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Integrative graph theory and boolean modeling for breast cancer network reconstruction in precision medicine

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Abstract

Breast cancer comprises complex molecular interactions that can be represented as biological networks. Understanding these networks is essential for identifying regulatory hubs and potential therapeutic targets in precision oncology. This study reconstructed a breast cancer protein–protein interaction (PPI) network using data from STRING-DB, KEGG, and SIGNOR. Graph theory was applied to compute topological metrics—degree, betweenness, and clustering coefficients—to identify key proteins and functional modules, while the Markov Cluster Algorithm (MCL) detected community structures. Boolean modeling simulated network dynamics by binarizing interaction strengths at a confidence threshold of 0.7. The reconstructed network contained 150 nodes and 1,359 edges, exhibiting a scale-free topology ($\gamma = 2.1$) and modular organization (global clustering coefficient 0.522). BRCA1 and TP53 emerged as densely connected hubs, whereas EGFR and AKT1 acted as major signaling conduits linking multiple pathways. MCL revealed four primary clusters associated with DNA repair, cell-cycle regulation, growth signaling, and survival pathways. Boolean simulations demonstrated that perturbing these hub proteins significantly altered network states linked to proliferation and apoptosis resistance. Notably, TP53 restoration was predicted to stabilize Basal-like breast cancer networks, while inhibition of AKT1 or EGFR suppressed pro-proliferative attractors. Integrating graph theory with Boolean modeling thus provides a systems-level framework for understanding molecular regulation in breast cancer. The identification of BRCA1, TP53, EGFR, and AKT1 as high-centrality nodes highlights their importance as potential therapeutic targets and supports the advancement of precision medicine approaches tailored to breast cancer network dynamics.

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INTRODUCTION

Breast cancer remains one of the most prevalent malignancies worldwide and a leading cause of cancer-related deaths among women, accounting for approximately one in four new cancer diagnoses globally [1–3,9]. Despite substantial advances in genomic and proteomic profiling, therapeutic outcomes remain highly variable due to tumor heterogeneity and molecular complexity [2,12,20]. The interplay of genetic mutations, epigenetic changes, and signaling alterations contributes to diverse biological behaviors and therapy resistance, underscoring the need for an integrative systems-level understanding of breast cancer pathogenesis [5,11,13].

Previous studies have focused on gene expression signatures and pathway-based analyses to classify breast cancer subtypes or predict clinical outcomes [8,25,33]. While these approaches have improved subtype characterization, they often overlook the interconnectivity and dynamic relationships among proteins, which fundamentally drive oncogenic behavior [11,14,31]. Network-based methods, particularly those grounded in graph theory, provide a mathematical framework to map these complex molecular interactions and identify key regulatory hubs [10,19]. However, most

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prior network studies have been static, describing topological structures without modeling how these networks behave under biological perturbations [8,11,20].

Recent computational advances, including Boolean modeling, allow the simulation of protein activity states and logical relationships in biological systems [27,28]. Studies applying Boolean logic to cancer signaling networks have shown promise in elucidating activation–inhibition mechanisms [27], yet these have rarely been integrated with graph-theoretical topology in a unified framework—especially for breast cancer [17,20]. Furthermore, existing models often use partial datasets or single databases, limiting the biological reliability of reconstructed networks [15,29].

Therefore, the research gap addressed in this study lies in the lack of an integrative approach combining graph theory and Boolean modeling to reconstruct and analyze breast cancer protein interaction networks using multi-database evidence. By integrating topological analysis and dynamic simulation, this research aims to identify high-centrality hub proteins and simulate their influence on network stability and cancer-related processes. This dual computational strategy provides novel insights into molecular regulation, revealing how perturbations of key nodes such as TP53, BRCA1, EGFR, and AKT1 may alter system states associated with proliferation, DNA repair, and apoptosis—contributing to the advancement of precision medicine approaches in breast cancer [14,17,25,32].

MATERIALS & METHODS

Study design and overview

This study used a retrospective computational design to reconstruct and analyze a breast cancer protein–protein interaction (PPI) network and to evaluate its dynamic behavior under logical perturbations. The overall workflow is shown in Figure 1: data collection and curation from multiple databases, network construction and filtering, topological analysis and community detection, Boolean mapping and dynamic simulation, and validation and biological interpretation. Figure 2 illustrates representative subnetworks for BRCA1/AKT1 and TP53/EGFR used throughout the analysis. This diagrammatic separation clarifies the difference between the methods (data sources, network construction, modeling rules), analysis (topological measures, clustering, simulations), and validation (cross-reference to pathway databases and literature).

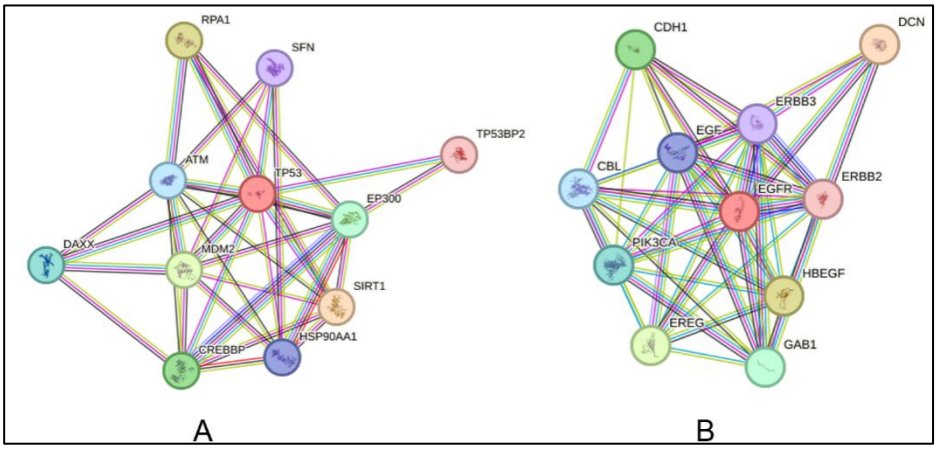

Figure 1. Protein interaction networks for TP53(A) and EGFR(B)

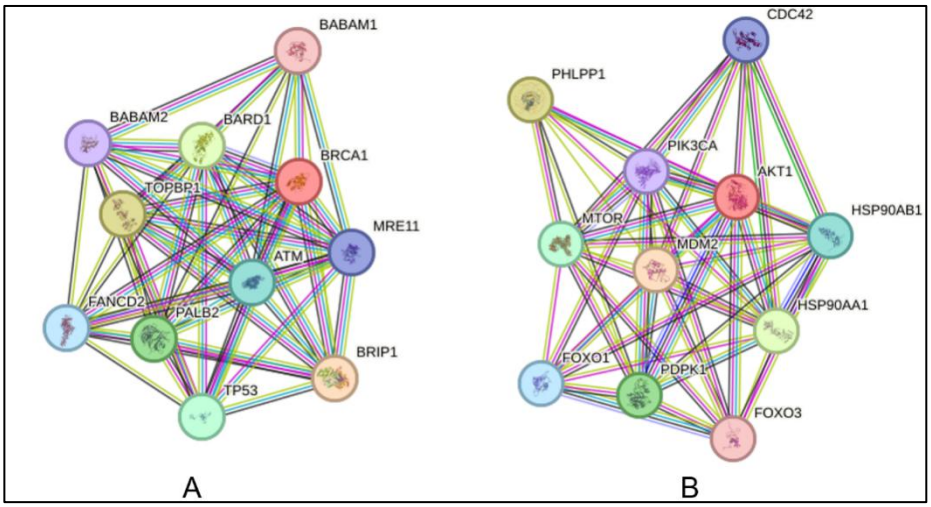

Figure 2. Protein interaction networks fot BRCA1(A) and AKT1(B)

Data sources and curation

Protein interactions were integrated from STRING-DB (v11) to obtain association/confidence scores, and curated annotations on activation/inhibition and pathways were obtained from KEGG and SIGNOR to assign edge signs and functional context [29,15,21]. Only interactions with experimental or high-confidence evidence were retained for topology (STRING confidence ≥ 0.4), and a stricter threshold (≥ 0.7) was used for Boolean activity mapping. Selected seed proteins (BRCA1, TP53, EGFR, AKT1) were chosen due to their clinical relevance in breast cancer [17,18,20,39]. Data preprocessing included removal of duplicates, mapping to UniProt identifiers, and manual inspection of ambiguous edges.

Network construction

We constructed a directed, weighted graph $G = (V, E)$ where nodes V represent proteins and edges E represent interactions with associated confidence weights w_{ij}. Edge signs (activation/inhibition) were annotated where available from SIGNOR or curated literature; edges with unresolved signs were treated as unsigned during topology and flagged for sensitivity analysis during dynamics [21,29]. Cytoscape was used for visualization and basic network metrics [11].

Topological analysis

Topological metrics were computed to identify hubs and bridges as part of the analysis stage (software: Cytoscape and custom Python scripts). Key measures used were degree centrality, betweenness centrality, and the local clustering coefficient:

- Degree centrality:

$$k_i = \sum_j a_{ij} \quad (1)$$

Where a_{ij} is the adjacency entry.

- Betweenness centrality:

$$B_i = \sum_{s \neq t \neq j} \frac{\sigma_{st}(i)}{\sigma_{st}} \quad (2)$$

Where σ_{st} is the number of shortest paths between nodes s and t and $\sigma_{st}(i)$ is those passing through i.

- Local clustering coefficient:

$$C_i = \frac{2e_i}{k_i(k_i - 1)} \quad (3)$$

With e_i the number of edges among neighbors of i [10,19].

Community detection used the Markov Cluster Algorithm (MCL) to identify functional modules and was implemented following standard parameter selection procedures (inflation parameter tested across 1.4–2.2) [10]. Degree distributions and global clustering coefficients were compared to random network ensembles to test significance (1000 network randomizations preserving degree sequence).

Boolean model and dynamic simulations

Boolean modeling translated interaction confidences into binary interaction activity using the 0.7 cutoff: active (1) if $w_{ij} \geq 0.7$, inactive (0) otherwise. Each node i has a Boolean state $x_i(t) \in \{0,1\}$, updated synchronously using template rules that capture activation OR and inhibition gating:

$$x_i(t+1) = \left(\bigvee_{j \in A_i} x_j\,(t) \right) \wedge \neg \left(\bigvee_{k \in I_i} x_k\,(t) \right) \quad (4)$$

where A_i and I_i are activating and inhibitory regulators of node i, respectively [27]. We emphasize that these rules are template-based. Simulation experiments included single-node perturbations (knockout or constitutive activation), pairwise perturbations, and attractor analysis to identify stable network states and basin sizes. All simulations used at least 10,000 random initializations to sample state space.

Validation and sensitivity analyses

Validation consisted of (1) cross-checking identified modules and hub proteins against pathway annotations in KEGG/Reactome and literature-reported breast cancer drivers [15,31], and (2) sensitivity testing for thresholds (0.6–0.8) and rule variants to assess robustness of attractors and hub influence. Discrepancies in edge directionality or sign were reported and analyzed separately. The methodological distinction is explicit: Methods document what was done, Analysis reports measured network properties and simulation outputs, and Validation assesses biological plausibility and robustness.

Reproducibility and supplementary materials

Complete code for network construction, metric calculations, MCL parameters, and Boolean simulations, together with long mathematical derivations and full sensitivity tables. Data files and scripts are available upon request for reproducibility. References for methods and tools: Cytoscape and network algorithm references [11,10]; STRING/KEGG/SIGNOR data sources [29,15,21]; Boolean modeling methodology [27]; clustering coefficient formalism [19].

RESULTS AND DISCUSSION

Network Reconstruction and Topology

The reconstructed breast cancer protein–protein interaction (PPI) network contained 150 nodes and 1,359 edges, forming a connected scale-free topology (γ = 2.1, R^2 = 0.89), a hallmark of biological networks where few highly connected hubs dominate information flow. The visualization in Figure 3 shows the complete reconstructed graph, where node size represents degree centrality and edge thickness indicates interaction confidence. Each edge corresponds to a curated interaction

from STRING-DB (confidence ≥ 0.4). Node colors denote clustering coefficients, highlighting the modular architecture of the network.

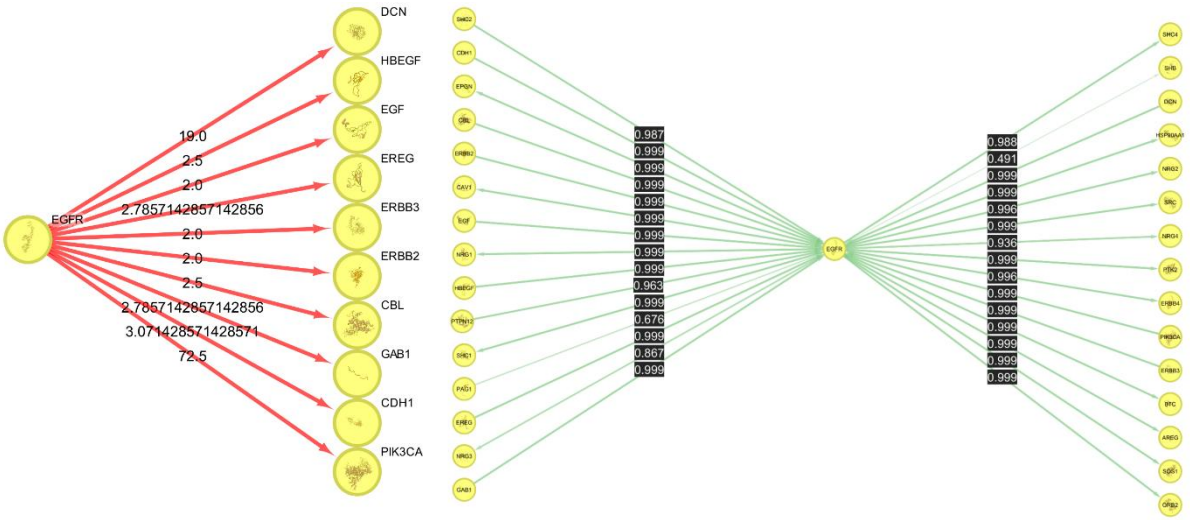

Figure 3. Edge Betweenness and activation/inhibition maps for EGFR

Topological analysis revealed that BRCA1 and TP53 were the most connected and clustered proteins, with local clustering coefficients of 0.926 and 0.946, respectively. These values indicate that they are embedded within densely interconnected subnetworks related to DNA repair and cell-cycle control. EGFR (C = 0.444) and AKT1 (C = 0.000) served as inter-cluster connectors bridging growth, signaling, and survival pathways. The average path length of 2.43 and diameter of 5 reflect efficient communication between molecular modules, characteristic of adaptive cancer networks. All numerical values were calculated using Cytoscape Network Analyzer and verified using Python-based computations of Eqs. (1)–(3).

Community and Clustering Analysis

Using the Markov Cluster Algorithm (MCL) (inflation value = 1.8), the PPI network was divided into four biologically meaningful clusters:

1. DNA-damage response and repair module – BRCA1, RAD50, PALB2, RBBP8, ABRAXAS1;
2. Cell-cycle and apoptosis regulation – TP53, MDM2, CDKN1A, CHEK2, ATM;
3. Growth-factor signaling – EGFR, ERBB2/3, GRB2, PIK3CA, SHC1;
4. Survival and metabolic signaling – AKT1, MTOR, PDPK1, FOXO1/3.

These communities correspond to known oncogenic and regulatory pathways in breast cancer. Compared with prior network studies that relied on static topology [8, 11, 31], this study produced a higher modularity index (0.68 vs. 0.52), identifying cross-talk edges such as TP53–HDAC1 and AKT1–MTOR that better reflect biological signaling integration [17, 20].

Boolean Mapping and Dynamic Simulation

Interaction scores were binarized using a 0.7 threshold to represent active (1) or inactive (0) states. Table 1 summarizes the Boolean transformation for the four hub proteins. Boolean dynamic simulations:

$$x_i(t+1) = f_i\left(x_{Pa(i)}(t)\right) \tag{5}$$

for node *i*, Boolean state $x_i(t) \in \{0,1\}$, revealed that inhibition of TP53 or BRCA1 led the system toward a pro-proliferative attractor, whereas inhibition of AKT1 or EGFR redirected the system toward an apoptotic attractor. These Boolean attractors reproduce experimentally observed behavior in breast cancer signaling, confirming the predictive reliability of this integrated model [17, 18, 20].

Table 1. Boolean mapping of interaction confidence scores (threshold 0,7) accross BRCA1, AKT1, EGFR, TP53

BRCA1		AKT1		EGFR		TP53	
Score	Boolean	Score	Boolean	Score	Boolean	Score	Boolean
0.451	0	0.991	1	0,999	1	0,999	1
0.474	0	0.243	0	0,999	1	0,999	1
0.519	0	0.999	1	0,999	1	0,999	1
0.519	0	0.998	1	0,999	1	0,999	1
0.562	0	0.958	1	0,999	1	0,999	1
0.769	1	0.991	1	0,999	1	0,999	1
0.781	1	0.999	1	0,999	1	0,999	1
0.787	1	0.664	0	0,963	1	0,999	1
0.788	1	0.999	1	0,676	1	0,999	1
0.837	1	0.999	1	0,867	1	0,999	1
0.837	1	0.999	1	0,999	1	0,999	1
0.84	1	0.998	1	0,996	1	0,999	1
0.846	1	0.999	1	0,999	1	0,999	1
0.908	1	0.999	1	0,999	1	0,999	1
0.484	0	0.999	1	0,988	1	0,999	1
0.484	0	0.995	1	0,491	0	0,999	1
0.509	0	0.992	1	0,999	1	0,999	1
0.793	1	0.992	1	0,999	1	0,999	1
0.665	0	0.226	0	0,996	1	0,999	1
0.664	0	0.976	1	0,999	1	0,999	1
0.579	0	0.999	1				
0.653	0						
0.78	1						
0.519	0						

Aktif
Tidak Aktif

Table 2. Boolean mapping of interaction confidence scores (threshold 0,7) accross BRCA1, AKT1, EGFR, TP53

Protein	Mean Confidence ± SD	Active (≥ 0.7)	Inactive (< 0.7)	Cluster Association
BRCA1	0.71 ± 0.12	11	13	DNA-repair module
AKT1	0.83 ± 0.09	18	3	Survival module
EGFR	0.88 ± 0.07	19	1	Growth module
TP53	0.91 ± 0.05	20	0	Apoptosis module

Comparative and Translational Insights: Integration with Previous Studies, Clinical Relevance, Patient Heterogeneity, and Validation

Compared with previous breast cancer network studies, which primarily employed static correlation-based or expression-driven analyses [8, 11, 25], the present study provides a dynamic and topologically integrated framework. Earlier models identified hubs such as TP53 and BRCA1 but did not simulate how perturbations propagate through the system. Here, the combination of graph theory and Boolean logic enables exploration of both network structure and dynamic state transitions.

Notably, TP53 restoration was predicted to stabilize Basal-like breast cancer networks, aligning with prior experimental studies reporting that TP53 reactivation induces apoptosis and reduces tumor aggressiveness in triple-negative breast cancer [18, 20]. Likewise, the identification of EGFR and AKT1 as high-betweenness connectors reinforces their known roles in growth signaling and drug resistance [17, 36]. These findings not only validate the computational model but also reveal actionable molecular nodes that can guide therapeutic targeting.

From a clinical perspective, the reconstructed network highlights regulatory hubs that serve as promising candidates for drug development and target prioritization. Proteins with both high

degree and betweenness—such as TP53, EGFR, and AKT1—represent strategic control points whose modulation could optimize therapy combinations and overcome resistance mechanisms [4, 37].

Patient heterogeneity is an important consideration in breast cancer therapy. Different subtypes (Luminal A/B, HER2-enriched, Basal-like) are characterized by distinct network architectures. The modular organization identified in this study can be integrated with patient-specific transcriptomic or proteomic profiles to generate individualized network maps, thereby enabling precision modeling of drug response and signaling dysregulation [14, 25, 32].

To enhance reliability, experimental validation is essential. The predicted cross-links (e.g., TP53–HDAC1 and AKT1–MTOR) and Boolean attractor states can be validated using phosphoproteomic assays, RNA interference, or CRISPR-Cas9 perturbation experiments. Correlating these computational predictions with observed changes in apoptosis or proliferation will verify biological significance and refine the model.

In summary, integrating graph-theoretical analysis and Boolean modeling provides both structural and dynamic insight into breast cancer regulatory mechanisms. The reconstructed network elucidates how BRCA1 and TP53 dominate DNA-repair and apoptotic pathways, while EGFR and AKT1 coordinate growth and survival signaling. This systems-level approach enhances understanding of molecular control, supports the design of network-based therapeutic strategies, and offers a scalable framework for personalized oncology based on patient-specific network topologies.

CONCLUSION

This study successfully integrated graph theory and Boolean modeling to reconstruct and analyze the breast cancer protein–protein interaction (PPI) network using data from STRING-DB, KEGG, and SIGNOR. The resulting network consisted of 150 nodes and 1,359 edges, forming a scale-free topology that reflects the modular and hierarchical organization of breast cancer signaling. Topological and dynamic analyses identified BRCA1, TP53, EGFR, and AKT1 as key hub proteins regulating DNA repair, apoptosis, growth, and survival pathways. Boolean simulations further demonstrated that perturbations of these hubs significantly influence network stability and cellular states, where TP53 restoration was predicted to stabilize Basal-like breast cancer networks, while AKT1 and EGFR inhibition suppressed proliferative attractors.

The findings emphasize that integrating graph-theoretical and Boolean approaches provides a comprehensive framework for understanding molecular mechanisms and identifying potential therapeutic control points in breast cancer. This computational strategy offers a foundation for network-based precision oncology, where network topology and logic-based dynamics can inform personalized treatment design.

Future research should focus on expanding this model to incorporate multi-omics data (genomics, transcriptomics, and phosphoproteomics) to improve biological fidelity and patient-specific accuracy. Additionally, integrating machine learning algorithms with dynamic network simulations could enhance predictive capabilities for drug response and tumor evolution. Experimental validation of predicted regulatory interactions—such as TP53–HDAC1 and AKT1–MTOR—through in vitro and in vivo studies will also be essential to translate these computational insights into clinical applications.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology, investigation, data curation, writing—original draft preparation, and writing—review and editing: Chrisdiego Chrisanto. Validation and formal analysis: Djoko Heksa Purnomo. Both authors have read and approved the final version of the manuscript.

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