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COMPUTER APPLICATIONS

HAMILTONIAN ENERGY-BASED VULNERABILITY ANALYSIS OF NOTCH SIGNALLING INTERACTION NETWORKS: MULTI-CENTRALITY BOTTLENECK MODELLING

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Abstract

Understanding the strength of pathways and the most effective therapeutic interventions depends on identifying structurally significant proteins in biological interaction networks. While local significance is calculated by Traditional centrality measures, they often fail to find the global structural instability caused by targeted attacks. In this work, we suggest a deterministic vulnerability analysis framework that combines a Hamiltonian structural energy model with a hybrid bottleneck centrality measure. A protein–protein interaction (PPI) network centred on NOTCH pathway mechanisms was extracted from BioGRID, consisting of 682 nodes and 9,592 edges. To compute the network's structural collection, we introduce a degree-difference Hamiltonian energy function of degree. Targeted combinatory removal of top bottleneck-ranked proteins proves that deletion of 5 proteins (NOTCH2, NOTCH1, ZRANB1, JAG2, and RHOG) results in a 68.24% structural energy reduction, indicating severe network destabilization. The results reveal that a small subset of proteins directs the global structural organization of the NOTCH-associated interaction network. The proposed framework provides a physics-inspired deterministic approach for vulnerability assessment in complex biological systems.

Keywords: Protein-Protein Interaction Network, Bottleneck Centrality, Hamiltonian Energy, Network Robustness, Structural Vulnerability, Notch Signalling Pathway

Introduction

Protein-Protein Interaction (PPI) networks are essential to understanding cellular processes and disease mechanisms [1]. These networks represent proteins as nodes and interactions as edges, creating a complex system that rules biological functions. Identifying key proteins within these networks is important for discovering disease-related genes and drug targets, as well as understanding how diseases spread at a molecular level. Graph theory and network analysis bring a powerful tool for learning PPI networks, with centrality measures playing a significant role in computing node importance. Degree centrality identifies highly connected nodes, closeness centrality highlights nodes with short paths to others, betweenness centrality detentions nodes acting as bridges, and eigenvector centrality imitates influence spread through connected nodes [2]. However, these traditional measures often fail to address broad detention network bottlenecks—nodes that are both structurally important and energetic for maintaining connectivity. To address this, bottleneck centrality is introduced as a hybrid approach, combining aspects of betweenness and degree centrality to identify critical nodes in the network. By removing these bottleneck nodes, we can evaluate their impact on network stability, showing how their absence disrupts information flow. Recent developments in network science suggest that physics-inspired energy models provide deeper insight into structural heterogeneousness and strength. Motivated by this perception, we introduce a deterministic Hamiltonian energy-based framework to measure structural collapse under targeted combinatorial attacks. The primary objectives of this study are as follows:

1. Identifying influential proteins by analysing multiple centrality measures and defining their intersection.
2. Assessing network stability by scientifically removing bottleneck nodes and evaluating structural changes.

The results of this research provide insights into the mechanisms of disease propagation in biological networks [3]. By identifying and analysing key proteins, this study contributes to computational biology, precision medicine, and drug discovery, offering a data-driven approach to understanding disease-related molecular interactions.

2. Methodology

2.1 Data Collection

The Biological General Repository for Interaction Datasets serves as the foremost data source for this learning. BioGRID is a well-accurate database containing logically validated Protein-Protein Interactions (PPIs)[4], which affords a reliable foundation for network analysis. The dataset includes protein interaction pairs, metadata as such as interaction types, and experimental evidence. From this database, an input file is generated, containing a filtered list of protein interactions relevant to learning. This structured dataset serves as the foundation for constructing a PPI network, allowing further computational analysis.

2.2 Network Construction

When the dataset is processed, a network structure is constructed, where proteins are represented as nodes and their interactions as edges Figure: 1. This network is exposed as an undirected graph, confirming that all connections are bidirectional, it is common in biological systems. A protein–protein interaction (PPI) network was constructed from the BioGRID database using key components of the NOTCH signalling pathway, including NOTCH1, NOTCH2, JAG1, JAG2, DLL1, and DLL4 as seed proteins.

The network was constructed by gathering all experimentally verified interaction partners linked to these key proteins. This subnetwork consists of 682 nodes and 9,592 edges, with a network density of 0.0413, indicating a moderately light but highly interconnected biological interaction structure suitable for structural robustness analysis.

2.3 Centrality Computation

Five centrality measures are calculated to evaluate the structural and functional significance of individual nodes within this network [5].

1. **Degree centrality:** Degree centrality measures the number of direct connections a node has Figure 2. Nodes with high degree centrality are highly connected, letting them to spread signals or employ impact more quickly across the network.

2. **Closeness centrality:** Nodes with high closeness centrality are positioned to quickly access other network areas, making them suitable for quick measures of a node's closeness to other nodes within a network, as shown in Figure 3.

3. **Betweenness centrality:** Betweenness centrality measures the significance of nodes that simplify communication between distinct network segments, connecting isolated regions. Figure 4. Nodes with high-betweenness centrality play a vital role in directing the flow of information.

4. **Eigenvector Centrality:** Eigenvector centrality identifies nodes connected to other highly influential nodes Figure 5. Nodes with high eigenvector centrality may not directly connect with a large number of other nodes, but their connections to highly influential nodes increase their overall importance.

2.4 Hybrid Bottleneck Centrality

Proteins controlling information flow were identified through the averaging of betweenness and degree centrality measures (Figure 6), which, if removed, would likely cause significant network disruption, making them key targets for studying vulnerabilities in biological systems [6]. We define bottleneck centrality as a weighted combination of normalized degree and betweenness centrality to identify structurally leading proteins.

$$C_{BN}(v) = w_1 \tilde{C}_{degree}(v) + w_2 \tilde{C}_{betweenness}(v) \quad \textbf{(1)}$$

Where:

- $w_1 = w_2 = 0.5$
- Centralities are min-max normalized.

This hybrid measure captures both local connectivity and global flow control.

2.5 Top Hub Node Identification

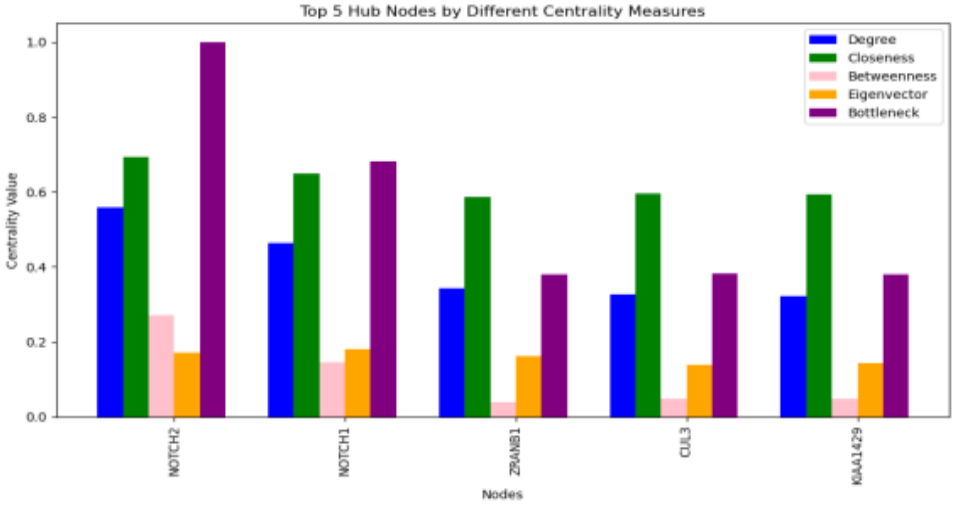
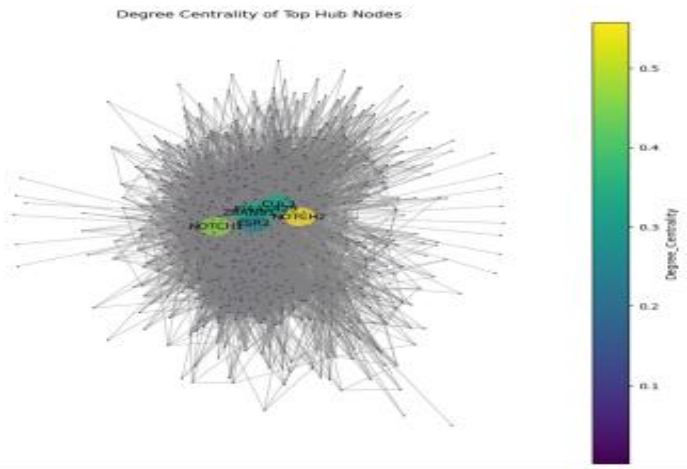


Figure 1: The chart represents the Top five Hub Nodes in a Protein-Protein Interaction (PPI) network based on different centrality measures.

The graph helps identify key proteins that play a thoughtful role in network connectivity and biological processes Figure 1. The measurement of hub importance via bottleneck centrality reveals its significance in facilitating information exchange and network connectivity. Intersections of many top nodes, being global hubs, indicate an intersection between local and global influence.

2.6 Graphical representation of overall centralities

The graph provides a visual representation of key centrality measures in a Protein-Protein Interaction (PPI) network, helping to identify influential nodes that play a critical role in the network's stability and communication [7].



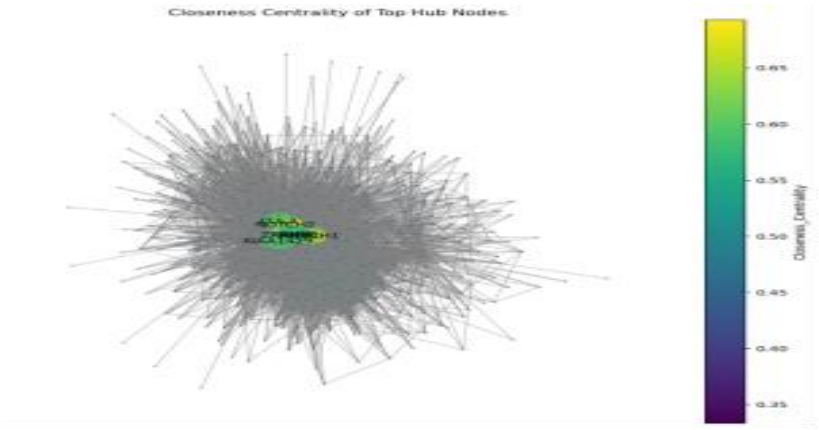
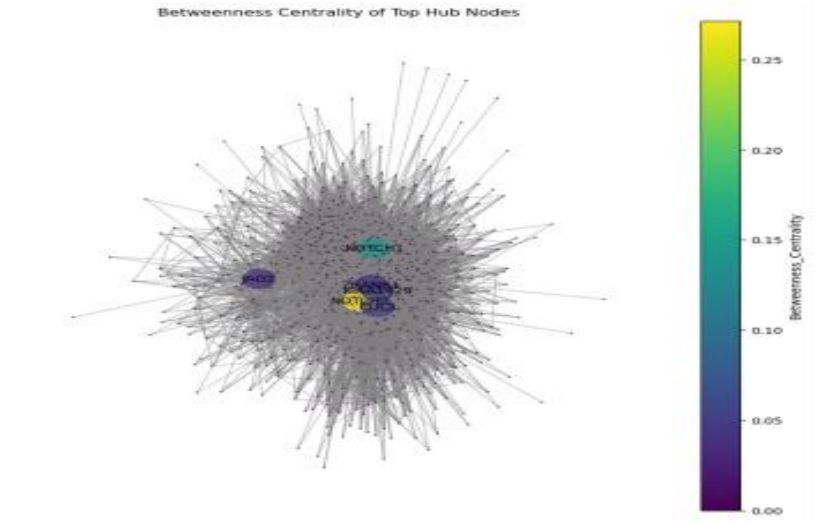


Figure 2: Degree Centrality with top hub nodes *Figure 3- Closeness centrality with top hubs*



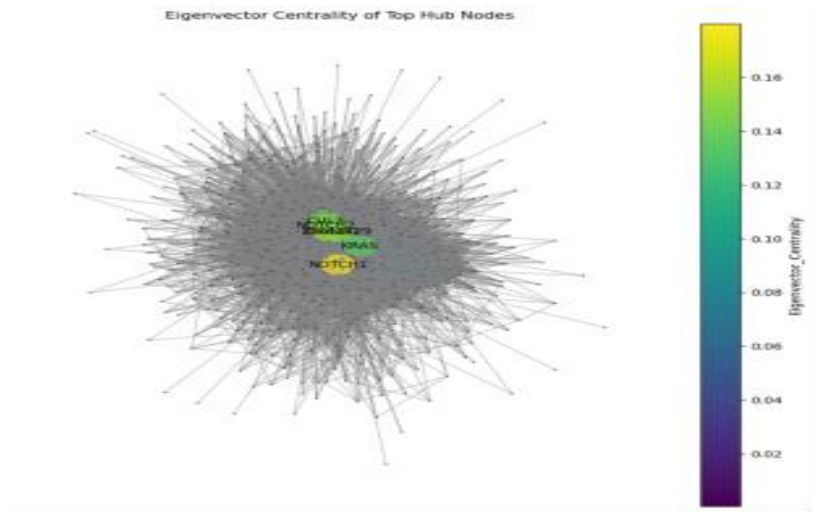
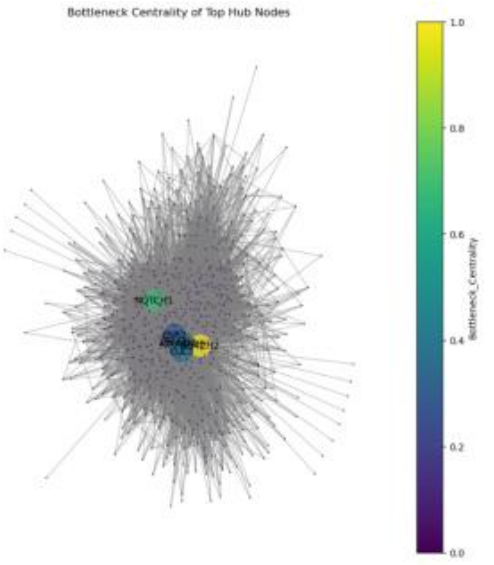


Figure 4: Betweenness centrality with top hubs Figure 5- Eigenvector centrality with top hubs



Degree Centrality	'NOTCH2', 'NOTCH1', 'ZRANB1', 'CUL3', 'KIAA1429', and 'ESR2'
Closeness Centrality	'NOTCH2', 'NOTCH1', 'CUL3', 'KIAA1429', 'ZRANB1', and 'ESR2'
Betweenness Centrality	'NOTCH2', 'NOTCH1', 'CUL3', 'KIAA1429', 'ZRANB1', and 'JAG2'
Eigenvector Centrality	NOTCH1, NOTCH2, ZRANB1, KIAA1429, CUL3, and 'KRAS'
Bottleneck Centrality	'NOTCH2', 'NOTCH1', 'CUL3', 'ZRANB1', 'KIAA1429', and 'ESR2'

Figure 6-Bottleneck centrality with top hubs

Table 1: Top 1% of nodes with highest values of each centrality metric

This visualization is important in understanding network robustness, identifying critical proteins, and designing approaches for targeted involvement in biological systems [8]. Following the computation of these measures, the top 1% of nodes with the highest values for each centrality metric are selected for visualization. This visualization provides insight into which proteins have the most influence in the network, forming the source for further analysis [9].

2.7 Degree Difference in Hamiltonian Structural Energy

To compute the structural organization of the network, we introduce a Hamiltonian-based structural energy formulation. The energy of a graph $H(G)$is defined as

$$H(G) = \sum_{(i,j) \in E}(k_i - k_j)^2 \quad \textit{(2)}$$

The sum of squared degree differences across all connected node pairs in the network, such that for every edge $(i,j) \in E$, the squared difference between the degrees of k_i k_j is calculated and stored. Here, $k_i$and $k_j$represent the degrees of nodes I and j, respectively. This formulation shows the extent of degree heterogeneity across interacting proteins. Larger degree differences contribute to higher energy values, indicating structural imbalance and hub–periphery gaps within the network. Therefore, the Hamiltonian structural energy helps to find a global measure of topological irregularity, enabling quantitative assessment of network destabilization under targeted node removal. Comparisons between centralities were then executed to determine which metric most effectively identifies nodes whose removal leads to maximal network destabilization.

2.8 Deterministic combinatorial vulnerability analysis

To assess the network's structural robustness, we performed a deterministic combinatorial analysis focusing on the top-

ranked bottleneck proteins. In this analysis, all possible k-node combinations (where $k = 1$ to 5) of these critical proteins were sequentially removed from the network. For each combination, the structural Hamiltonian energy $H(G)$(2) was recomputed to measure the impact of node removal. The percentage energy reduction was calculated as follows:

$$\Delta H(\%) = \frac{H_{initial} - H_{after}}{H_{initial}} \times 100$$

(3)

Where $H_{initial}$represents the structural energy of the original network, and $H_{after}$is the energy following node removal. Combinations of nodes were then ranked according to the scale of structural energy loss, providing a prioritized list of vulnerabilities that critically influence network integrity. Combinatorial analysis serves as a key indicator of important nodes whose removal significantly disturbs the network [10]. To identify these nodes, the knowledge focuses on proteins that appear at the intersection of high degree and high-betweenness centrality nodes [11]. These top-ranked bottleneck proteins are essential in controlling communication and structural integrity within the network.

Iterative Removal:

In this analysis, combinations of top hub nodes are iteratively removed from the network Figure 7. This helps predict the effects of disrupting the network's key players and observe how the overall structure responds to these removals.

To assess their impact, a node removal strategy is implemented:

1. The identified bottleneck nodes are systematically removed from the network.

2. Structural changes were assessed by analysing network fragmentation, average shortest path length, and connectivity patterns before and after removal [12].

3. To calculate the energy reduction using Hamiltonian Energy and find out the importance of the key node in the network based on the drop percentage of energy reduction.

This analysis helps to gain insight into the influence of hub proteins in a biological network. The significant drop in bottleneck centrality after removing key nodes suggests their important role in the biological network. Identifying these proteins helps in understanding disease development and potential drug targets in biological systems. The comparative analysis of centrality distributions before and after node removal helps determine whether these bottleneck proteins act as key regulators in disease propagation.

Centrality Reassessment:

After each hub node removal, centrality measures are recalculated to assess the impact on the remaining network. The goal is to assess how the loss of these key nodes influences the network's connectivity and dynamics [13].

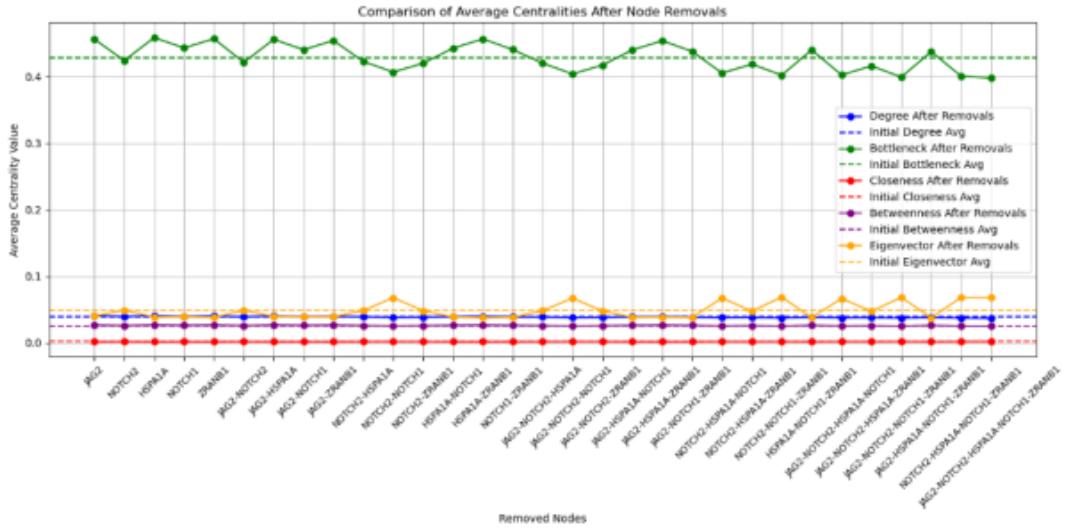


Figure 7: The line chart compares the average centrality values before and after the removal of key hub nodes in a Protein-Protein Interaction (PPI) network. The graph helps visualize how removing critical proteins affects the overall network structure.

2.9 Network Modifications and Analysis Neighbourhood Networks:

Neighbourhood networks are constructed around the top hub nodes, focusing on their direct interactions Figure 8. This provides an understanding of how these hubs influence their local networks and contribute to the overall system [14]. The interaction network exhibits a dense core–periphery structure with a small subset of high-connectivity bottleneck nodes governing global network integrity.

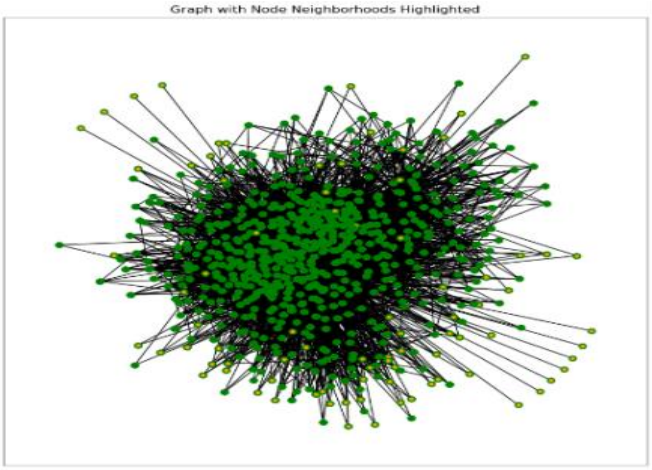


Figure 8: Networkraph illustrating node neighbourhoods, with central nodes highlighted in green and peripheral nodes in yellow, showing the connectivity and clustering patterns within the network.

2.10 Random Walk Signal Propagation:

A random walk algorithm was implemented to simulate signal propagation starting from a randomly selected node [15]. This method evaluates how signals travel through the network and measures the influence of hub nodes on the spread process Table 2. By observing how information spreads, the study highlights which hubs act as central points for controlling the flow of biological signals.

Visited Nodes during Random Walk:	'ZYX', 'GOLGA2', 'ZYX', 'ESR2', 'XPO5', 'MAPK1', 'EGLN3', 'NOTCH2', 'IGFL3', 'FBN2', 'CUL3'

Table 2: Using random walk signal propagation, we can identify which hubs act as central points for controlling the flow of biological signals.

3. Results and Discussion

The outcomes of this process determine how bottleneck centrality, combined with Hamiltonian energy, enhances the identification of critical nodes within a PPI network. The findings provide insights into the structural stability of the network [16].

3.1 Initial structural energy

The initial Hamiltonian structural energy of the network was calculated as $H_{initial} = 120{,}976{,}112$, providing an initial measure of the network's topological heterogeneity. The PPI subnetwork consists of 682 nodes and 9,592 edges, representing proteins and their interactions, respectively, as shown in Figure 9. This energy metric is derived from the squared differences in degrees between connected nodes, effectively computing how unevenly interactions are distributed across the network. A high energy value indicates significant variation in connectivity, where a few hub proteins have many interactions, whereas most nodes have relatively few. Establishing this initial energy allows us to assess the impact of subsequent perturbations—such as targeted removal of key proteins—on the network's structural integrity and identify the proteins most important for maintaining overall network stability.

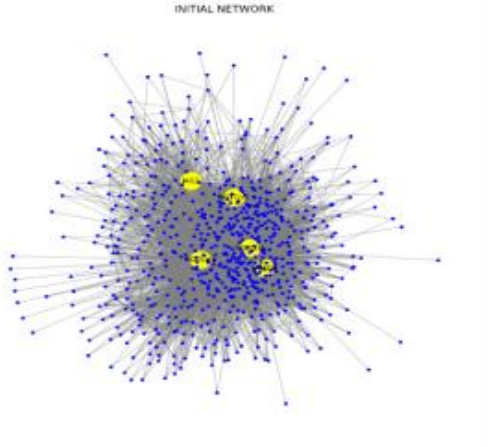


Figure 9. Initial network overview and structural energy

The protein–protein interaction network consists of 682 nodes representing proteins and 9,592 edges representing interactions among them. The network exhibits a heterogeneous degree distribution, with a few hub proteins having a high number of connections, whereas most nodes have fewer interactions. The initial Hamiltonian structural energy, $H_{initial} = 120{,}976{,}112$*, is visualized as a heatmap of node connectivity or a spring-layout network diagram where node sizes correspond to their degree. This representation highlights the network's topological heterogeneity and provides a baseline for evaluating the effects of targeted protein removal in subsequent analyses.*

3.2 Top structural regulators

Analysis of multiple centrality measures constantly identified a set of proteins as key structural regulators: **NOTCH2, NOTCH1, ZRANB1, CUL3,** and **KIAA1429**. Among these, **NOTCH2** has the highest degree (380), followed by **NOTCH1** (315), pinpointing the important role in maintaining network connectivity. The centrality analysis to identify the top 1% of nodes with the highest values for each centrality metric is selected for visualization [17]. These hub nodes represent the most influential proteins in the Protein-Protein Interaction (PPI) network, Table 1. These names represent well-known proteins that are typically involved in critical cellular processes such as signal transduction, cell cycle regulation, and disease pathways (such as cancer). Based on the specific dataset you are utilizing, you can substitute these general names with the particular protein names identified in your PPI network.

Degree centrality discovered the most connected nodes in the network, emphasizing proteins with many direct interactions. Betweenness Centrality identified proteins positioned at critical junctions serving as bridges between different parts of the network. Other centralities, such as closeness and Eigenvector, determined proteins that were highly accessible or connected to influential nodes [18]. Bottleneck Centrality identifies the most important nodes for maintaining the network's flow.

3.3 Visualization of the Network Structure and Key Hub Nodes

A graphical representation of the PPI network is generated to visualize key hub nodes based on various centrality measures [19]. Nodes with high centrality values are highlighted to indicate their significance in network connectivity and information flow. The top 1% of nodes identified through degree, closeness, betweenness, eigenvector, and bottleneck centrality measures are particularly marked, revealing significant overlaps among centrality rankings.

3.4 Structural collapse under targeted removal

Targeted removal of the top-ranked proteins resulted in a maximum structural energy reduction of 68.24%. The specific removal set responsible for this collapse included **JAG2, NOTCH2, NOTCH1, ZRANB1, and RHOG**. This finding indicates that just five key proteins collectively direct more than two-thirds of the network's structural energy, highlighting their critical role as structural regulators and potential points of vulnerability within the protein–protein interaction network [20].

3.5 Impact of Bottleneck Node Removal on Network Structure

Targeted removal experiments revealed that bottleneck centrality [21] consistently caused the highest reduction in Hamiltonian structural energy compared to other measures (degree, betweenness, closeness, eigenvector). Specifically, the removal of the top five nodes ranked by bottleneck centrality reduced network energy by approximately 79.96%, whereas degree- and betweenness-based removals returned slightly lower reductions, and closeness- and eigenvector-based removals caused even smaller disruptions Table 3. These findings underscore that bottleneck centrality more effectively identifies globally influential proteins that govern the structural integrity of the NOTCH network [22].

Strategy	**Energy Reduction**
Eigenvector Centrality	21.4%

Closeness Centrality	38.9%
Degree Centrality	39.7%
Betweenness Centrality	40.2%
Hybrid Bottleneck Centrality (Proposed)	79.96%

Table 3 reveals that bottleneck centrality consistently caused the highest Energy reduction compared with other centrality measures.

4. Discussion

The analysis of the NOTCH-associated protein–protein interaction network [23] discloses a highly centralized structural organization, in which a small subset of proteins excessively controls the network's stability. Across different centrality measures, bottleneck centrality consistently identifies the most influential regulators, outperforming classical measures such as degree, betweenness, closeness, and eigenvector centralities. While degree and betweenness highlight highly connected or shortest-path–critical nodes, and closeness or eigenvector centrality capture local accessibility or influence within the network, bottleneck centrality uniquely integrates these aspects to identify nodes whose removal causes maximal disruption of global network structure [24]. Using Hamiltonian structural energy as a measurable metric, we show that targeted removal of bottleneck proteins results in greater destabilization than removal based on other centralities, reflecting significant loss of structural heterogeneity beyond simple connectivity. Unlike classical robustness analyses that focus exclusively on the largest connected components, our approach captures the understated, yet important, perturbations in network topology, demonstrating that a small number of key proteins [25] direct large-scale structural stability. This highlights their potential as strategic targets for therapeutic intervention or biological modulation [26].

5. Conclusion

This study effectively reveals the usefulness of bottleneck centrality in exploratory key nodes within Protein-Protein Interaction (PPI) networks. By employing a combination of graph-theoretic methods and Hamiltonian Energy techniques, the research offers valuable insights into network stability and the structural consequences of removing important nodes. The results suggest that bottleneck nodes, characterized by their intersection of high-degree and high-betweenness, are essential for maintaining network connectivity and simplifying information flow. Through a comparative analysis of centrality, the study shows that eliminating these key nodes results in structural fragmentation, which increases the shortest path length and disrupts functional interactions within the network. The outcomes of this research have significant implications for biomedical applications, especially in disease modelling and drug target identification. Identifying critical nodes in disease-related networks can help in prioritizing therapeutic targets, potentially leading to more effective intervention strategies. In summary, this study highlights the significance of bottleneck centrality as a predictive measure for network robustness and biological relevance. The combination of network science and Hamiltonian Energy provides a robust framework for investigating complex biological interactions, with applications that extend

to systems biology, precision medicine, and computational drug discovery.

References

[1] T. Rout, A. Mohapatra, M. Kar, and D. K. Muduly, "Centrality-Based Approach for Identifying Essential Cancer Proteins in PPI Networks," *SN Comput Sci*, vol. 6, no. 1, p. 6, Dec. 2024, doi: 10.1007/s42979-024-03480-2.

[2] P. Sharma, D. K. Bhattacharyya, and J. K. Kalita, "Centrality analysis in PPI networks," in *2016 International Conference on Accessibility to Digital World (ICADW)*, IEEE, Dec. 2016, pp. 135–140. doi: 10.1109/ICADW.2016.7942528.

[3] Najma and A. Farooqui, "Biological Networks Analysis," in *Biological Networks in Human Health and Disease*, Singapore: Springer Nature Singapore, 2023, pp. 15–49. doi: 10.1007/978-981-99-4242-8_2.

[4]S. Wimalagunasekara, S. Tirimanne, and P. C. Fernando, "Protein-protein interaction (PPI) network analysis reveals important hub proteins and subnetwork modules for root development in rice (Oryza sativa)", doi: 10.1101/2022.06.06.494990.

[5] T. Rout, A. Mohapatra, M. Kar, S. Patra, and D. Muduly, "Centrality Measures and Their Applications in Network Analysis: Unveiling Important Elements and Their Impact," *Procedia Comput Sci*, vol. 235, pp. 2756–2765, 2024, doi: 10.1016/j.procs.2024.04.260.

[6] L. Zhou, "Analysis of bottleneck technology identification and development characteristics in the electronic manufacturing industry," *PLoS One*, vol. 19, no. 12, p. e0310176, Dec. 2024, doi: 10.1371/journal.pone.0310176.

[7] X. Liu *et al.*, "Computational methods for identifying the critical nodes in biological networks," *Brief Bioinform*, vol. 21, no. 2, pp. 486–497, Mar. 2020, doi: 10.1093/bib/bbz011.

[8] P. Perlasca *et al.*, "Multi-resolution visualization and analysis of biomolecular networks through hierarchical community detection and web-based graphical tools," *PLoS One*, vol. 15, no. 12, p. e0244241, Dec. 2020, doi: 10.1371/journal.pone.0244241.

[9] Z. Y. J. L. William L. Hamilton, "Inductive Representation Learning on Large Graphs," *Neural Information Processing Systems*, Jun. 2017.

[10] K. Hajarathaiah, M. K. Enduri, S. Anamalamudi, A. Abdul, and J. Chen, "Node Significance Analysis in Complex Networks Using Machine Learning and Centrality Measures," *IEEE Access*, vol. 12, pp. 10186–10201, 2024, doi: 10.1109/ACCESS.2024.3355096.

[11] B. Mishra, N. Kumar, and M. Shahid Mukhtar, "A rice protein interaction network reveals high centrality nodes and candidate pathogen effector targets," *Comput Struct Biotechnol J*, vol. 20, pp. 2001–2012, Jan. 2022, doi: 10.1016/j.csbj.2022.04.027.

[12] L. L. Njotto, "Centrality Measures Based on Matrix Functions," *Open Journal of Discrete Mathematics*, vol. 08, no. 04, pp. 79–115, 2018, doi: 10.4236/ojdm.2018.84008.

[13] I. Stamos, "Transportation Networks in the Face of Climate Change Adaptation: A Review of Centrality Measures," Sep. 01, 2023, *Multidisciplinary Digital Publishing Institute (MDPI)*. doi: 10.3390/futuretransp3030049.

[14]M. Hasan, N. Kumar, A. Majeed, A. Ahmad, and S. Mukhtar, "Protein-Protein Interaction Network Analysis Using

NetworkX," in *Methods in Molecular Biology*, vol. 2690, Humana Press Inc., 2023, pp. 457–467. doi: 10.1007/978-1-0716-3327-4_35.

[15]M. Shi, W. Hu, M. Li, J. Zhang, X. Song, and W. Sun, "Ensemble regression based on polynomial regression based decision tree and its application in the in-situ data of tunnel boring machine," *Mech Syst Signal Process*, vol. 188, p. 110022, Apr. 2023, doi: 10.1016/j.ymssp.2022.110022.

[16] O. M. Balogh *et al.*, "Efficient link prediction in the protein–protein interaction network using topological information in a generative adversarial network machine learning model," *BMC Bioinformatics*, vol. 23, no. 1, doi: 10.1186/s12859-022-04598-x.

[17] L. L. Njotto, "Centrality Measures Based on Matrix Functions," *Open Journal of Discrete Mathematics*, vol. 08, no. 04, pp. 79–115, 2018, doi: 10.4236/ojdm.2018.84008.

[18] E. Fenoy, A. A. Edera, and G. Stegmayer, "Transfer learning in proteins: evaluating novel protein learned representations for bioinformatics tasks," *Brief Bioinform*, vol. 23, no. 4, Jul. 2022, doi: 10.1093/bib/bbac232.

[19] T. Charitou, K. Bryan, and D. J. Lynn, "Using biological networks to integrate, visualize and analyze genomics data," *Genetics Selection Evolution*, vol. 48, no. 1, p. 27, Dec. 2016, doi: 10.1186/s12711-016-0205-1.

[20]X. Zeng, F.-F. Meng, X. Li, K.-Y. Zhong, B. Jiang, and Y. Li, "GHGPR-PPIS: A graph convolutional network for identifying protein–protein interaction site using heat kernel with Generalized PageRank techniques and edge self-attention feature processing block," *Comput Biol Med*, vol. 168, p. 107683, Jan. 2024, doi: 10.1016/j.compbiomed.2023.107683.

[21] A. Alexiou, S. Chatzichronis, A. Perveen, A. Hafeez, and G. Md. Ashraf, "Algorithmic and Stochastic Representations of Gene Regulatory Networks and Protein-Protein Interactions," *Curr Top Med Chem*, vol. 19, no. 6, pp. 413–425, May 2019, doi: 10.2174/1568026619666190311125256.

[22] G. He, M. Chen, Y. Bian, and E. Yang, "MTM: a multi-task learning framework to predict individualized tissue gene expression profiles," *Bioinformatics*, vol. 39, no. 6, Jun. 2023, doi: 10.1093/bioinformatics/btad363.

[23] B. A. Bhat, G. Singh, R. Sharma, M. Yaseen, and N. A. Ganai, "Biological Networks: Tools, Methods, and Analysis," in *Essentials of Bioinformatics, Volume I*, Cham: Springer International Publishing, 2019, pp. 255–286. doi: 10.1007/978-3-030-02634-9_12.

[24] Y. Zhang, Z. Lin, X. Lin, X. Zhang, Q. Zhao, and Y. Sun, "A gene module identification algorithm and its applications to identify gene modules and key genes of hepatocellular carcinoma," *Sci Rep*, vol. 11, no. 1, p. 5517, Mar. 2021, doi: 10.1038/s41598-021-84837-y.

[25] C.-H. Chin, S.-H. Chen, H.-H. Wu, C.-W. Ho, M.-T. Ko, and C.-Y. Lin, "cytoHubba: identifying hub objects and sub-networks from complex interactome," *BMC Syst Biol*, vol. 8, no. S4, p. S11, Dec. 2014, doi: 10.1186/1752-0509-8-S4-S11.

[26] S. Haider, K. Ponnusamy, R. K. B. Singh, A. Chakraborti, and R. N. K. Bamezai, "Hamiltonian energy as an efficient approach to identify the significant key regulators in biological networks," *PLoS One*, vol. 14, no. 8, p. e0221463, Aug. 2019, doi: 10.1371/journal.pone.0221463.