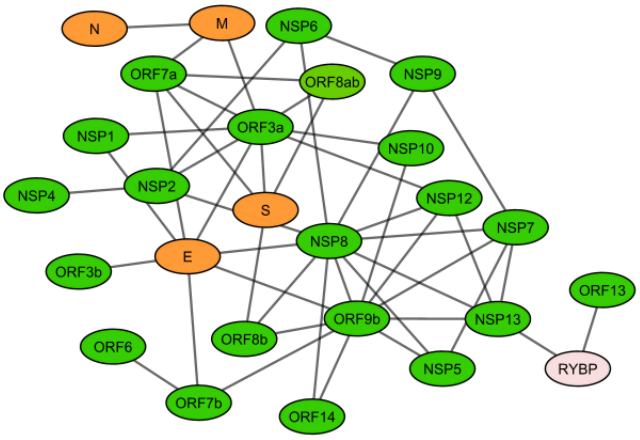

Figure 4: MCDS taken from the LCC of the PPIN

4.4 Statistical Test

Finding rank correlation is useful because it shows how two sets of data are related, even if they don't follow a straightforward pattern. It helps to identify whether an increase in one variable consistently matches an increase or decrease in the other. It is also good for handling data that doesn't fit normal assumptions or has outliers, since it uses rankings instead of exact values. This makes it a helpful tool for comparing different rankings or uncovering patterns in complex datasets. It is calculated by using the following formula.

$$\rho = 1 - \frac{6 \sum d_i^2}{n(n^2 - 1)}$$

where, d_i is the difference between the ranks of corresponding values in the two datasets and n is the number of data points. ρ ranges from -1 (perfect negative correlation) to +1 (perfect positive correlation). Positive correlation reflects that the behavior or role of the proteins in the two different networks is consistent, suggesting functional or structural similarities between the two PPINs. Positive correlations often highlight key proteins that play significant roles across both networks.

5. RESULTS AND DISCUSSION

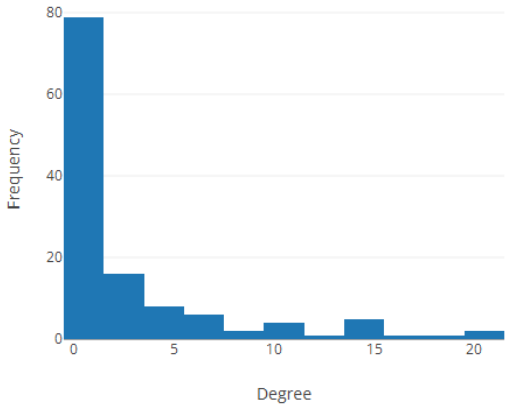

Figure 5: Degree distribution of LCC of PPIN

The figure 5 shows that *H* has a few nodes with many connections and many nodes with only a few connections. This pattern means the PPIN follows a power-law degree distribution with a scaling exponent of 2.1852, which indicates it is a scale-free network. Hence it contains hubs.

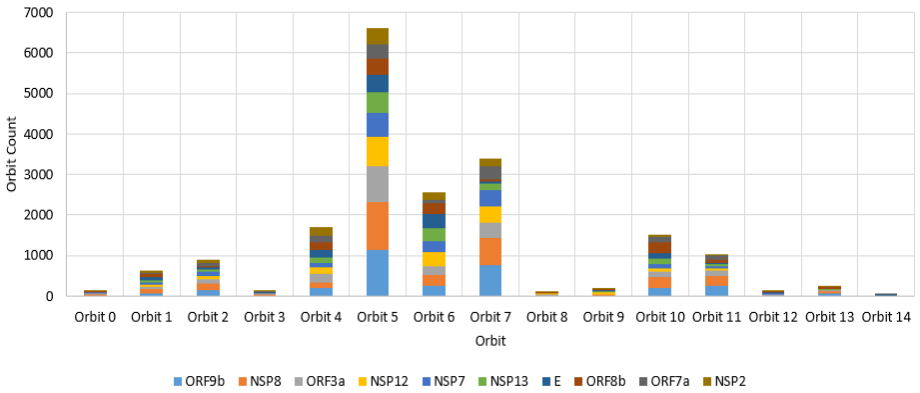

Figure 6: The stacked bar diagram 6 presents the orbit counts for the top 10 proteins that belong to the LCC

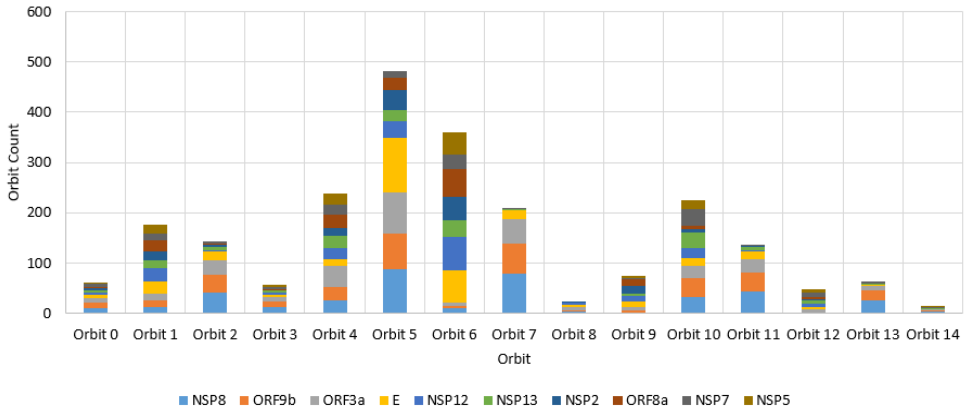

Figure 7: The stacked bar diagram presents the orbit counts for the top 10 proteins that belong to the MCDS

From the stacked bar charts in figure 6-7, we observe that ORF9b and NSP8 consistently emerge as the most influential proteins across both PPIN, particularly in Orbits 5, 6 and 7, they acting as key hubs in central substructures like cliques. In both PPIN, ORF3a shows a consistent presence in Orbits 5 and 7, though its values are slightly lower compared to ORF9b and NSP8. Protein E has high values in Orbit 6 in the LCC based PPIN and in Orbits 5 and 6 in the MCDS based PPIN, indicating a specialized role in central network regions. Other proteins, such as NSP13, NSP2, NSP7 and NSP5 show moderate influence, suggesting specialized roles in specific parts of the network. Thus, proteins like ORF9b and NSP8 are central to the network, while proteins like ORF3a and NSP12 serve as intermediaries and those like NSP2 and NSP5 are involved in more peripheral and niche substructures.

S.No	Maximal Clique of LCC	S.No	Nodes involved in Maximal Clique
1	ORF9b NSP7 NSP5 NSP8	16	MARK3 ORF9b NSP13
2	ORF9b NSP7 NSP13 NSP8	17	ORF9b NSP15 ORF8a
3	ORF9b E NSP8 ORF8b	18	ORF3a NSP2 NSP3N
4	ORF9b NSP13 NSP8 NSP12	19	ORF3a NSP2 NSP3C
5	ORF9b NSP8 ORF14 ORF8b	20	NSP14 ORF9b NSP8
6	ORF7b ORF9b E ORF8b	21	SERPING1 NSP2 NSP8

7	ORF3a S ORF7a ORF8b	22	SERPING1 NSP13 NSP8
8	ORF8ab ORF3a S ORF7a	23	SERPING1 NSP8 ORF14
9	ORF9b ORF8a NSP8 ORF8b	24	BCL2L1 E ORF7a
10	M ORF3a ORF7a ORF8b	25	ORF8a S ORF8b
11	ORF3a NSP3N ORF7a ORF8b	26	ORF3a PFDN5 NSP12
12	NSP7 NSP8 NSP9	27	SERPING1 NSP14 NSP8
13	NSP2 NSP8 NSP6	28	ORF9b NSP3N ORF8b
14	NSP1 ORF3a E	29	ORF3a NSP10
15	NSP14 ORF9b NSP10	30	NSP2 NSP4

Table 1: Proteins involved in Maximal Clique of LCC

From the table 1, we observe that NSP8 appears in 13 of 30 cliques and ORF9b is present in 12 cliques. ORF8b and ORF3a are found in 9 cliques, which contribute to various parts of the network but are less central compared to NSP8 and ORF9b.

S.No	Maximal Clique of MCDS based PPIN
1	S ORF3a ORF7a ORF8ab
2	NSP13 NSP7 NSP8 ORF9b
3	ORF9b NSP8 NSP5 NSP7
4	ORF9b NSP8 NSP13 NSP12
5	E ORF3a NSP1
6	ORF14 ORF9b NSP8
7	ORF8b ORF9b NSP8
8	E ORF9b NSP8
9	NSP9 NSP8 NSP7
10	NSP9 NSP8 NSP6
11	NSP2 NSP8 NSP6
12	E ORF9b ORF7b
13	E ORF3a ORF7a
14	M ORF3a ORF7a

Table 2: Proteins involved in Maximal Clique of MCD based PPIN

Similarly, from table 2, we observe that NSP8 appears in 9 of 14 cliques, ORF9b is present in 12 cliques and ORF3a and E are involved in 5 cliques. These frequencies highlight the roles of these nodes in maintaining the network's overall structure and connectivity. Their high occurrence suggests they are key hubs within the network and reveals the important biological interactions that are essential for cellular function.

Next to filter the crucial proteins based on global metrics, ranks are assigned to the various metrics of both LCC based PPIN and MCDS based PPIN since directly ordering the metrics values is a little complicated due to its decimation. Initially, the top 20 proteins are filtered from both PPIN and shown in the bar diagrams (refer figures 8, 9, 10 and 11) for readers' understanding. Out of 20 proteins, 18 proteins are common in both data sets which reflect that the MCDS based PPIN is enough to identify the crucial proteins of PPIN.

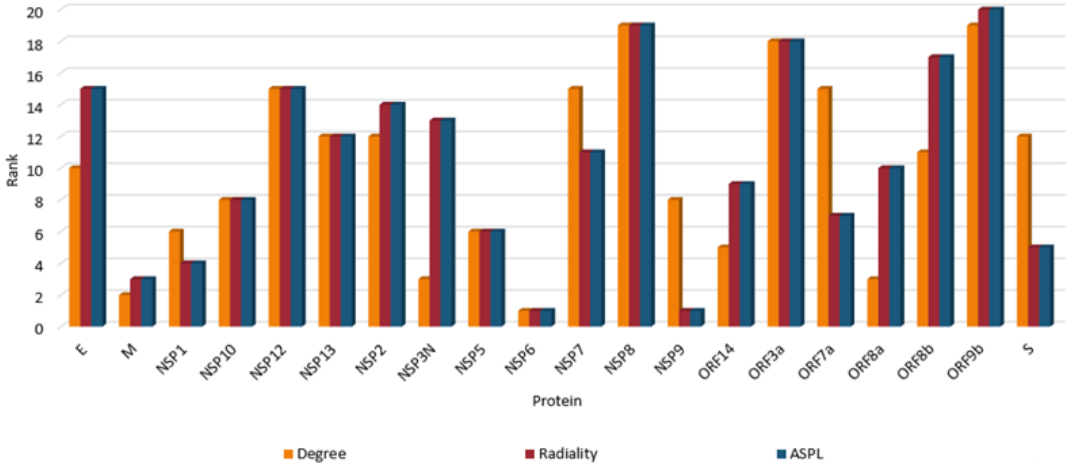

Figure 8: Bar diagram based on the top 20 proteins that belong to the LCC based PPIN

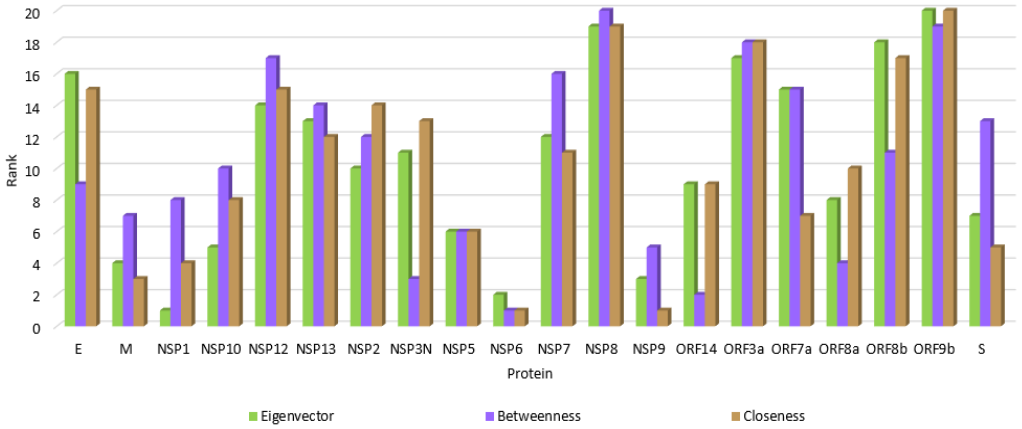

Figure 9: Bar diagram based on the top 20 proteins that belong to the MCDS based PPIN

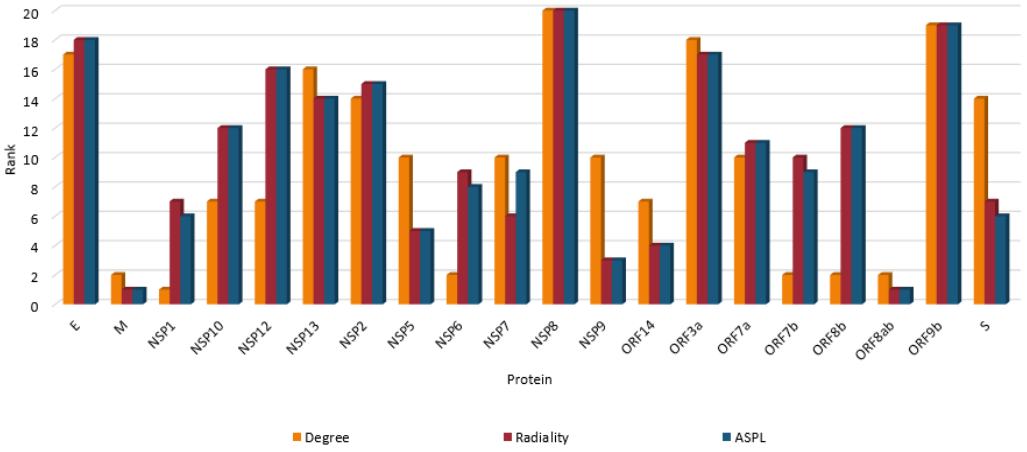

Figure 10: Bar diagram based on the top 20 proteins that belong to the LCC based PPIN

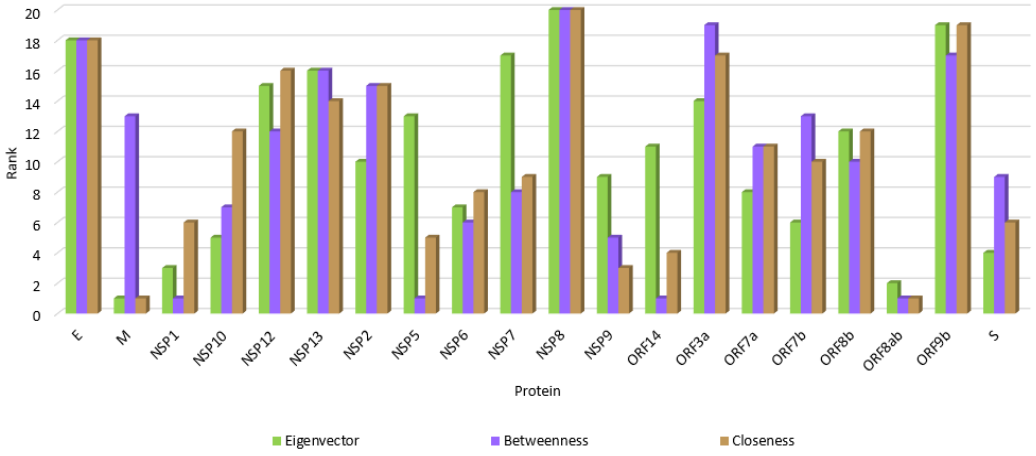

Figure 11: Bar diagram based on the top 20 proteins that belong to the MCDS based PPIN

From the bar diagrams figure 8-11, we observe that NSP8 and ORF9b are constantly lead in all the metrics. This indicates that NSP8 and ORF9b have the most significant impact on network integration, control, and accessibility, while ORF3a also maintain the third position in most of the metrics and hence it plays a significant role in these aspects. The rank correlation between the various metrics of 18 common proteins are explored in the following table 3 and indicated that the metrics based on both PPIN are strongly positively related. It reflects the rank similarity between the metrics of both PPINs and emphasizes that both networks possess common crucial proteins. For better understanding, the scatter plot is shown in figure 12.

Metrics	***ρ***
Degree	0.8107
Radiality	0.8943
ASPL	0.8943
Eigenvector	0.8088
Betweenness	0.7080
Closeness	0.8943

Table 3: Rank Correlation between metrics of LCC and MCDS based PPIN

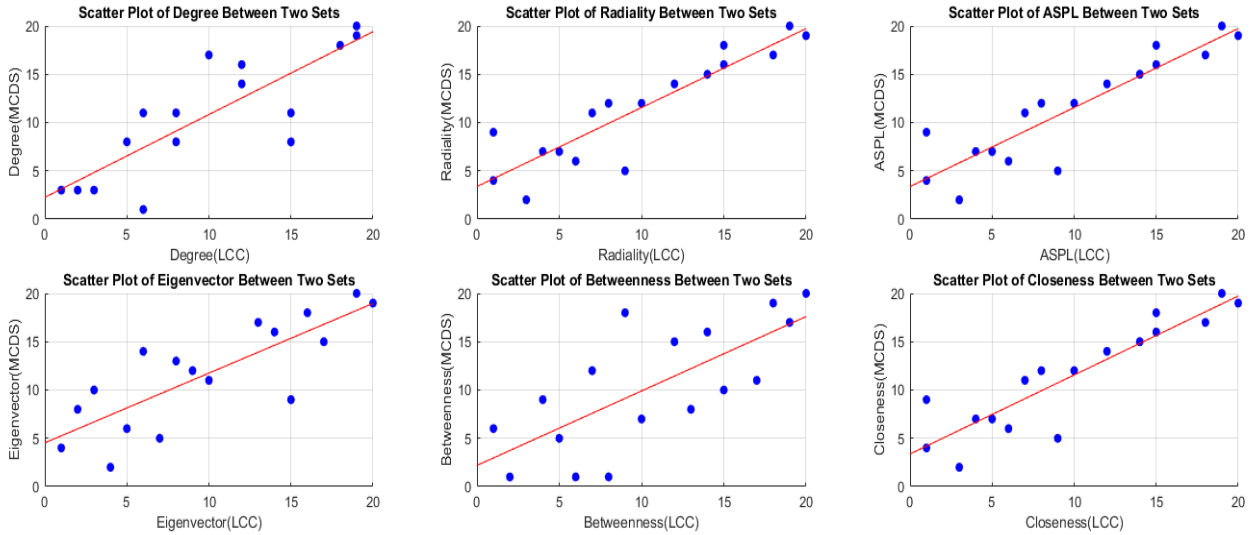

Figure 12: Scatter plot of rank of metrics in LCC based PPIN vs MCDS based PPIN

Out of 20 proteins, the top 10 are selected based on centrality metrics and orbit counts rather than other metrics such as degree, radiality, and ASPL. Centrality metrics consider both the quantity and quality of connections to assess a protein's overall importance in the network by taking into account its position and influence. In contrast, degree, radiality, and ASPL provide a more limited view by focusing only on direct connections or distance without considering the broader context of the network structure.

The top 10 proteins, shown in table 4 are common in both PPIN with little different rank positions. The rank correlation matrix of top 10 proteins based on centralities and orbit counts are presented in table 5, which helps to understand the relation between the LCC based PPIN and MCDS based PPIN and to explore the goodness of MCDS based PPIN.

Ranks	Centralities (LCC)	Centralities (MCDS)	Orbit (LCC)	Orbit (MCDS)
1	ORF9b	NSP8	ORF9b	NSP8
2	NSP8	ORF9b	NSP8	ORF9b
3	ORF3a	E	ORF3a	ORF3a
4	NSP12	ORF3a	NSP12	E
5	ORF8b	NSP13	NSP7	NSP12
6	E	NSP12	NSP13	NSP13
7	NSP13	NSP2	E	NSP2
8	NSP7	NSP7	ORF8b	ORF8b
9	ORF7a	ORF8b	ORF7a	NSP7
10	NSP2	ORF7a	NSP2	ORF7a

Table 4: Top 10 proteins in both PPIN based on centrality and orbit counts

	Centralities(LCC)	Centralities(MCDS)	Orbit (LCC)	Orbit (MCDS)
Centralities (LCC)	1.0000	0.8576	0.8788	0.7303
Centralities (MCDS)	0.8576	1.0000	0.7818	0.9758
Orbit(LCC)	0.8788	0.7818	1.0000	0.8697
Orbit (MCDS)	0.7303	0.9758	0.8697	1.0000

Table 5: Rank Correlation matrix

The correlation matrix (Table 5) reflects a strong correlation between the centralities and orbit counts of the same PPIN. Furthermore, the centralities and orbit counts of the LCC-based PPIN are strongly correlated with those of the MCDS-based PPIN. The strong correlation between the LCC-based and MCDS-based networks shows that the MCDS keeps the main features of the full network. This means we can use the smaller MCDS network for further study or to find possible drug targets, without losing important information.

6. CONCLUSION

This study highlights the importance of using graph metrics to understand the complex interactions within PPIN. Through this study, we identified that the PPIN is a scale-free network. Based on the evaluation of local and global metrics, E, NSP12, NSP13, NSP2, NSP7, NSP8, ORF3a, ORF7a, ORF8b, ORF9b are identified as the top 10 key proteins and NSP8, ORF9b, and ORF3a emerged as protein targets. Consequently, focusing drug development efforts on these proteins could be the most effective strategy for disrupting the PPIN. Also, this study confirms that instead of analyzing the entire network to identify key proteins, using the MCDS based PPIN is sufficient to fix the targets and to pinpoint the key proteins, as it encompasses all the essential proteins.

However, it is essential to acknowledge that other studies may have identified additional proteins as potential therapeutic targets. The true adaptability of our approach can only be fully assessed when researchers apply the same graphical analysis

to different biological networks and subsequently develop medications based on their findings. Such experimental validation is crucial to determining the practical effectiveness and worthiness of our approach in therapeutic development. Moreover, we can extend this type of work to distinct networks with distinct domination parameters.

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