International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2025: 7.089

Centrality-Based Multi-Layer Network Modeling of Cancer Signaling Pathways

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Abstract: ***Cancer is a compound disorder that entails abnormal cellular signalling and structural alterations of cancerous cells. It is important to understand how tumour traits are tied to each other so as to determine significant indicators of cancer development. This paper uses a centrality-based network modelling technique in order to examine the relationship between tumour morphology features using the Breast Cancer Wisconsin database. The sample size of the dataset consists of 569 tumour samples where several quantitative measurements are given of the tumour cell nuclei structure. A correlation-based network was created in which the tumour features were expressed as nodes and statistical association between the features as edges. Network analysis was further conducted to study the structure of interaction of tumour characteristics. The degree centrality, betweenness centrality, and eigenvector centrality were centrality measures that were applied to identify influential features in the tumour interaction network. They are metrics that quantify the structural significance of nodes in complicated biological networks. The findings indicate that centrality scores are highest within the network on the tumour boundary irregularity features of concavity mean and concave points mean. The centre of the tumour interaction network is made up of these features and has a significant impact on various tumour properties. Studies based on biological networks suggest that the highly connected nodes tend to be important structural components that affect the behaviour of the biological systems. The results indicate that network analysis by centrality can help to show significant structural relationships between tumour characteristics. The method is a good way of analysing the complicated cancer data and determining the driving tumour features to aid in cancer diagnosis and disease analysis.***

Keywords: Network biology, Tumour morphology, Centrality measures, Breast cancer diagnosis, Correlation-based network.

Mathematics Subject Classification (2020): Primary 92C50; Secondary 05C82, 62H20, 92B15.

1. Introduction

1.1 Global Cancer Burden

Cancer is currently one of the gravest health problems on the global scale due to the possibility of uncontrolled tumour growth and cell proliferation through abnormal cellular signalling. There is a close association between cancer development and dysregulated systems of molecular signalling that control cell division, apoptosis, and immune responses (Vishwa et al., 2025).

Cellular signalling networks represent interactions of genes, proteins, and metabolites which provide coordination of biological responses in human tissues (Panditrao et al., 2022). The interactions produce massive molecular systems that regulate vital biological processes and dis-ease pathways in most forms of cancer (Hasin et al., 2017). It has been demonstrated that molecular networks are present in biological systems and are composed of thousands of inter-acting molecules, which combine to ensure cell stability and biological control (Koutrouli et al., 2020). Other studies have also indicated that the activation of abnormal genes by interference with the signalling pathways like the hedgehog pathway can facilitate tumour growth and cancer progression (Jager et al., 2017). This has made the study of the structure and connectivity of signalling networks an important goal in contemporary cancer biology.

1.2 Limitations of Traditional Pathway Analysis

Conventional methods of cancer research tend to analyse signalling pathways in isolation and not in interactions between different biological systems. It makes biological processes complex easier to understand and restricts the capacity to identify system-level patterns in molecular interaction networks (Alcala-Corona et al., 2021).

Biological systems consist of tightly connected networks of molecules in which genes and proteins interact in multiple pathways and not in isolated structures (Panditrao et al., 2022). Research indicates too that the key genes are frequently engaged in massive molecular inter-action networks, but not separately functioning in individual biological pathways (Guo et al., 2021). Thus, the conventional pathway analysis tools are incapable of realizing the complexity of cancer signalling systems.

1.3 Network Biology and Multi-Layer Modelling

Network biology has become one of the effective methods of studying complex biological systems by mathematical and computational modelling. Models of biological networks are modelling genes or proteins as nodes and their interactions as edges on a graph structure (Koutrouli et al., 2020). This modelling method allows the researcher to examine the structural trends of a biological network, including hubs, modules, and regulatory interactions (Alcala-Corona et al., 2021).

Multi-omics technologies have also extended this paradigm and combined genomic, tran-scriptomic, and proteomic data into single biological networks (Hasin et al., 2017). Multi-layer network modelling enables scholars to model various types of biological data in terms of being linked layers of one network system (De Domenico, 2018). This method enhances the compre-hension of disease mechanisms with complexities because it examines cross-interaction among numerous molecular layers at once (Zohari and Chehreghani, 2025).

2. Literature Review

2.1 Cancer Signalling Pathways

Signalling pathways in cancer control various processes in life like cell growth, immune regulation and programmed cell death. The loss of these signalling pathways may lead to the unregulated growth of cells and tumour development (J¨ager et al., 2017).

Molecular signalling networks are a type of biological interaction between various interacting proteins and genes, which relay biological signals in a series of biochemical reactions (Panditrao et al., 2022). Indicatively, mitochondrial stress response signalling has gained significant attention due to the fact that protein folding processes that ensure cellular stability are controlled by it (Ye et al., 2023). Studies indicate that dysfunctional signalling can influence and impact various biological processes at the same time and lead to cancer (Wang et al., 2023). Thus, signalling pathway analysis needs tools capable of realising large scale molecular interactions.

2.2 Network Biology Approaches in Cancer Research

Network biology is now a common method of studying complex systems in disease biology by using computational models of molecular interactions. Networks of molecular interactions com-bine protein interactions, gene regulations, and metabolic activities within a single framework of analysis (Panditrao et al., 2022).

The network-based methods are capable of determining the important regulatory elements and functional modules that can aid in disease progression (Koutrouli et al., 2020). Research additionally demonstrates that network analysis is capable of identifying the patterns of molecular interaction that cannot be easily detected by using conventional experimental methods (Zhao et al., 2022). Network modelling is also applied in cancer research to examine intricate biological interactions to determine significant regulatory molecules that govern tumour behaviour.

2.3 Centrality Metrics in Biological Networks

The centrality measures have been extensively employed to measure structural significance of nodes in biological networks. These measures are used to determine the degree in which a specific gene or protein is important to the connectivity of the entire network (Wang et al., 2022).

Degree centrality is a metric that determines the number of connections a node has with the rest in the network (Wang et al., 2022). The betweenness centrality is the degree to which a node is commonly present on the shortest communication path to other nodes within the network (Al Musawi et al., 2025). Eigenvector centrality is the evaluator of a node on the basis of the connection the node has with other nodes that are highly connected within the network (Wang et al., 2022). It has been demonstrated that hubs in biological networks are frequently important genes that are involved in the pathogenesis (Guo et al., 2021). Thus, the centrality analysis is a common practice to determine critical regulatory molecules of a biological network.

2.4 Multi-Layer Network Modelling in Systems Biology

The Multi-layer network modelling is a type of biological data representation in interconnected layers of a network. The layers describe varying biological processes like gene regulation, protein-protein interactions, or metabolic functions (De Domenico, 2018).

Multi-omics studies have proved that integration of several biological datasets can enhance the knowledge of intricate disease pathways (Hasin et al., 2017). It is also demonstrated that the multilayer biological networks are useful in drug discovery by studying their interactions among the genomic and proteomic systems with the help of integrative network pharmacology (Vishwa et al., 2025). Multi-layer modelling is also useful in the analysis of cross-layer interactions that affect the disease progression and treatment response (Zohari and Chehreghani, 2025).

2.5 Research Gap

Despite the fact that network biology has greatly enhanced the knowledge of molecular interactions in cancer systems, a number of research challenges are still there. Numerous works concentrate on the single layer molecular networks without incorporating the multiple biological data sources (Panditrao et al., 2022).

Such a restriction lowers the capacity to measure cross system interactions that affect the development of diseases. Besides this, computational techniques of predicting molecular inter-actions and network structures are another research aspect in systems biology (Al Musawi et al., 2025). Hence, the integrated analytical frameworks, which incorporate the multi-layer network modelling and centrality-based analysis are required in order to find the vital components of the cancer signalling systems.

3. Methodology

3.1 Data Sources

The Breast Cancer Wisconsin dataset collected in this study was obtained from the Kaggle data repository [Dataset available at: https://www.kaggle.com/datasets/uciml/breast-cancer-wisconsin-data]. The sample consists of 569 tumour samples with various morphological features indicating structural properties of the tumour cell nuclei, such as radius, texture, perimeter, and concavity. These measurements are frequently employed in cancer diagnosis research. The dataset consists of two diagnostic classes depicting malignant and benign tumours. At the feature level, the dataset contains quantitative data that can be analysed to determine relationships between the tumour characteristics using network modelling methods.

3.2 Network Construction

Network construction is performed by converting the tumour characteristics into a correlation-based network

structure. Within this network, all the tumour features are represented as nodes. The connections between features are depicted as edges based on the statistical correlation values of the variables. High correlation values suggest close relationships and potential biological dependencies between distinct tumour characteristics. This type of network enables the system-atic analysis of interactions between tumour properties using foundational concepts of graph theory.

3.3 Centrality Metrics Applied

Centrality analysis is applied to identify the most influential nodes within the network. Degree centrality is used to measure the exact number of connections a node maintains with the rest of the network. Betweenness centrality evaluates the degree to which a node lies on the shortest communication paths between other pairs of nodes. Eigenvector centrality measures a node's influence by accounting for the connectivity and importance of its immediate neighbours. These centrality measures are widely adopted in biological network analysis to isolate key regulatory elements, genes, and proteins within complex molecular interaction networks (Wang et al., 2022).

3.4 Computational Tools

Computational pipelines for network modelling, graph construction, and centrality analysis were implemented using Python. Data preprocessing and statistical manipulation were executed via the pandas library. The NetworkX library was utilized as the primary engine to perform graph building, edge mapping, and centrality computation. Visualizations of the underlying network topologies and their corresponding centrality distributions were generated using matplotlib.

3.5 Evaluation Method

The most significant tumour characteristics are determined by evaluating and ranking nodes based on their calculated centrality scores. Features that exhibit high centrality values are identified as critical structural components within the overall feature interaction network. Con-sequently, these highly ranked features can be regarded as significant biological indicators re-lated to the development and structural progression of cancer. Both network visualization and quantitative centrality rankings are utilized to extract key structural patterns from the global tumour interaction network.

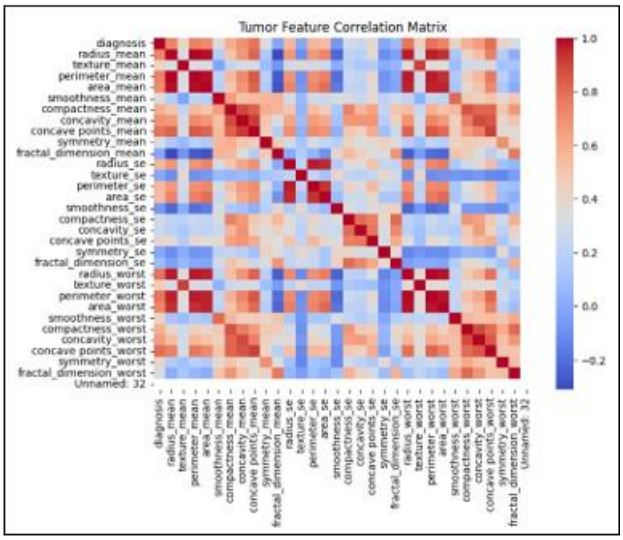

Figure 1: Correlation Matrix Analysis

4. Results and Analysis

4.1 Correlation Matrix Analysis

The tumour characteristic correlation matrix shows how the various tumour characteristics are statistically related. The heatmap demonstrates that a number of structural characteristics are significantly and positively associated with one another. As an illustration, there are strong positive relationships between the radius mean, perimeter mean, and area mean, which indicates that these measures are used to gauge the related geometric properties of tumour cell nuclei. This is expected since tumour radius, perimeter, and area are varying mathematical descriptions of the same morphological structure.

The heatmap also reveals that there is a strong correlation between concavity mean, concave points mean, and compactness mean. These aspects denote the irregularity of tumour borders. The fact that the correlation values between these variables are high indicates the presence of irregular nuclear shapes and deformed cell borders in malignant tumours. This tendency can be observed in the heatmap, where these variables are massively grouped and exhibit an intense correlation rate.

Conversely, other features have lesser associations with other tumour features. As an illustration, fractal dimension mean and symmetry mean exhibit lower correlation values throughout the matrix. These variables characterize the surface complexity and symmetry of tumour nuclei instead of size-related characteristics. They are therefore more independent in the network structure. On the whole, the correlation matrix demonstrates that there are a number of structural groups of tumour morphology: one group corresponds to size-associated tumour characteristics, and the other group corresponds to shape irregularity characteristics. The interaction network is built on the basis of this clustering pattern.

4.2 Feature Interaction Network Analysis

The feature interaction network is a graph with tumour features represented by nodes, and the correlation between

features represented by an edge. The network pattern displays a tight knot of nodes depicting well-linked tumour characteristics. The biggest cluster has variables like radius mean, perimeter mean, area mean, concavity mean, and concave points mean. These are highly connected nodes and they comprise the core region of the network.

There are also minor peripheral clusters revealed by the network that contain less connected features. For instance, texture mean and texture worst create a tiny, isolated element, which

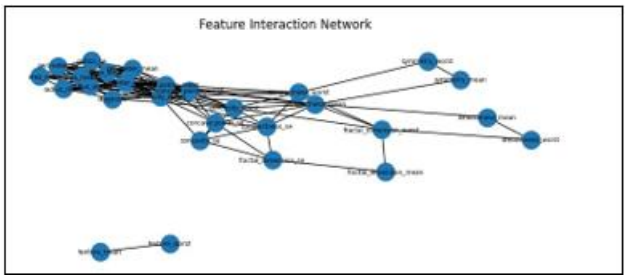

Figure 2: Feature Interaction Network Analysis

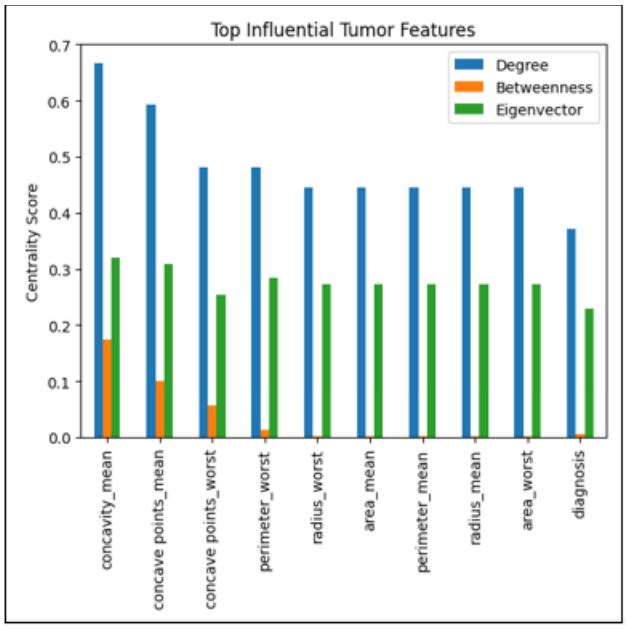

Figure 3: Centrality Analysis

means that texture-concerned measurements have less strong correlations with the principal tumour morphology characteristics. This indicates that the texture-based characteristics are able to represent various biological properties of tumour cells other than size- or shape-related variables.

Another observation that can be made based on the network visualization is the existence of bridge nodes that link various clusters of tumour features. The variables include radius and perimeter, which are located between clusters and offer links between multiple groups of tumour features. These bridge nodes can be significant in connecting various structural characteristics of tumour cells.

4.3 Centrality Analysis

The most influential tumour characteristics within the network were identified with the help of centrality analysis. The degree centrality takes into account the direct connections of a node and quantifies its overall number of interactions with other nodes in the network. The centrality analysis reveals that the degree centrality of concavity mean is the greatest, meaning that this

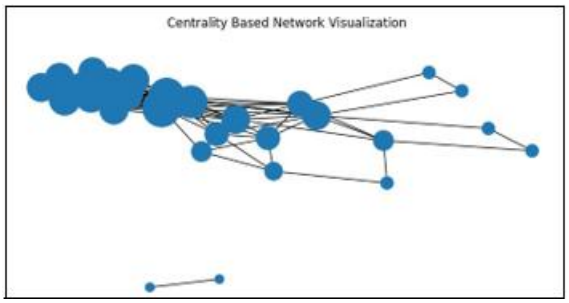

Figure 4: Centrality Based Network Visualization

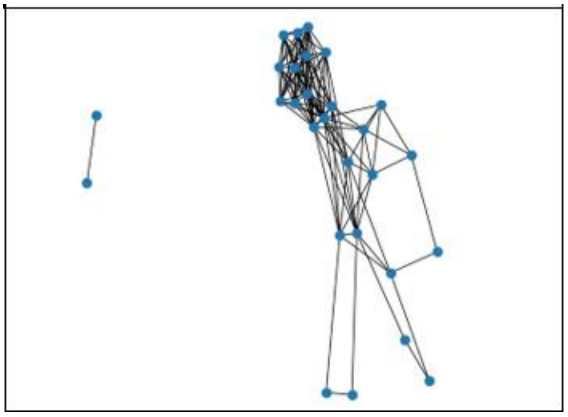

Figure 5: Centrality Based Network Visualization attribute interacts most dynamically with other tumour attributes

The second node with the highest impact is concave points mean, which exhibits both a high degree centrality and a high eigenvector centrality. These findings indicate that the count of concave points on the boundary of tumour nuclei has a strong impact on other morphological features. The high centrality of features associated with concavity emphasizes the significance of tumour boundary irregularity in cancer diagnosis.

Other highly influential nodes are concave points worst and perimeter worst, which also present high centrality scores. Such features represent extreme values of tumour shape and size characteristics. Their elevated centrality implies that severe tumour irregularity and increased tumour size are core structural characteristics that play a key role in governing the topology of the feature network.

The results of betweenness centrality are equally vital. The feature concavity mean has the largest betweenness centrality, implying that this characteristic lies on a large number of shortest paths between other node pairs in the network. This identifies concavity as a crucial structural mediator that interconnects multiple disparate groups of tumour features.

Centrality-Based Network Visualization

The centrality-based network visualization is useful in identifying influential tumour characteristics by scaling

node sizes proportional to their respective centrality values. The nodes corresponding to concavity mean, concave points mean, and concave points worst appear prominently in the visualization, presenting significantly larger diameters compared to other nodes. This visual pattern affirms their predominant position within the global tumour feature interaction network.

These characteristics constitute a central backbone within the network architecture, acting as a bridge that links various secondary clusters of alternative tumour properties. Their central positioning implies that variations in tumour boundary geometric properties are critical parameters that define and modulate the statistical associations between other morphological features. On the whole, the visualization underscores that shape-abnormal variables dominate the topology of the interaction network, whereas texture-based metrics occupy more isolated, peripheral roles. This observation confirms that structural abnormalities on the outer borders of tumour cell nuclei are major architectural determinants of the global network state.

5. Discussion

The findings from this study demonstrate that the morphological characteristics of tumours form a highly complex and integrated interaction network where specific variables structurally dominate the network topology. This arrangement is initially evidenced by the correlation matrix analysis, which highlights tight geometric clustering among size-dependent parameters including radius, perimeter, and area. In the domain of network biology, robust structural correlations between phenotypic variables typically denote underlying functional, biomechanical, or biological dependencies within complex systems (Koutrouli et al., 2020). The distinct clustering observed here suggests that these size-associated variables represent redundant but highly reliable geometric proxies for tracking the growth dynamics of tumour cell nuclei.

Furthermore, the topological visualization revealed that features linked to boundary irregularity constitute the most heavily interconnected hub within the network. Specifically, con-cavity mean and concave points mean form a densely packed core. In cancer systems biology, the emergence of structural aberrations and nuclear envelope irregularities is tightly bound to genomic instability, advanced tumour progression, and aggressive malignant behavior (Wang et al., 2018). Consequently, the high degree of interrelationship among concavity-related vari-ables suggests that boundary irregularity serves as a primary statistical footprint of malignant transformation.

The systematic calculation of centrality metrics provides deeper quantitative insights into these structural roles. Degree centrality analysis mathematically isolates concavity mean as the node with the highest local connectivity across the network. Biological network principles establish that such highly centralized “hub” nodes often operate as vital regulatory checkpoints that dictate the overall behavior or state of a complex system (Wang et al., 2022). The mas-sive local connectivity of concavity mean implies that structural distortions on the boundary heavily influence or correlate with the manifestation of almost all other nuclear parameters.

In parallel, betweenness centrality analysis highlights the critical path-mediation role played by concavity mean. Nodes exhibiting high betweenness values are known to regulate traffic and information flow between distinct, otherwise decoupled sub-graphs or functional modules (Guo et al., 2021). Our results position concavity-related metrics at the geographic center of the network, acting as structural mediators that string together size, shape, and peripheral texture dimensions.

This observation is strongly reinforced by the eigenvector centrality metrics, where both concavity mean and concave points mean demonstrate preferential attachment to other highly influential, well-connected nodes. In graph-theoretic analysis of biological systems, nodes with high eigenvector scores point directly to the core functional entities driving systemic changes (Panditrao et al., 2022). Therefore, this collective dominance of concavity features highlights that irregular boundary contours represent the single most structurally descriptive feature group in the dataset.

Taken together, these results confirm that network-based paradigms excel at extracting critical diagnostic hallmarks from multivariate clinical datasets. Moving forward, this morphological network analysis can be expanded into a comprehensive multi-layer framework by integrating micro-level molecular layers- such as gene expression patterns and protein-protein interaction (PPI) networks- with macro-level tumor tissue morphology layers (De Domenico, 2018).

6. Conclusion

This study successfully evaluated the multivariate relationships among tumour morphology characteristics using a centrality-based single-layer network modeling approach. The results show that nuclear features map out a complex, non-random interaction network governed by a small, highly influential subset of structural nodes. Statistical correlation analysis identified distinct size- and shape-based modules, while topological graph analysis demonstrated that the core of the feature space is dominated by boundary irregularity metrics.

Quantitatively, concavity mean and concave points mean emerged as the top-ranked nodes across degree, betweenness, and eigenvector centrality measures. This confirms that variations in the border regularity of cell nuclei exercise significant structural influence over the remaining features in the network, underscoring their clinical value as critical signs of malignant cellular behavior.

Ultimately, this research highlights that network biology principles can be applied directly to clinical morphology data to expose key structural interdependencies that conventional isolated analysis tools fail to capture. Centrality-based graph modeling represents a mathematically sound, highly scannable workflow for

prioritizing driving diagnostic features, providing a reliable baseline for automated cancer screening, disease staging, and multi-layer omics integration.

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